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ARTICLE

Comparison of repeated transcranial stimulation and transcranial direct-current stimulation on primary motor cortex excitability and inhibition: A pilot study

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Abstract – Repeated transcranial magnetic stimulation (rTMS) is a well-known clinical neuromodulation technique, but transcranial direct-current stimulation (tDCS) is rapidly growing interest for neuro-rehabilitation applications. Both methods (contralesional hemisphere inhibitory low-frequency: LF-rTMS or lesional hemisphere excitatory anodal: a-tDCS) have been employed to modify the interhemispheric imbalance following stroke. The aim of this pilot study was to compare aHD-tDCS (anodal high-definition tDCS) of the left M1 (2 mA, 20 min) and LF-rTMS of the right M1 (1 Hz, 20 min) to enhance excitability and reduce inhibition of the left primary motor cortex (M1) in five healthy subjects. Single-pulse TMS was used to elicit resting and active (low level muscle contraction, 5% of maximal electromyographic signal) motor-evoked potentials (MEPs) and cortical silent periods (CSPs) from the right and left extensor carpi radialis muscles at Baseline, immediately and 20 min (Post-Stim-20) after the end of each stimulation protocol. LF-rTMS or aHD-tDCS significantly increased right M1 resting and active MEP amplitude at Post-Stim-20 without any CSP modulation and with no difference between methods. In conclusion, this pilot study reported unexpected M1 excitability changes, which most likely stems from variability, which is a major concern in the field to consider.

Keywords: non-invasive brain stimulation, contralateral hemisphere, interhemispheric interactions

Résumé – Comparaison entre les effets de la stimulation magnétique transcrânienne répétée et la stimulation transcrânienne à courant continu sur l'excitabilité du cortex moteur primaire : une étude pilote. En neuro-réhabilitation, la stimulation magnétique transcrânienne répétée (rTMS) est reconnue alors que la stimulation transcrânienne à courant continu (tDCS) tend à fortement se développer. Chacune des méthodes (inhibition controlatérale *via* rTMS basse fréquence, LF-rTMS, ou renforcement de l'hémisphère lésé *via* tDCS anodale, a-tDCS) est utilisée pour rétablir le déséquilibre interhémisphérique suite à un accident vasculaire cérébral. Le but de cette étude pilote était de comparer les effets induits par aHD-tDCS (tDCS anodale haute-définition, 20 min, 2 mA) du cortex moteur primaire (M1) gauche et LF-rTMS (20 min, 1 Hz) de M1 droit pour augmenter l'excitabilité et diminuer l'activité inhibitrice de M1 gauche chez cinq sujets sains adultes. Les potentiels moteurs évoqués (MEP) par TMS au repos et lors de faibles contractions (actif, 5 % de l'activité électromyographique maximale) associés aux périodes de silences (CSP) étaient recueillis au niveau des muscles extenseurs radial du carpe droit et gauche avant (Baseline), immédiatement après et 20 min après (Post-Stim-20) chaque méthode. Aucune variation des CSP n'a été observée pour les deux méthodes mais l'amplitude des MEP de repos et actif de M1 droit était significativement plus importante à Post-Stim-20. Cette étude pilote rapporte des modulations d'excitabilité majoritairement attribuables à la variabilité des réponses interindividuelles.

Mots clés : interactions interhémisphériques, hémisphère controlatéral, stimulation corticale non invasive

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1 Introduction

Experimental interventions that might alleviate post-stroke motor impairments include non-invasive brain stimulation (NIBS) in order to inhibit activity in the contralesional primary motor cortex (M1) and facilitate activity in the ipsilesional M1. Although repeated transcranial magnetic stimulation (rTMS) is a well-known clinical neuromodulation technique (Corti, Patten, & Triggs, 2012; Hoyer & Celnik, 2011; Schulz, Gerloff, & Hummel, 2013), transcranial direct-current stimulation (tDCS) is rapidly growing interest as a more simple and affordable method. Based on the interhemispheric inhibition principle, stating a mutual inhibition between hemispheres (Ferbert *et al.*, 1992), low frequency rTMS (LF-rTMS) is applied to the contralesional hemisphere (Corti *et al.*, 2012; Schambra, Sawaki, & Cohen, 2003); while anodal tDCS (a-tDCS) is applied to the affected/ipsilesional hemisphere (Schlaug, Renga, & Nair, 2008). Both NIBS methods aim to counterbalance the loss in excitability of the affected hemisphere and restore the balance between hemispheres (Hao, Wang, Zeng, & Liu, 2013; Nowak, Grefkes, Ameli, & Fink, 2009).

Repeated transcranial magnetic stimulation (rTMS) was derived from single-pulse transcranial magnetic stimulation (TMS) developed 30 years ago (Barker, Jalinoous, & Freeston, 1985). The magnetic stimuli are repeated over time to modulate the M1 excitability and induce neuroplasticity (Schulz *et al.*, 2013). Since its approval as a recognized therapy for depression by the Food and Drug Administration (Wassermann, 1998), rTMS has become a gold NIBS standard in neurorehabilitation. LF-rTMS is generally known to decrease the M1 excitability when applied with a 1 to 5 Hz interstimulus interval at intensities ranging ~70–90% of the motor threshold (Ridding & Rothwell, 2007) and durations ranging from 0 to 30 min (Arai *et al.*, 2007; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000); at high frequency (HF-rTMS > 5 Hz), M1 excitability is increased. Furthermore, decreasing one M1's excitability with LF-rTMS would reduce its inhibitory activity toward the opposite M1 that sees in turn its excitability increases as previously reported in healthy subjects (Gilio, Rizzo, Siebner, & Rothwell, 2003). It is important to note that LF-rTMS is preferred to HF-rTMS due to its propensity to trigger seizures (Dobek, Blumberger, Downar, Daskalakis, & Vila-Rodriguez, 2015; Pereira, Muller, da Mota Gomes, Rotenberg, & Fregni, 2016).

The tDCS research field is growing interest as a promising neurorehabilitation technique (Chang, Kim, & Park, 2015; Di Lazzaro *et al.*, 2014; Jo *et al.*, 2009; Simonetta-Moreau, 2014). With a conventional anodal tDCS (a-tDCS) montage, a large rubber-sponge anode electrode is applied onto the scalp overlying the M1 region of interest and the cathode as the reference electrode is placed on the contralateral supra orbital area. In healthy subjects, this montage has usually shown to increase M1 excitability as determined by TMS motor-evoked potentials (MEP) amplitude (Gandiga, Hummel, & Cohen, 2006; Nitsche & Paulus, 2000). For example, an increase in M1 MEP amplitude up to 35% above baseline has been documented after 2 mA anodal tDCS of the left M1 (Jeffery, Norton, Roy, & Gorassini, 2007). Recently, advances in the research field led to the development of high-definition (HD)-tDCS to constrain the current in the area of interest and increase its efficiency (Edwards *et al.*, 2013; Kuo *et al.*, 2013; Muthalib, Besson, Rothwell, Ward, & Perrey, 2016b; Villamar *et al.*, 2013). This particular montage uses an active electrode (anode, in the case of anodal stimulation) surrounded by four return reduced size electrodes 35 mm away instead of the standard bi-electrode montage.

To the best of our knowledge, only a few studies (Priori, Hallett, & Rothwell, 2009) directly compared rTMS and tDCS techniques in a same experimental design. By comparing a-tDCS with HF-rTMS protocol, Simis *et al.* (2013) found an expected increased MEP amplitude following HF-rTMS but also found a surprising decreased M1 excitability with a-tDCS. They argued that this unexpected tDCS result was due to the neuronal counter-regulation principle (homeostatic metaplasticity) that prevents over-excitation of the neurons, which caused this reversal in M1 excitability (Monte-Silva *et al.*, 2013).

The aim of this pilot study in healthy subjects was to compare anodal high-definition tDCS (aHD-tDCS) of the left M1 and LF-rTMS of the right M1 to modulate excitability and reduce inhibition (TMS evoked cortical silent period, CSP) in the left M1. Based on the literature, we hypothesized that aHD-tDCS would increase the excitability and decrease inhibition of the stimulated left M1 while LF-rTMS would decrease stimulated right M1 excitability and increase right M1 inhibition but also increase the left M1 excitability and decrease left M1 inhibition through interhemispheric inhibition principle.

Left M1 was chosen as a reference as it is the dominant hemisphere for right-handers.

2 Materials and methods

2.1 Participants

Five healthy right-handed subjects (4 males and 1 female, aged 33.2 ± 9 yr) volunteered to participate in this pilot study. All participants were free from any known neuromuscular injury or neurological disorders. The experimental procedures and protocols conformed to the recommendations of the local Human Research Ethics Committee in accordance with the latest version of the Declaration of Helsinki, and all subjects gave their informed written consent prior to the experiments. The handedness was quantified using the Edinburgh inventory test (Oldfield, 1971) and presented a mean right laterality quotient of 96.4 ± 8.1. The experiments were run at the hospital of Grau-du-Roi (CHU Nîmes, 30240, France).

2.2 Experimental procedure

Figure 1 shows a schematic of the experimental design. Participants were randomly assigned to undergo aHD-tDCS of the left M1 (2 mA, 20 min) or LF-rTMS of the

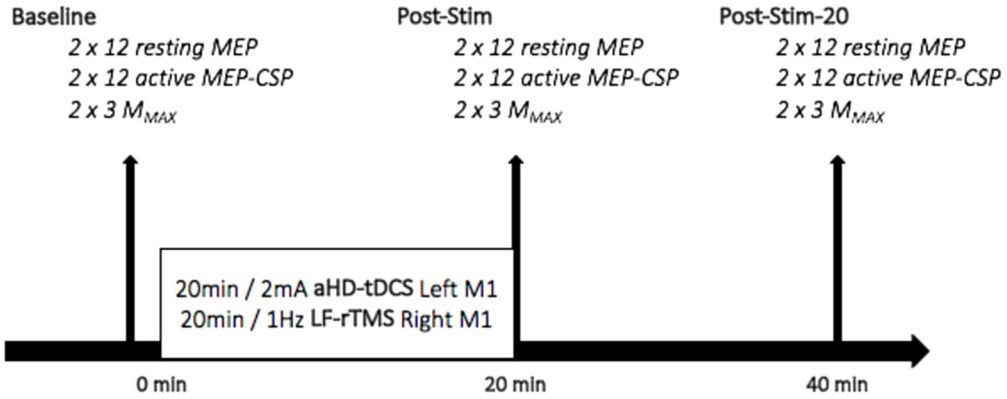

Figure 1. Schematic description of the experimental design. TMS (MEP and CSP) and nerve stimulation (M_{MAX}) measurements were performed for the left and right (as indicated by two series of measurements) M1 of each participant at Baseline, immediately (Post-Stim) and 20 min (Post-Stim-20) after the end of a 20-min period of neuromodulation brought by either anodal high-density-tDCS (aHD-tDCS) or low frequency-repeated TMS (LF-rTMS).

right M1 (1 Hz, 20 min) in a crossover design with at least 48 hrs between each session.

TMS measurements were alternatively performed from both left and right M1 in a randomised and counterbalanced order under two conditions: Resting (both arms) or Active (contralateral arm contracting in order to extent the wrist in line with the forearm to induce ~5% of maximal electromyograhic – EMG – activity) (Teo *et al.*, 2015). TMS measurements were tested at Baseline, immediately (Post-Stim) and 20 min (Post-Stim-20) after the end of the LF-rTMS or aHD-tDCS session. For each TMS measurement, 12 single-pulse MEPs were elicited from left and right M1 towards the contralateral extensor carpi radialis (ECR) muscle with a 5 s inter-stimulus interval; this muscle was chosen as previously used as target muscles in previous TMS studies using similar experimental design (Hendy & Kidgell, 2014; Muthalib, Cabibel, Rothwell, Teo, & Perrey, 2017; Teo *et al.*, 2015). At the end of each time-point, three maximal M-waves (M_{MAX}) were alternatively and randomly evoked from the left and right ECR muscles.

The maximal EMG activity was determined prior to the experiment for each arm during maximal voluntary contractions against a fixed support, with the best performance in three trials out of 5 s with a resting period of 60 s between each.

2.3 Experimental setup

Participants were sitting in a chair with the two forearms supported in a horizontal and pronated position on an armrest. The forearm and wrist were in a position such that the palm was faced down and the fingers were in line with the straight wrist. The legs were flexed and the trunk was resting on the back of the chair.

Surface EMG activity of the left and right ECR muscles was recorded with two pairs of self-adhesive silver chloride electrodes (Contrôle Grahique Medical, France) in bipolar configuration with a 20 mm electrode distance (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000). Low impedance (<5 kΩ) between electrodes was obtained by shaving, gently abrading the skin with sandpaper and cleaning it with modified alcohol. Electrodes were positioned lengthwise over the muscle belly and the reference electrode was attached to the left wrist radial styloid process.

EMG data were recorded at a sampling frequency of 2000 Hz with a Biopac MP100 (Biopac Systems Inc., Santa Barbara, CA, USA) and a computer running AcqKnowledge software (Biopac Systems Inc., Santa Barbara, CA, USA). The EMG signal was amplified (500 gain) with a bandwidth frequency ranging from 10 to 500 Hz. The root mean square of the EMG signal (rmsEMG) was calculated for the left and right ECR over 200 samples during the whole experiment. The rmsEMG was used to measure the level of EMG activity level (Li *et al.*, 2014) during the EMG activity plateau (~1 s, with less than 10% of peak-to-peak variation of the mean rmsEMG level during this 1 s). The rmsEMG signals were displayed to the participants on a computer screen throughout the experiment so they can match the required levels of contraction during the tasks.

2.4 Transcranial magnetic stimulation

TMS was performed using a MagPro R30 (MagPro R30, MagVenture, Farum, DK) with single-pulse mode stimulator connected to a figure-of-eight coil with windings of 70 mm diameter. The TMS coil was positioned tangentially to the head over the M1 in order to induce a posterior-anterior current flow. The optimal sites of stimulation were determined by starting initial exploration over C3 and C4 standard landmarks of left and right M1, respectively (Jasper, 1958). Left and right M1 were determined as the stimulation site which elicited the largest and most consistent MEPs from the contralateral ECR muscle in at least 5 out of 10 trials. The optimal stimulation position "hot-spot" was marked on the scalp through the hair with ink to allow an accurate repositioning of the coil throughout the whole experiment. Resting motor threshold (RMT) was defined as the lowest TMS intensity eliciting MEPs of 50 μV peak-to-peak in 5 out of 10 trials (Rossini *et al.*, 1994). Active motor threshold

(AMT) was defined as the lowest TMS intensity eliciting MEPs of 200 μV peak-to-peak in 5 out of 10 trials (Rothwell *et al.*, 1999). Corticospinal excitability was then determined for the left and right M1 at 130% of RMT and 130% of AMT (Muthalib *et al.*, 2017; Teo *et al.*, 2015) for resting and active MEPs, respectively. The peak-to-peak amplitude of these 12 evoked MEPs were normalized to the concomitant peripheral evoked response (see nerve stimulation section) to take account of possible alterations in signal conduction at any level from the motor cortex to within the muscle.

A 5 μV pre-stimulus rmsEMG threshold was chosen to exclude subjects with a background EMG value too high that could potentially influence resting MEP amplitude. Since no subjects showed this effect, all 12 MEPs were averaged and included for statistical analysis. Active MEPs and CSPs were evoked during wrist extension rmsEMG levels of ~5% maximal rmsEMG (*i.e.*, a-tDCS: left: 5.37 ± 2.72%, right: 6.9 ± 3.49%; LF-rTMS: left: 4.65 ± 1.77%, right: 6.58 ± 2.95%). CSP duration was defined as the interval between the onset of the MEP to the reappearance of at least 50% of the mean pre-TMS stimulus background EMG activity (Davidson & Tremblay, 2013).

2.5 Nerve stimulation

The evoked M-wave potentials were obtained from both left and right ECR muscles by supramaximal electrical stimulation (DS7A, Digitimer, UK) of the radial nerve superior to the elbow joint. First, the position of the stimulation was determined by an initial exploration using a stylus. The stimulation site was determined as the site which elicits the largest and most consistent response for the minimal stimulation intensity. Afterward, the intensity of the stimulator was increased by 10 mA every 10 s until no further increase of the recorded M-wave amplitude was observed. The M_{MAX} was defined as 130% of this intensity and was tested along with the TMS measurements at each time point.

2.6 Repeated transcranial magnetic stimulation

The rTMS was applied through the MagPro R30 biphasic magnetic generator on the right M1 representation of the non-dominant left ECR. The stimulation was delivered during 20 min at an intensity of 90% of RMT (Kaminski *et al.*, 2013) with a 1 Hz frequency (1200 total pulses).

2.7 Transcranial direct-current stimulation

Direct electrical current was generated by a tDCS stimulator (Starstim®, Neuroelectrics NE, Spain) and delivered to the left M1 representation of the dominant right ECR of the subject though a 4×1 ring HD a-tDCS montage with the active anode on the TMS "hot-spot" (see TMS measurement section) surrounded by four return electrodes, each at a distance of 35 mm from the active electrode (Muthalib, Besson, Rothwell, Ward, & Perrey, 2016a). The five electrodes (3.14 cm^2 AgCl electrodes) were secured on the scalp using conductive paste (Ten20®, Weaver and Company, USA). At the beginning of the sessions, stimulation ramped up during 30 s until the 2 mA current level was reached and continued at this level for a further 20 min duration.

2.8 Statistical analysis

Statistica 13.0 (Statsoft, Tulsa Oklahoma, USA) software was used for statistical analysis. Data were first screened for normality of distribution, homogeneity and sphericity of variances using a Shapiro-Wilk normality test, the Levene's and Mauchly's test, respectively A Greenhouse-Geisser correction was applied in case of sphericity violation in the analysis of variance (ANOVA). Following the ANOVA rules, *post hoc* LSD tests were performed only on significant main or interaction effects. All the Baseline TMS parameters, MEP, CSP and M_{MAX} values were compared between sessions (LF-rTMS, aHD-tDCS) by performing Wilcoxon tests.

A two-way repeated-measures (RM) ANOVAs were used on each M1 during each condition (Resting, Active) on the MEPs expressed as percent of M_{MAX} (MEP/M_{MAX}) and CSP values to assess the effects of the neuromodulation techniques. Partial eta-squared (n_p^2) values are reported as measures of effect size, with moderate and large effects considered for $n_p^2 \geq 0.06$ and $n_p^2 \geq 0.14$ respectively (Richardson, 2011). Results are present as mean ± SD. Significant threshold was set at $p < 0.05$.

3 Results

3.1 Control measures

No significant differences were found between aHD-tDCS and LF-rTMS sessions for the Baseline TMS parameters (see Table 1), MEP, CSP and M-wave values. Also, no significant differences were found during and across sessions for the pre-stimulus rmsEMG to ensure no deleterious pre-activation effect over MEPs.

3.2 CSP duration

The two-way RM-ANOVA on the CSP values showed no influence (144 ± 30 *vs.* 140 ± 30 *vs.* 135 ± 20 ms, from Baseline to Post-Stim to Post-Stim-20) of the neuromodulation ($F_{2,\ 16} = 2.54$; $n_p^2 = 0.24$; $p = 0.11$) with no significant difference (140 ± 30 *vs.* 150 ± 40 ms between tDCS and rTMS, respectively) between sessions ($F_{1,\ 8} = 0.29$; $n_p^2 = 0.04$; $p = 0.6$) or interaction ($F_{2,\ 16} = 0.29$; $n_p^2 = 0.04$; $p = 0.75$) in the left M1. Similarly, no neuromodulation influence (143 ± 20 *vs.* 149 ± 20 *vs.* 147 ± 20 ms, from Baseline to Post-Stim to Post-Stim-20) was found in the right M1 ($F_{2,\ 16} = 0.31$; $n_p^2 = 0.04$; $p = 0.74$) with no significant difference (142 ± 20 *vs.* 144 ± 20 ms between tDCS and rTMS, respectively) between sessions ($F_{1,\ 8} = 0.04$; $n_p^2 < 0.01$; $p = 0.85$) or interaction ($F_{2,\ 16} = 0.02$; $n_p^2 < 0.01$; $p = 0.98$).

Table 1. TMS parameters (expressed as % of stimulator output) for each session. Resting (RMT) and active (AMT) motor thresholds were stable and not statistically different across sessions.

	Left M1-tDCS	Left M1-rTMS	Right M1-tDCS	Right M1-rTMS
RMT	45 ± 6	50 ± 5	46 ± 4	50 ± 6
AMT	40 ± 6	43 ± 5	43 ± 5	45 ± 7

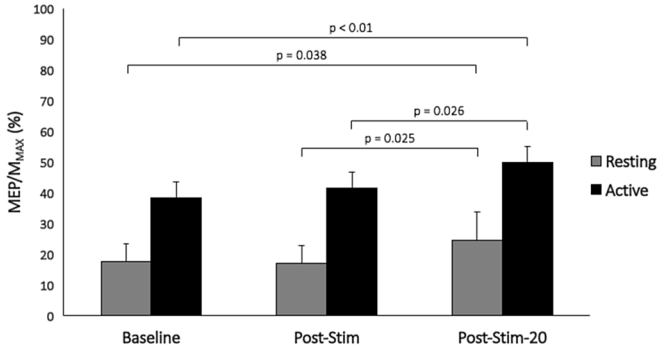

Figure 2. Excitability (MEP/M_{MAX}) changes in the right M1 immediately (Post-Stim) and 20 min (Post-Stim-20) following the neuromodulatory intervention (anodal high-density-tDCS and low frequency-repeated TMS) for resting and active MEPs. We show that both resting (+38%) and active (+30%) MEPs were significantly increased from Baseline to Post-Stim-20. Furthermore, both resting (+44%) and active (+20%) MEPs were significantly increased from Post-Stim to Post-Stim-20.

3.3 MEP amplitude

In the left M1, the two-way RM-ANOVA revealed no effect of the neuromodulatory intervention ($F_{2,\ 16} = 0.24$; $n_p^2 = 0.03$; $p = 0.68$) or any difference between sessions ($F_{1,\ 8} = 0.78$; $n_p^2 = 0.09$; $p = 0.4$) with no interaction ($F_{2,\ 16} = 0.6$; $n_p^2 = 0.07$; $p = 0.48$) for the resting MEPs. The active MEPs were also not influenced by the neuromodulation ($F_{2,\ 16} = 0.12$; $n_p^2 = 0.02$; $p = 0.89$) with any difference between sessions ($F_{1,\ 8} = 0.70$; $n_p^2 = 0.08$; $p = 0.43$) or any interaction ($F_{2,\ 16} = 1.28$; $n_p^2 = 0.14$; $p = 0.3$).

In the right M1, the RM-ANOVA revealed an effect of the neuromodulation ($F_{2,\ 16} = 3.77$; $n_p^2 = 0.32$; $p = 0.045$) without difference between sessions ($F_{1,\ 8} = 0.1$; $n_p^2 = 0.01$; $p = 0.76$) or interaction ($F_{2,\ 16} = 1.21$; $n_p^2 = 0.13$; $p = 0.32$) on the resting MEPs. *Post hoc* tests showed increased MEP values (see Figure 2) from Baseline to Post-Stim-20 (+38%; $p = 0.038$) and from Post-Stim to Post-Stim-20 (+44%; $p = 0.025$). Active MEPs were also influenced (see Figure 2) by the neuromodulation ($F_{2,\ 16} = 6.14$; $n_p^2 = 0.43$; $p = 0.01$) with no differences between sessions ($F_{1,\ 8} = 0.21$; $n_p^2 = 0.03$; $p = 0.66$) or interaction ($F_{2,\ 16} = 1.07$; $n_p^2 = 0.12$; $p = 0.37$). *Post hoc* tests revealed increased active MEPs values from Baseline to Post-Stim-20 (+30%; $p < 0.01$) and from Post-Stim to Post-Stim-20 (+20%; $p = 0.026$).

4 Discussion

In the present pilot study, we compared aHD-tDCS and LF-rTMS, two currently used neuromodulation techniques in the field, to enhance left M1 excitability. Against our hypothesis, we found that both aHD-tDCS of the left M1 and LF-rTMS of the right M1 did not significantly modulate left M1 excitability; rather we found a significantly increased right M1 (see Figure 2) excitability 20 min after the respective stimulation session. Thus, both aHD-tDCS and LF-rTMS sessions indiscriminately induced a facilitatory effect in the right M1 without modulating the left M1.

4.1 Effects of LF-rTMS

The overall increased right M1 excitability suggests that left M1 aHD-tDCS or right M1 LF-rTMS produced excitatory effects contrary to the expected inhibitory effects (Arai *et al.*, 2007; Maeda *et al.*, 2000). The reversal in the LF-rTMS effects is quite surprising but previous studies reported that 1 Hz LF-rTMS may not be inhibitory for everyone (see Figure 3) but excitatory in some subjects (Caparelli *et al.*, 2012). This finding goes along with evidence on lack of real effects and the variability of the responses to rTMS (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; Wassermann, 1998). For example, a review that analysed several rTMS studies reported that some of them displayed no effect following the rTMS protocol (Fitzgerald, Fountain, & Daskalakis, 2006). Apart from variability in MEP responses, insufficient stimulation pulses may have also been a reason for LF-rTMS effects. A study from Maeda *et al.* (2000) compared the MEP responses of subjects following 240 or 1600 pulses applied at frequencies of 1 Hz, 10 Hz, 15 Hz and 20 Hz rTMS at an intensity of 90% of RMT. They reported that 1 Hz rTMS at an intensity of 90% of RMT only significantly decreased MEP values in the stimulated M1 with 1600 pulses as compared to 240 pulses and added that interindividual variability was still high in the 1600 pulses condition with some subjects showing increased MEP amplitude. Therefore, an assumption is that our protocol consisting of 1200 pulses at 90% of RMT was likely still not sufficient to induce significant effects on MEP responses in all subjects.

The absence of decrease of CSP in the stimulated right M1 is providing another evidence that rTMS did not produce the expected inhibitory effects on the right M1. Interestingly, CSP was not modulated in the left M1, thus even though right M1 excitability was increased there was no effect on the opposite left M1 excitability and therefore no modulation of the interhemispheric interactions toward opposite left M1, contrary to previous studies (Gilio *et al.*, 2003; Schambra *et al.*, 2003). While it is in contradiction with the traditional interhemispheric balance model (Ferbert *et al.*, 1992) it is in line with more recent critical point view on this model (Di Pino *et al.*, 2014). Even with increased right M1 MEP changes, the absence of CSP modulation in the stimulated right M1 indicates the

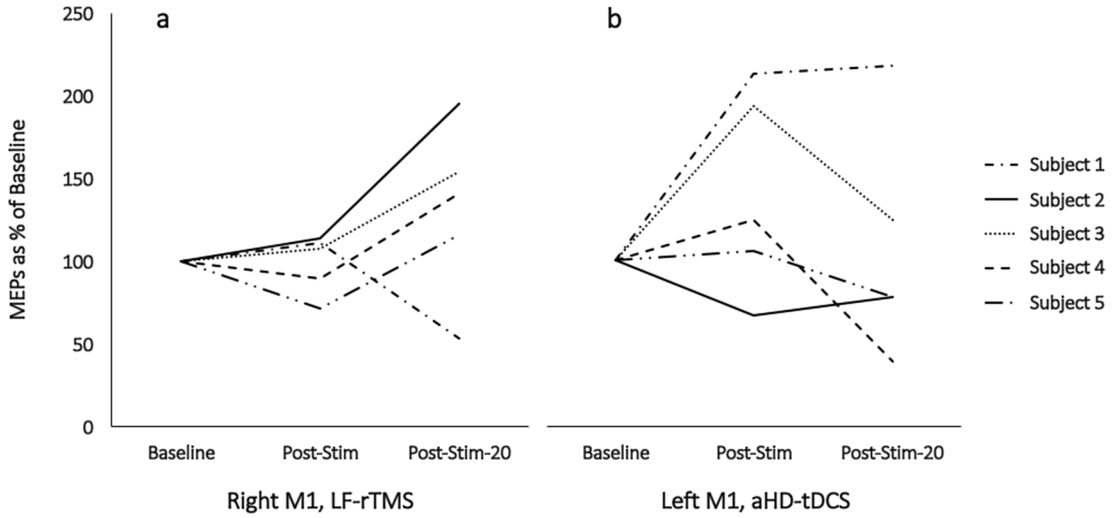

Figure 3. Individual excitability (Post-Stim and Post-Stim-20 resting MEPs expressed as percent of baseline resting MEPs) changes in the right M1 following right M1 low frequency-repeated TMS (LF-rTMS; a, left panel) and in the left M1 following left M1 anodal high-density-tDCS (aHD-tDCS; b, right panel).

overall poor effect of LF-rTMS for modulating the inhibitory processes and thus may explain the absence of interhemispheric interaction modulation on the left M1.

4.2 Effects of tDCS

The left M1 aHD-tDCS intervention produced a surprising increase in excitability in the opposite right M1. Pioneer tDCS study claimed the impossibility to modulate the cortical excitability of the opposite M1 *via* transcallosal pathways (Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004). However, the increase of current intensities and protocol durations may bring this possibility as recent research reported contralateral effects of tDCS (Davidson, Bolic, & Tremblay, 2016; Muthalib *et al.*, 2016a; Tazoe, Endoh, Kitamura, & Ogata, 2014; Teo *et al.*, 2015). These studies show the direct impact of tDCS of one M1 on the opposite M1 most likely *via* transcallosal pathways.

The absence of effects of the tDCS on the stimulated left M1 is questionable. A well-known issue in the tDCS research field is the variability of MEP responses. Many studies demonstrated that subjects are responders and some subjects are non-responders (Wiethoff, Hamada, & Rothwell, 2014) or even that subjects can switch from responders to non-responders between sessions (Lopez-Alonso, Fernandez-Del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015) and vice versa. We thus assume that this variability along with the small sample played a role in our pilot study.

4.3 Interhemispheric balance model

Overall, the results tend to be contrary to the well-known interhemispheric balance model often used to describe how brain hemispheres interact (Ferbert *et al.*, 1992; Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995; Nowak *et al.*, 2009). First, no modulation of excitability in the left M1 was observed and right M1 LF-rTMS increased right M1 excitability. Furthermore, no decreased left M1 excitability was observed anyway. Also, left M1 aHD-tDCS did not modulate the stimulated left M1 but increased active right M1 MEP amplitude. However, these first results are quite inconclusive along with the small sample size. As reported by recent papers focusing on stroke (Chhatbar *et al.*, 2016, 2017), modulating interhemispheric imbalance is possible. A hypothesis is that these studies performed in patients with interhemispheric excitability alterations allowed the neuromodulation to be more effective than in our healthy sample.

5 Conclusion

In this preliminary work, we have shown that neuromodulation techniques may not bring the expected effects. The low sample size may have been the primary reason to not being able to find the expected findings. However, the interesting finding of right M1 facilitatory effects with either right M1 LF-rTMS or left M1 aHD-tDCS provides some clue to changing preconceived ideas about models of how NIBS modulates local and interhemispheric pathways.

Authors' contributions

VC, JF and SP designed the study. VC conducted the study, data collection and data analysis. VC and SP prepared the manuscript draft with important intellectual input from JF and MM. All authors approved the final manuscript.

Glossary

a-tDCS	anodal transcranial direct-current stimulation
AMT	active motor threshold
CSP	cortical silent period
ECR	extensor carpi radialis (muscle)
EMG	electromyography
aHD-tDCS	high-definition transcranial direct-current stimulation
HF-rTMS	high frequency repeated transcranial magnetic stimulation
LF-rTMS	low-frequency repeated transcranial magnetic stimulation
M1	primary motor cortex
MEP	motor-evoked potential
M_{MAX}	maximal M-wave
NIBS	non-invasive brain stimulation
RMS	root mean square
RMT	resting motor threshold
rTMS	repeated transcranial magnetic stimulation
tDCS	transcranial direct-current stimulation
TMS	transcranial magnetic stimulation

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