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Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: The dimension of timing

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Abstract

BACKGROUND—Combining tDCS with robotic therapy is a new and promising form of neurorehabilitation after stroke, however the effectiveness of this approach is likely to be influenced by the relative timing of the brain stimulation and the therapy.

OBJECTIVE—To measure the kinematic and neurophysiological effects of delivering tDCS before, during and after a single session of robotic motor practice (wrist extension).

METHODS—We used a within-subjects repeated-measurement design in 12 chronic (>6 months) stroke survivors. Twenty minutes of anodal tDCS was delivered to the affected hemisphere before, during, or after a 20-minute session of robotic practice. Sham tDCS was also applied during motor practice. Robotic motor performance and corticomotor excitability, assessed through transcranial magnetic stimulation (TMS), were evaluated pre- and post-intervention.

RESULTS—Movement speed was increased after motor training (sham tDCS) by ~20%. Movement smoothness was improved when tDCS was delivered before motor practice (~15%). TDCS delivered during practice did not offer any benefit, whereas it reduced speed when delivered after practice (~10%). MEPs were present in ~50% of patients at baseline; in these subjects motor practice increased corticomotor excitability to the trained muscle.

CONCLUSIONS—In a cohort of stroke survivors, motor performance kinematics improved when tDCS was delivered prior to robotic training, but not when delivered during or after training.

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The temporal relationship between non-invasive brain stimulation and neurorehabilitation is important in determining the efficacy and outcome of this combined therapy.

Keywords

tDCS; TMS; stroke; robotic training; timing

1. Introduction

Two promising modern approaches to chronic stroke rehabilitation are modulation of brain function by noninvasive brain stimulation, such as with transcranial direct-current stimulation (tDCS) (Butler et al., 2012; Nitsche & Paulus, 2000), and by robotic physical rehabilitation therapy, through which great precision is achieved (Volpe et al., 2009). It is accepted that tDCS is unlikely to be optimal for functional recovery on its own, but that it is a promising way to augment rehabilitation therapies by enhancing brain plasticity. Robotic-assisted motor retraining programs offer a level of precision unprecedented in stroke rehabilitation, and have been shown to be effective for functional recovery after stroke (Lo et al., 2010). Both of these approaches target the modulation of brain plasticity, and therefore there is a rationale for determining whether combining these modalities could lead to an additive benefit. However, the optimal approach for a combined therapy, and whether the effects of a combination are co-operative or conflicting, has not been fully explored. One fundamental question is the temporal relationship between brain stimulation and robotic therapy; brain stimulation could precede, be contemporaneous, or follow robotic practice for example, and is likely to have differential effects under each of these circumstances. In a previous study we have shown that an increase in corticomotor excitability arising from a period of tDCS is still present if the brain stimulation is followed by robotic practice (Edwards et al., 2009), suggesting that these modalities could be synergistic. In the present study we have compared, in a blinded crossover design in a cohort of chronic stroke survivors, the kinematic and neurophysiological effects of delivering tDCS before, during and after a single session of robotic motor practice. The purpose of this study was to investigate the value of combined tDCS and robotic therapy for stroke rehabilitation, and to understand the mechanisms of this interaction and its relationship to motor outcome.

2. Methods

2.1. Study design

We used a within-subjects repeated-measurement design to assess the effects of timing of real or sham tDCS on motor performance when associated with one motor practice session. Patients were block-randomized to receive four different treatment conditions on separate occasions separated by one week. For each session, robotic motor performance was evaluated pre- and post-intervention, with movement kinematics as the principal outcome measure.

2.2. Subjects

Twelve participants, 7 with right hemiparesis and 5 with left hemiparesis, volunteered for the study (6 Males, 6 Females; mean 4.0 yrs since stroke, range 2–7.2 yrs; mean age = 64

yrs, range 41–75 yrs; Table 1). Subjects were included if they met the following criteria: a) a first, single focal unilateral lesion with diagnosis verified by brain imaging (MRI or CT scans) that occurred at least 6 months prior; b) Motor Power score of 3 to 4/5 (Medical Research Council muscle strength grading; neither hemiplegic nor fully recovered motor function in the wrist extensor muscles, sufficient to generate some voluntary extension); and c) cognitive function sufficient to understand the experiments and follow instructions (Mini-Mental Status Score of 22 or higher or interview for aphasic subjects). Subjects were excluded with TMS/tDCS risk factors such as history of epileptic illness, presence of metallic objects implanted in the brain or pacemaker, or the presence of a fixed contraction deformity of the wrist. All subjects gave written informed consent before participating, and the study was approved by the Institutional Ethics Committee of Burke Rehabilitation Hospital, White Plains, NY.

2.3. Robotic motor practice setup

2.3.1. Apparatus—This study used an InMotion3 wrist robot (Interactive Motion Technologies, Watertown, MA) designed for clinical neurological applications. The robot had three actuated degrees of freedom (dof), namely radial-ulnar deviation (RUD), flexion-extension (FE), and pronation-supination. Here we employed only flexion/extension and radial-ulnar deviation movements [6]. A complete description of the hardware is reported in (Krebs et al., 2007). The angular positions of three encoders located at the joints of the robot were acquired digitally (sampling frequency $f_s = 200$ Hz, 16-bit quantization).

2.3.2. Protocol—At the start of each practice session, patients were set up in the wrist device and given passive stretching of wrist flexion/extension by the robot, to reduce muscle tone prior to the practice session. For the robotic practice protocol, the robot allowed low-friction movement with gravity compensation. For each subject, the robot was initially calibrated in order to ensure a static neutral position for the wrist. During the practice, patients performed single contractions towards a visually displayed target, indicated by the experimenter (Fig. 1), in the direction that always took their wrist into extension (East or West depending on the side of paresis). Patients performed 20 minutes of practice, comprising 4 sets of movements: 4 minutes of active movement into extension (the hand was subsequently returned passively to the starting position by the robotic device) at a frequency of 0.2 Hz, followed by 1 minute of complete rest. There was no resistance during the active movement. Friction and inertia of the robotic manipulandum were negligible. Patients were given the instruction “to move as quickly and accurately as possible to each target” and presented with a visual preparatory cue.

2.3.3. Transcranial direct current stimulation—A 2mA current was delivered by a battery-driven, constant current stimulator (maximum output 10 mA); patients received stimulation for 20 minutes while seated before, during or after motor training. For stimulation setup the anode was placed over the optimal site of primary motor cortex (M1) for the flexor carpi radialis (FCR) and the extensor carpi radialis (ECR) muscles, as identified using TMS (or centered approximately over C3 using the EEG 10–20 referencing system), while the cathode was placed on the contralateral supraorbital area. *Sham tDCS*:

comparable setup to real tDCS, with current ramping up to 2mA (30 seconds) at the start and then ramping down to 0 after 10 seconds.

2.4. Motor evoked potential recordings

Single (biphasic) pulse TMS was delivered to the brain through a Figure-8 shaped coil (inner diameter: 35 mm, outer diameter: 75 mm, MagVenture), using a MagPro $\times$ 100 stimulator (Mindcare Co.). We used a lycra cap positioned over the head with the vertex marked as the mid-point intersection between the nasion-inion and inter-aural lines to identify the area of stimulation. The optimal site on the scalp was found by exploration of the area of motor cortex that best corresponded to movement of the wrist with TMS pulses: using a supra-threshold stimulus intensity, the coil was moved over motor cortex to determine the optimal location for eliciting maximal amplitude MEPs in the FCR and ECR muscles, with the subject at rest. Stimulus sites were marked on the cap using the vertex as a reference point, in 1-cm steps in the coronal and sagittal planes, over the region of M1. During stimulation, the center of the coil was placed tangentially to the scalp with the handle pointing posterior and laterally rotated at a 45° angle from the midline. Surface EMG activity was recorded from pre-amplified electrodes (SX230, fixed electrode distance: 20 mm, Biometrics Ltd.) positioned over the muscle belly of the FCR and ECR muscles. EMG signals were amplified ($\times$ 1000) at the site and band-pass filtered between 20 and 400 Hz. The signals were collected and digitized at a frequency of 1000 Hz using an A/D converter (CED 1401) and a data-collection program, then stored in the computer for further off-line analysis. EMG of the FCR and ECR muscles was monitored during MEP recordings to ensure muscle relaxation.

Resting Motor Threshold (RMT) was determined as the lowest stimulus intensity evoking an MEP of 50 μ V in 3 of 5 trials in the relaxed muscle. Stimulus intensity was adjusted to 120% RMT and 10 MEPs were collected at approximately 0.2 Hz pre and post intervention. Peak-to-peak MEP amplitude for each collection was determined off-line and reported as the measure of cortico-motor excitability. Data are reported as mean $\pm$ standard error. Pre-post differences in MEP amplitude for FCR and ECR muscle were determined using a two-tailed paired *t*-test, with post-intervention normalized data tested relative pre-intervention using a *z*-test (alpha level <0.05). Data were included in the pre-post TMS analysis if baseline MEP amplitude was >20 μ V.

2.5. Robotic performance evaluation

The robotic evaluation comprised 60 total un-aided wrist movements in the flexion-extension plane with the following order: center-to-extension (same as practice movement), extension-to-center, center-to-flexion, and flexion-to-center.

2.5.1. Analysis of kinematic data—The portion of data related to the movement from the central target to and from the outer targets was extracted from the full set of data. A movement was considered to begin when the speed first became greater than 2% of the peak speed and was considered to end after the speed dropped and remained below the 2% threshold.

Lateral deviation D of subjects' movements from a straight line connecting the targets was calculated as:

$$D = \sqrt{\frac{1}{(N-1)} \sum_{i=1}^N (s(i) - p(i))^2}$$

where $s(i)$ is the wrist position at sample i , $p(i)$ is the coordinate of the intersection between the straight line connecting the targets and its perpendicular passing through $s(i)$, and N is the total number of samples. This metric has been widely used in motor learning experiments on reaching movements. Note that the hand paths produced during wrist rotations lie on a roughly spherical surface surrounding the wrist joint. However, for wrist rotations of the magnitudes used in this study, the spherical surface is shallow and the hand paths can be approximated as lying in a plane tangential to this spherical surface. In other words, for the moderate-sized wrist rotations we used, the difference between a path on this sphere and its projection onto the tangential plane is small: the maximum error associated with this approximation is 1.6° in FE (5% of FE at that point) and 1.0° in RUD (10% of RUD at that point).

In addition, the following metrics were extracted from speed profiles of the pointing movements, which were calculated as summed squares of the first order difference of the X and Y trajectory components, smoothed with a 0–4 Hz bandwidth FIR filter.

Movement Aim A was calculated as:

$$A = \frac{1}{(N-1)} \sum_{i=1}^N \left| \tan^{-1}(\dot{s}(i)) - \text{ref}(j) \right|$$

where $\dot{s}(i)$ is the wrist velocity at sample i , $\text{ref}(j)$ is the angle of the straight line connecting the center target to the outer target j , and N is the total number of samples.

Movement Mean speed M was calculated as:

$$M = \sqrt{\frac{1}{(N-1)} \sum_{i=1}^N (\dot{s}(i))^2}$$

Movement Peak speed P was calculated as:

$$P = \max(\dot{s}(i))$$

One smoothness metric was also computed as mean speed divided by peak speed. This smoothness metric is dimensionless and increases monotonically with movement smoothness.

For each experimental condition, a repeated measures ANOVA test ($p = 0.05$) was used to compare the amount of lateral deviation, aim, mean and peak speed, and smoothness across different blocks.

3. Results

Each of the intervention paradigms (combined training and stimulation) were well tolerated, with 100% compliance across the four experimental days. The characteristics of the patients included in this study are summarized in Table 1.

3.1. Motor performance – kinematics

Robotic training in the absence of tDCS (sham condition) resulted in a significant (~20%, Fig. 2) increase in volitional movement speed without change in deviation, or other kinematic measures; mean speed: pre $3.1 \pm 0.1 \times 10^{-1}$ rad/s, post $3.7 \pm 0.2 \times 10^{-1}$, $p = 0.006$; peak speed: pre $13.1 \pm 0.8 \times 10^{-1}$, post $16.6 \pm 1.1 \times 10^{-1}$, $p = 0.009$; deviation: pre $3.6 \pm 0.4 \times 10^{-2}$ rad, post $4.4 \pm 0.5 \times 10^{-2}$, $p = 0.168$; smoothness: pre $2.8 \pm 0.1 \times 10^{-1}$, post $2.6 \pm 0.1 \times 10^{-1}$, $p = 0.317$; duration: pre 3.74 ± 0.23 s, post 3.48 ± 0.24 , $p = 0.432$; aim: pre $7.9 \pm 0.4 \times 10^{-1}$ rad, post $8.8 \pm 0.35 \times 10^{-1}$, $p = 0.095$.

With tDCS preceding robotic training, movement smoothness was significantly (>15%, Fig. 2) enhanced following training, although speed was no longer increased and other kinematic variables were not affected; smoothness: pre $2.5 \pm 0.1 \times 10^{-1}$, post $2.9 \pm 0.1 \times 10^{-1}$, $p = 0.001$; deviation: pre $4.7 \pm 0.5 \times 10^{-2}$, post $3.7 \pm 0.4 \times 10^{-2}$, $p = 0.133$; mean speed: pre $3.65 \pm 0.2 \times 10^{-1}$, post $3.8 \pm 0.2 \times 10^{-1}$, $p = 0.43$; peak speed: pre $16.4 \pm 1.0 \times 10^{-1}$, post $14.9 \pm 1.0 \times 10^{-1}$, $p = 0.297$; duration: pre 3.1 ± 0.3 , post 3.2 ± 0.2 , $p = 0.062$; aim: pre $9.3 \pm 0.3 \times 10^{-1}$, post $8.3 \pm 0.4 \times 10^{-1}$, $p = 0.052$.

When tDCS was delivered concurrently with robotic training, the aim metric became significantly (~15%, Fig. 2) worse, while movement speed and other kinematic measures remained unaltered following training; aim: pre $7.1 \pm 0.3 \times 10^{-1}$, post $8.2 \pm 0.3 \times 10^{-1}$, $p = 0.019$; mean speed: pre $3.4 \pm 0.2 \times 10^{-1}$, post $3.6 \pm 0.2 \times 10^{-1}$, $p = 0.53$; peak speed: pre $13.9 \pm 1.0 \times 10^{-1}$, post $14.6 \pm 0.9 \times 10^{-1}$, $p = 0.585$; deviation: pre $3.6 \pm 0.3 \times 10^{-2}$, post $4.2 \pm 0.5 \times 10^{-2}$, $p = 0.239$; smoothness: pre $2.8 \times 10^{-1} \pm 0.1$, post $2.9 \pm 0.1 \times 10^{-1}$, $p = 0.554$; duration: 3.01 ± 0.22 , post 3.08 ± 0.21 , $p = 0.987$.

TDCS delivered following robotic training resulted in a significant reduction (>10%, Fig. 2) in mean movement speed (pre $4.1 \pm 0.2 \times 10^{-1}$, post $3.6 \pm 0.2 \times 10^{-1}$, $p = 0.032$). The remaining kinematic measures were not altered by this training and stimulation combination; peak speed: pre $15.7 \pm 0.9 \times 10^{-1}$, post $15.0 \pm 1.0 \times 10^{-1}$, $p = 0.595$; aim: pre $8.0 \pm 0.4 \times 10^{-1}$, post $7.8 \pm 0.3 \times 10^{-1}$, $p = 0.65$; deviation: pre $3.6 \pm 0.4 \times 10^{-2}$, post $4.8 \pm 0.5 \times 10^{-2}$, $p = 0.087$; smoothness: pre $3.0 \pm 0.1 \times 10^{-1}$, post $2.9 \pm 0.1 \times 10^{-1}$, $p = 0.529$; duration: pre 2.58 ± 0.18 , post 2.94 ± 0.19 , $p = 0.158$.

3.1.1. Motor evoked potentials—Despite all patients recruited being able to voluntarily activate the extensor muscles (sufficient to generate extension torque as evaluated clinically), only 50% of these (6 of 12) had detectable MEPs in the ECR muscle (>20 uV),

while one patient had MEPs only in the FCR muscle. The amplitude range across subjects was 48 – 1432 uV in the FCR (mean 430 ± 19 uV, $n = 7$) and 25 – 621 uV in the ECR (mean 340 ± 10 uV, $n = 6$); FCR and ECR mean difference, $p = 0.23$.

Motor training significantly enhanced agonist ECR mean MEP amplitude ($141 \pm 22\%$ baseline, $p = 0.03$, $n = 6$) with only a mild and non-significant reduction in mean antagonist FCR excitability ($90 \pm 20\%$ baseline, $p = 0.68$). TDCS stimulation delivered at any of the time points in relation to training resulted in no significant ($p > 0.05$) changes in MEP amplitude (tDCS pre-training: FCR $97 \pm 9\%$ baseline, ECR $124 \pm 21\%$ baseline, $n = 6$; tDCS during training: FCR $139 \pm 43\%$ baseline, ECR $115 \pm 29\%$ baseline, $n = 5$; tDCS post training: FCR $110 \pm 19\%$ baseline, ECR $103 \pm 16\%$ baseline, $n = 5$).

Patients without a TMS response at baseline did not gain a TMS response under any of the conditions (robotic training combined with tDCS at different time points).

4. Discussion

The present study showed that a 20-minute session of robotic practice with the affected wrist of stroke patients led to an increase in movement speed. TDCS delivered before, during or after the practice had a differential effect on motor outcome. The optimal combination was tDCS delivered pre-training, where movement smoothness improved. TDCS during practice had the effect of worsening aim, while tDCS in the post-practice period had no apparent benefit and slowed movement speed. Our findings suggest that tDCS is best applied prior to training, and that the effects may not be simply additive but may change the nature of the training effect.

Robotic upper limb therapy is a well-defined and effective contemporary therapy (Volpe et al., 1999, 2000; Fasoli et al., 2004; Kahn et al., 2006; Macclellan et al., 2005), that typically delivers a high number of repetitions – an important ingredient for recovery of motor function in stroke hemiplegia (Lang et al., 2009). Conventional physical therapies involve varied and alternating movements, and in some cases bilateral training incorporating the unaffected arm (Hesse et al., 2011). In the present study we used a robotic practice task of movement into a single direction (wrist extension), which was clinically important for the participants (who had poor extensor muscle activation). An advantage of this approach was that it was possible to minimize confounding interactions that could arise from more complex movements and that could have influenced outcome measures. We also used a specific outcome measure, precisely the same one as the training task, using previously validated kinematic metrics (Bosecker et al., 2010), and assessed outcome directly after every session. These metrics are both clinically relevant and sensitive to the motor training task. Selecting sensitive, reliable and relevant outcome measures is warranted for single practice sessions where the effect size is likely to be small.

This is the first clinical study to systematically investigate the time at which tDCS is delivered in relation to motor practice. While there have been previous studies combining tDCS with motor training in stroke (Hesse et al., 2011, 2007; Bolognini et al., 2011), most have applied tDCS concurrently with training, and the period of training often extends well beyond that of stimulation. In the present study we made the duration of practice and tDCS

the same so that when applied concurrently, the training was always accompanied by brain stimulation. We then explored the order in which tDCS and practice were administered. We hypothesized that the order of application could have differential effects, since the mechanisms of action of tDCS are different during and after stimulation (Nitsche et al., 2003). The present study indicates that the training is best delivered during the after-effects of tDCS.

While separately tDCS and robotic practice can increase corticomotor excitability, we found that this was not the case for any combination of tDCS and robotic interventions. This suggests that the effects of these interventions are not necessarily additive, and that concurrent or subsequent practice-related synaptic activity can mask or reverse tDCS after-effects. It is known that various combinations of consecutive non-invasive brain stimulation interventions can have markedly different after-effects to the interventions acting alone (Nitsche et al., 2007; Lang et al., 2004; Siebner et al., 2004). Here we demonstrated a similar phenomenon with tDCS and motor training. However, when robotic wrist training involved multiple directions and was extended to one hour, an increase in corticomotor excitability could again be observed (Edwards et al., 2009).

In conclusion, we demonstrated that the combination of tDCS and upper-limb robotic practice improved motor performance after stroke, but only when the practice was preceded by tDCS. When tDCS was applied during therapy or after therapy, it conferred no additional advantage. It remains to be determined whether our findings, in relation to the effects of this ordering, may apply more generally to more complex forms of motor training, for multiple bouts of practice, and with non-motor therapies involving language, vision, and higher cognitive function.

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Movement Training Paradigm **Fig. 1.**

20-minute motor practice paradigm showing: (a) the visual cue display on a monitor in front of the patient, full circle = current position, open circle = target, and (b) the patient moves the wrist to extension, and upon reaching the target, the robotic device returns the wrist to neutral. This is repeated at a rate of 1 movement per 5 seconds.

Fig. 2.

Group normalized data for each of the experimental conditions, showing mean speed to be increased as a consequence of practice (left bar). When tDCS was delivered before practice, the increase in speed was substituted for enhanced movement smoothness. With tDCS delivered during practice or after practice (the two right-hand bars), there was no improvement in performance. Aim worsened (tDCS during) and speed slowed (tDCS post), suggesting a non-beneficial effect with tDCS delivered at these time points.

Table 1

Patient demographic and clinical information

Demographic			Clinical			
Patient #	Age yrs	Gender M/F	Affected Hem. right/left	Time Since Stroke (days)	Impairment Level (Tual-Meyer) upper extremity/66	Wrist-hand/30
1	70	M	R	774	43	15
2	41	F	L	874	19	4
3	64	F	L	937	13	2
4	74	F	L	1083	28	10
5	66	F	R	767	56	24
6	76	M	L	1404	48	21
7	58	M	L	2175	59	26
8	72	M	R	2065	39	13
9	50	F	R	2626	43	16
10	52	M	R	2225	63	27
11	75	M	L	725	17	4
12	75	F	L	1657	31	7

Corticospinal Integrity MEP presence

✗ ✗ ✗ ✗ ✗ ✗ ✓ ✗ ✓ ✓ ✓ ✗ ✓ ✓ ✗