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Effects of simultaneous bilateral tDCS of the human motor cortex

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Background
Transcranial direct current stimulation (tDCS) is a noninvasive technique that has been investigated as a therapeutic tool for different neurologic disorders. Neuronal excitability can be modified by application of DC in a polarity-specific manner: anodal tDCS increases excitability, while cathodal tDCS decreases excitability. Previous research has shown that simultaneous bilateral tDCS of the human motor cortex facilitates motor performance in the anodal stimulated hemisphere much more than when the same hemisphere is stimulated using unilateral anodal motor cortex tDCS.

Objective
The main purpose of this study was to determine whether simultaneous bilateral tDCS is able to increase cortical excitability in one hemisphere whereas decreasing cortical excitability in the contralateral hemisphere. To test our hypothesis, cortical excitability before and after bilateral motor cortex tDCS was evaluated. Moreover, the effects of bilateral tDCS were compared with those of unilateral motor cortex tDCS.

Methods
We evaluated cortical excitability in healthy volunteers before and after unilateral or bilateral tDCS using transcranial magnetic stimulation.

Results
We demonstrated that simultaneous application of anodal tDCS over the motor cortex and cathodal tDCS over the contralateral motor cortex induces an increase in cortical excitability on the anodal-stimulated side and a decrease in the cathodal stimulated side. We also used the electrode montage

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(motor cortex-contralateral orbit) method to compare the bilateral tDCS montage with unilateral tDCS montage. The simultaneous bilateral tDCS induced similar effects to the unilateral montage on the cathode-stimulated side. On the anodal tDCS side, the simultaneous bilateral tDCS seems to be a slightly less robust electrode arrangement compared with the placement of electrodes in the motor cortex-contralateral orbit montage. We also found that intersubject variability of the excitability changes that were induced by the anodal motor cortex tDCS using the bilateral montage was lower than that with the unilateral montage.

Conclusions
This is the first study in which cortical excitability before and after bilateral motor cortex tDCS was extensively evaluated, and the effects of bilateral tDCS were compared with unilateral motor cortex tDCS. Simultaneous bilateral tDCS seems to be a useful tool to obtain increases in cortical excitability of one hemisphere whereas causing decreases of cortical excitability in the contralateral hemisphere (e.g.,to treat stroke).

Keywords transcranial direct current stimulation; motor cortex; transcranial magnetic stimulation; rTMS; stroke

Neuronal excitability in the brain can be modified by application of direct current (DC). Surface-positive polarisation of the cerebral cortex of both rats and cats increases the mean firing rates of neurons recorded in deep cortical layers, whereas surface-negative polarization reduces the spontaneous firing.[1-4] If DC is continuously applied for 5 minutes or more, it can provoke sustained changes in neuronal firing rates that can last for many hours after the current is switched off.[1]

In humans, transcranial DC stimulation (tDCS) of the primary motor cortex (M1) modulates corticospinal excitability in a polarity-specific manner when assessed using transcranial magnetic stimulation (TMS). Motor-evoked potentials (MEPs) in contralateral hand muscles are facilitated by anodal tDCS and reduced by cathodal tDCS.[5-7]

As tDCS is portable, relatively inexpensive, and free from any major side effects, it is ideally suited for use in stroke recovery therapies.[8-10] Applying anodal tDCS to the stroke-impaired motor cortex results in improved motor functioning.[11,12] Anodal tDCS may stimulate preserved areas of the motor cortex to enhance synaptic efficiency along the corticospinal tract. In contrast, applying cathodal tDCS to the spared hemisphere may also have a beneficial effect in patients by diminishing maladaptive inhibitory projections onto the stroke-affected hemisphere.[9-12] In summary, the main goal of improving motor recovery in stroke is to increase cortical excitability on the affected side while reducing excitability on the unaffected side. Therefore, it is conceivable that the application of anodal tDCS over the affected hemisphere and cathodal tDCS over the nonaffected hemisphere can be used to boost motor recovery in stroke.

The hypothesis that anodal and cathodal tDCS of the motor cortex can be achieved simultaneously and produce an additive effect was tested in healthy subjects by Vines and colleagues[13] when they placed the anode over one hemisphere and the cathode over the contralateral one. These authors reported that dual-hemisphere tDCS stimulation of human motor cortex facilitated motor performance in the anode-stimulated hemisphere to a higher level than when the same hemisphere was stimulated using unilateral anodal tDCS. Furthermore, bilateral tDCS combined with unilateral motor training, achieved by contralateral hand restraint, has been reported to enhance the motor effects of constraint-induced movement therapy.[14]

The main purpose of this study was to examine if simultaneous bilateral tDCS is able to produce an increase in cortical excitability in one hemisphere while decreasing cortical excitability in the contralateral hemisphere.

We evaluated cortical excitability using bilateral simultaneous tDCS stimulation and a bilateral sham stimulation of the motor cortex. Our a priori hypothesis was that cortical excitability would increase in the hemisphere receiving anodal stimulation, whereas that in the contralateral hemisphere receiving cathodal stimulation would simultaneously decrease. Furthermore, bilateral sham stimulation would have no effect on cortical excitability. To test cortical excitability, we used TMS. Moreover, in a subgroup of the same subjects, we compared the effects of bilateral simultaneous tDCS of the motor cortex with the data obtained using unilateral anodal and cathodal tDCS of the motor cortex using the motor cortex-contralateral orbit montage.

Methods

Subjects

Fifteen healthy subjects were included in the study and participated in a total of 97 experimental sessions. The participants were screened for a history of hormonal, metabolic, circulatory, psychiatric, and neurologic disorders and were medication-free at the time of the study. The participants were seated comfortably in a semidarkened room, were instructed to refrain from speaking, and were

told to remain awake while in a calm, relaxed state. All participants gave their informed consent. The procedures had the approval of the hospital ethics committee and were conducted in accordance with the Declaration of Helsinki.

Experimental setup

We used a crossover design. The bilateral motor cortex tDCS and the unilateral motor cortex tDCS experiments will be described separately. The different tDCS experiments were conducted in a random order, and subjects underwent no more than one experiment per week.

We compared the resting motor threshold (RMT) and the motor responses evoked by a fixed TMS pulse, immediately before, immediately after, and 20 minutes after the end of tDCS. The experimental setup is described in Figure 1.

tDCS of the motor cortex

DC stimulation was delivered by a battery-powered electrical stimulator (Eldith DC-Stimulator, Germany) connected to a pair of thick (0.3 cm) saline-soaked synthetic surface sponge electrodes (surface area: 35 cm^2 each) placed on the scalp.

Sessions were separated by an interval of at least 1 week. The tDCS consisted of a 5-minute period of stimulation with a constant current. We chose this duration because when it is applied over the motor cortex it produces stable effects in most of the subjects for about 5 minutes.[15]

The experiments were conducted using a stimulation intensity of 2 mA. We used two different electrode montages: (1) bilateral motor cortex tDCS (Experiment 1) and (2) unilateral motor cortex tDCS (Experiment 2).

Bilateral motor cortex tDCS (Experiment 1, Figure 1A)

Fifteen healthy subjects were included (six males and nine females, mean age 30.9 ± 4.2; range 26-40) in experiment 1.

The electrodes were fixed bilaterally over the area representing the first dorsal interosseous muscle (FDI) as identified by TMS. We determined the optimal position for

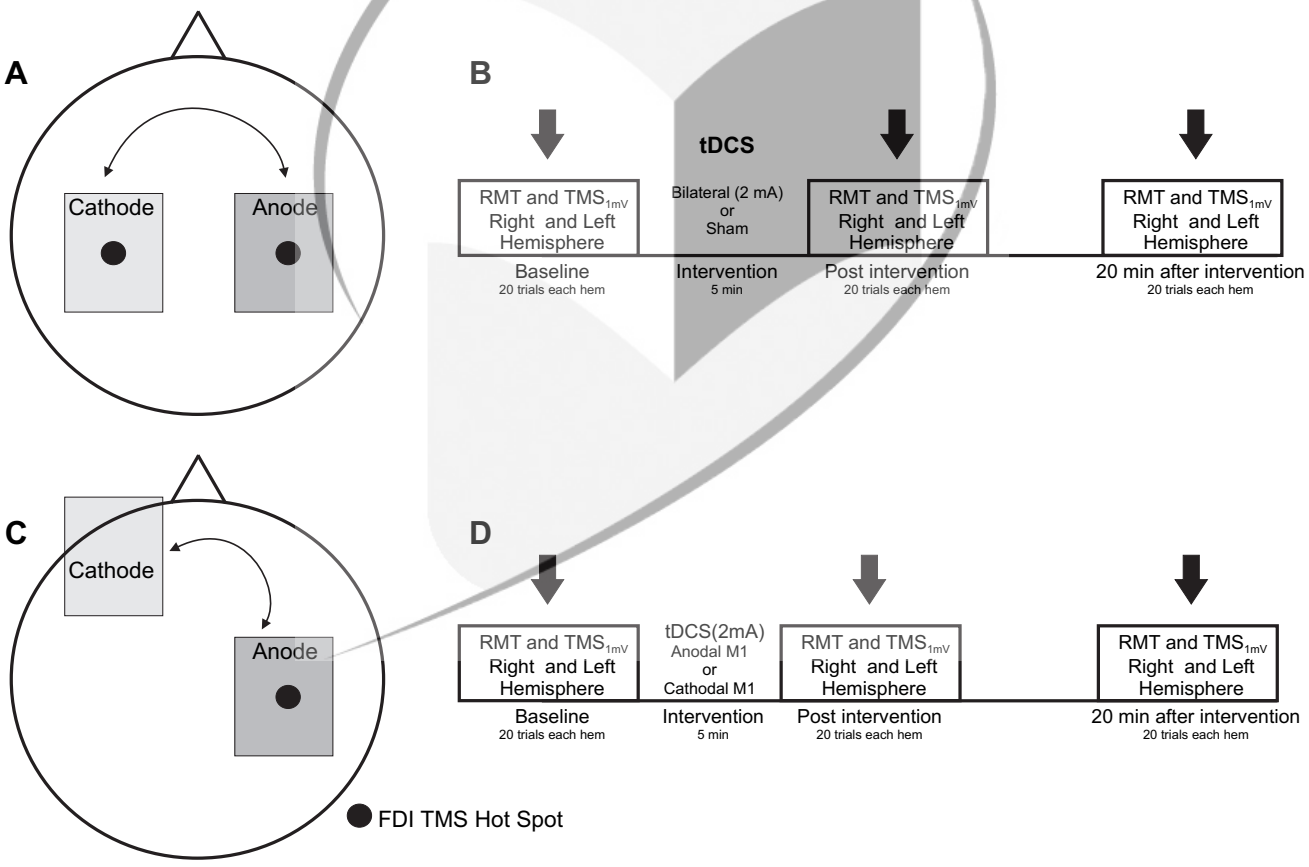

Figure 1 **A**, Bilateral motor cortex tDCS. The DC electrodes were positioned over the motor cortex bilaterally. The motor cortex was identified using TMS (FDI Hot spot). **B**, The experimental setup for real and sham stimulation with different intensities and polarities. **C**, Unilateral motor cortex tDCS. The DC electrodes were positioned over the motor cortex and the contralateral orbit. The motor cortex was defined using TMS (FDI Hot Spot). The montage of the unilateral tDCS of the left motor cortex is not shown. **D**, Experimental setup for anodal and cathodal stimulation.

activation of the first dorsal interosseous (FDI) by moving the coil in 0.5 cm steps around the presumed motor area of the hand in the left motor cortex. The site where stimuli of slightly suprathreshold intensity consistently produced the largest MEPs with the steepest negative slope in the target muscle was labelled on the skin as the "hot spot" with a marker.

We performed three different stimulation conditions (Figure 1B). In the first condition, the anode was placed over the right hemisphere and the cathode over the left hemisphere. In the second condition, the anode and cathode were reversed. Stimulation was applied for 5 minutes (8 second phase fade in/fade out for a total stimulation time of 316 seconds) with total current density of 0.057 mA/cm^2. The current intensity and duration were within the safety limits.[16] For the third condition, we used sham stimulation that involved the same electrode placement and duration as the real conditions; however, the constant current was delivered for only 30 seconds. Most subjects experienced a mild tingling sensation at the site of electrode contact that was independent of polarity and usually subsided after a period of a few seconds.

Unilateral motor cortex tDCS (Experiment 2, Figure 1C)

Thirteen healthy subjects were studied in all of the different conditions of experiment 2 (4 males and 8 females; 30.9 ± 4.2, range 26-40). These subjects were a subgroup of the subjects studied during experiment 1.

The electrodes were positioned over the motor cortex and contralateral orbit[5] using the hot spot identified with TMS as the centre of the cortical electrode. Four different conditions were used: (1) the anode was positioned above the motor cortical representation of the left FDI (right motor cortex anodal stimulation), whereas the cathode was placed above the contralateral orbit; (2) the anode was positioned above the motor cortical representation of the right FDI (left motor cortex anodal stimulation), whereas the cathode was placed above the contralateral orbit; (3) the cathode was positioned above the motor cortical representation of the left FDI (right motor cortex cathodal stimulation), whereas the anode was placed above the contralateral orbit; and (4) the cathode was positioned above the motor cortical representation of the right FDI (left motor cortex cathodal stimulation), whereas the anode was placed above the contralateral orbit (Figure 1D). Experiments were conducted using a stimulation intensity of 2 mA for a duration of 5 minutes.

Measurement of motor cortex excitability by TMS

MEPs were recorded from the FDI after determination of its motor-cortical representational field by single-pulse TMS (duration 300 μs). These pulses were induced using a Magstim 200 magnetic stimulator (Magstim Company, Whiteland, Dyfed, UK) and a figure-of-eight magnetic coil (diameter of one winding, 70 mm; peak magnetic field, 2.2 Tesla). The coil was held tangentially to the skull, with the handle pointing backward and laterally at 45° from midline. The optimum coil position was defined as the site where TMS consistently resulted in the largest MEP. Surface electromyography (EMG) was recorded from the FDI using adhesive electrodes in a belly-tendon montage. MEPs were amplified and filtered (bandwidth 3 Hz–3 kHz) using D360 amplifiers (Digitimer, Welwyn Garden City, Hertfordshire, UK). Data were sampled at 10 kHz, collected on a computer, and stored for later analysis using a CED 1401 A/D converter (Cambridge Electronic Design, Cambridge, UK).

The resting motor threshold (RMT) was defined as the minimum TMS intensity that elicited a peak-to-peak MEP-amplitude of 50 μV or more in resting muscle in at least 5 of 10 measurements. RMT calculation in the baseline condition lasted approximately 5 minutes for each hemisphere. This time was reduced to 2-3 minutes after the tDCS intervention as we focused on measurements using stimuli around threshold values. Twenty MEPs with an amplitude of ~1 mV were obtained before tDCS for each side. More specifically, two series of 10 MEPs were alternatively obtained from each side and then averaged. The interpulse interval was 4.5 seconds. The same TMS intensity stimulus used in this baseline condition was then used immediately after tDCS and 20 minutes after the end of the tDCS stimulation.

Statistical analyses

Experiment 1, bilateral motor cortex tDCS. A repeated measures analysis of variance (ANOVA) was used to analyse the MEP amplitudes. Three time points (factor TIME: baseline, immediately after tDCS, and 20 minutes after the end of the tDCS) for the anode-stimulated hemisphere, cathode-stimulated hemisphere, and sham (factor INTERVENTION) for the right- and left-stimulated hemispheres (factor INTERVENED side) were entered into a three-way ANOVA. To examine significant interactions, we performed the appropriate follow-up ANOVAs. Duncan's test was used for post hoc comparisons. RMT values were analyzed using a repeated measures ANOVA using the same statistical design as for MEP amplitudes.

Possible differences in baseline MEP amplitudes were also tested using an ANOVA.

Experiment 2, unilateral motor cortex tDCS. A repeated measures ANOVA was used to analyze the MEP amplitudes. Three time points (factor TIME: baseline, immediately after tDCS, and 20 minutes after the end on the tDCS) for the anode-stimulated hemisphere, cathode-stimulated hemisphere, and sham (factor INTERVENTION) for right- and left-stimulated hemispheres (factor INTERVENED side) and for ipsilateral and contralateral hemispheres from which the MEPs were obtained (EVALUATED side) were entered

into a four-way ANOVA. For example, measurements for the ipsilateral evaluated hemisphere means that the TMS pulses were given to the same hemisphere where the tDCS was delivered. In cases of significant interaction, we performed the appropriate follow-up ANOVAs. Duncan's test was used for post hoc comparisons.

RMT values were analyzed using repeated measures ANOVA using the same statistical design as for MEP amplitudes. Possible differences in baseline MEP amplitudes were also tested using an ANOVA.

To test whether the tDCS-induced changes were different using bilateral and unilateral motor cortex tDCS we performed a further analysis. A repeated measures ANOVA was used to analyze the MEP amplitudes. Three time points (factor TIME: baseline, immediately after tDCS, and 20 minutes after the end on the tDCS) for anodal-stimulated hemisphere and cathodal-stimulated hemisphere (factor STIMULATION) and for unilateral and bilateral stimulation (factor MONTAGE) were entered into a three-way ANOVA. For unilateral stimulation, we considered only the ipsilateral-evaluated hemisphere. Unlike in experiments 1 and 2, the right- and left-stimulated hemispheres were not separated into an additional factor, so this analysis is technically a three-way repeated measures MANOVA. In cases showing a significant interaction, we performed the appropriate follow-up MANOVAs. Duncan's test was used for post-hoc comparisons. Possible differences in baseline MEP amplitudes were also tested using an ANOVA.

Because sphericity and compound symmetry assumptions were not verified in our data, all repeated measures ANOVAs described previously were performed with the multivariate approach. The multivariate method does not require sphericity or compound symmetry and was therefore preferred to the more traditional corrections of the univariate approach (e.g., Greenhouse-Geisser or Huynh-Feldt).

To investigate whether the intersubject variability of the percent changes induced by bilateral tDCS was different than the intersubject variability of the percent changes induced by unilateral tDCS, we used the Bartlett multiple-sample test for equal variances. This test was performed separately for anodal stimulation and cathodal stimulation to establish whether there was an overall significant difference in the variances across the four conditions: right- and left-stimulated hemispheres and bilateral and unilateral montage. In cases of an overall significant difference, we performed two-sample F-tests for equal variances to compare the intersubject variability between bilateral and unilateral tDCS separately in the right- and left-stimulated hemispheres. Specifically, with the F-test, we evaluated the null hypothesis that the percent changes induced by bilateral tDCS and unilateral tDCS come from normal distributions with the same variance, with the alternative hypothesis that differences in percent changes come from normal distributions with different variances.

The results were considered significant at $P < 0.05$. All data are expressed as the mean ± standard deviation.

Results

Experiment 1: Bilateral motor cortex tDCS

RMT did not change after 2 mA tDCS or Sham stimulation in both hemispheres (Table). Baseline MEP amplitudes were similar in all experiments ($F = 1.13$, $P = 0.353$).

A three-way repeated measures ANOVA was used to analyse the MEP amplitudes when tDCS with a 2 mA intensity or sham stimulation was applied (15 subjects evaluated), examining the factors TIME (three levels), INTERVENTION (three levels), and INTERVENED side (two levels). A significant interaction was found between TIME and INTERVENTION ($F_{4,11} = 45.98, P = 0.000001$),

Table Effects of tDCS protocols on RMT

Protocol	Baseline	Post tDCS (or Sham)	20 min Post tDCS (or Sham)	Statistics
		BILATERAL tDCS (n=15)		
An RH-Cat LH	RH (37.0 ± 2.2)	RH (36.9 ± 3.1)	RH (36.9 ± 3.1)	ns
Real, 2 mA	LH (38.1 ± 3.5)	LH (37.2 ± 3.3)	LH (37.8 ± 3.6)	
Cat RH-An LH	RH (38.3 ± 2.8)	RH (38.3 ± 3.3)	RH (38.0 ± 3.2)	ns
Real, 2 mA	LH (39.0 ± 2.9)	LH (38.4 ± 3.4)	LH (38.9 ± 4.1)	
SHAM	RH (39.3 ± 6.3)	RH (38.9 ± 5.4)	RH (38.8 ± 5.9)	ns
	LH (39.4 ± 6.7)	LH (39.3 ± 5.6)	LH (39.9 ± 6.4)	
		UNILATERAL tDCS (n=13)		
An RH	RH (37.4 ± 2.8)	RH (36.5 ± 2.9)	RH (37.5 ± 3.7)	ns
Real, 2 mA	LH (38.2 ± 3.6)	LH (38.8 ± 4.0)	LH (40.2 ± 5.1)	
An LH	RH (36.6 ± 3.9)	RH (37.0 ± 3.7)	RH (37.0 ± 3.8)	ns
Real, 2 mA	LH (36.6 ± 3.0)	LH (36.6 ± 3.3)	LH (36.6 ± 3.0)	
Cat RH	RH (38.2 ± 2.9)	RH (38.8 ± 3.6)	RH (37.8 ± 3.3)	ns
Real, 2 mA	LH (39.5 ± 4.3)	LH (38.8 ± 3.9)	LH (38.4 ± 4.4)	
Cat LH	RH (39.2 ± 3.2)	RH (39.5 ± 2.8)	RH (39.4 ± 3.4)	ns
Real, 2 mA	LH (39.1 ± 3.3)	LH (39.0 ± 3.9)	LH (39.3 ± 3.5)	

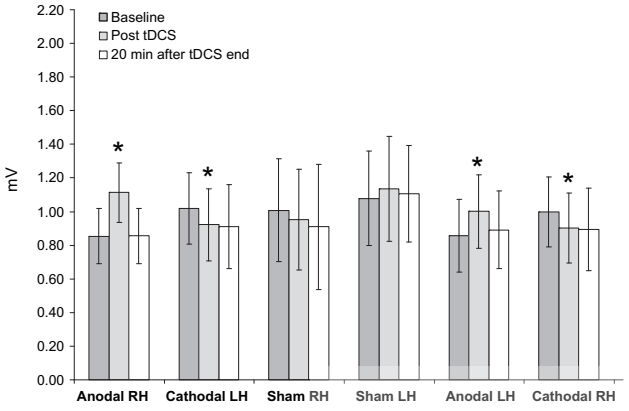

Figure 2 Effects of bilateral motor cortex tDCS on the amplitude of MEPs. After 2 mA tDCS, the mean MEP amplitude showed a significant increase on the anodal-stimulated side and a significant decrease in the cathode-stimulated one. Similar effects were observed for both montages (Anode right M1-Cathode left M1/Anode left M1-Cathode right M1). These effects lasted less than 20 minutes. Sham stimulation had no effect on the MEP amplitude. Error bars are standard deviations. $*P < 0.05$.

indicating an effect on MEP amplitudes over TIME depending on the INTERVENTION. Then we separately analyzed the anodal, cathodal, and sham intervention (follow-up ANOVAs). With the anodal tDCS, there was a significant effect for TIME ($F_{2,13} = 26.86$, $P = 0.00002$), but there was no interaction between TIME and INTERVENED side ($F_{2,13} = 1.63$, $P = 0.2332$). This finding indicates that the anodal tDCS had an effect on MEP amplitudes and that the effect was the same when anodal tDCS was applied over the left or right hemisphere. Post hoc analyses showed that the anodal tDCS produced an increase of MEP amplitude immediately after the stimulation ($P = 0.0006$), but the MEP amplitude had returned to the baseline values 20 minutes later ($P = 0.6157$). Examining the results of the cathodal tDCS indicated that there was a significant effect for TIME ($F_{2,13} = 8.69$, $P = 0.0040$) but no interaction between TIME and INTERVENED side ($F_{2,13} = 1.06$, $P = 0.3744$). This indicates that the cathodal tDCS had an effect on MEP amplitudes and that the effect was the same when cathodal tDCS was applied over the left or right hemisphere. Post hoc analyses showed that cathodal tDCS produced a decrease of MEP amplitude immediately after current application ($P < 0.0491$), and the MEP amplitude returned to near baseline values 20 minutes later ($P = 0.0694$). In the sham stimulation experiments, there were no significant effects on MEP amplitude ($P > 0.26$) (Figure 2).

Experiment 2: Unilateral motor cortex tDCS

RMT did not change after unilateral tDCS in either hemisphere with any of the four different montages used (Table). Baseline MEP amplitudes were similar in all the experiments ($F = 0.47$, $P = 0.854$).

A four-way repeated measures ANOVA was used to analyze the MEP amplitudes when unilateral motor cortex tDCS with a 2 mA intensity was applied (13 subjects evaluated), examining the factors TIME (three levels), INTERVENTION (two levels), INTERVENED side (two levels), and EVALUATED side (two levels). A significant interaction was found between TIME, INTERVENTION, and EVALUATED side ($F_{2,11} = 25.11$, $P = 0.000079$) and for TIME and EVALUATED side ($F_{2,11} = 4.45$, $P = 0.038$). The results indicate an effect on MEP amplitudes over TIME depending on the INTERVENTION and on the EVALUATED side (whether the hemisphere from which the MEPs were obtained were ipsilateral or contralateral to the tDCS). We used follow-up ANOVAs to separately analyze the ipsilateral and contralateral tDCS effects on MEP amplitude. There were no significant effects of contralateral tDCS on MEP amplitude ($P > 0.25$). There was a clear trend for anodal tDCS to produce a decrease in the MEP amplitude obtained from the contralateral hemisphere. There was also a trend for cathodal tDCS to produce an increase in the MEP amplitude obtained from contralateral hemisphere. However, neither reached the level of a significant difference. Examining the effects of ipsilateral tDCS on MEP amplitude indicated a significant effect for TIME ($F_{2,11} = 4.87$, $P = 0.0304$) and a significant interaction between TIME and INTERVENTION ($F_{2,11} = 17.10$, $P = 0.00042$). Subsequently, we separately analyzed the anodal and cathodal tDCS effects on MEP amplitude when they were applied and evaluated over the same hemisphere using follow-up ANOVAs. Using anodal tDCS, there was a significant effect for TIME ($F_{2,11} = 13.93$, $P = 0.0010$), but no interaction between TIME and INTERVENED side ($F_{2,11} = 0.96$, $P = 0.4105$). This result indicates that the anodal tDCS had an effect on MEP amplitudes and that the effect was the same when anodal tDCS was applied over either the left or right hemisphere. Post hoc analyses showed that the anodal tDCS produced an increase in MEP amplitudes immediately after the stimulation ($P = 0.0001$), and the amplitudes had returned to baseline values 20 minutes later ($P = 0.2878$). With cathodal tDCS, there was a significant effect for TIME ($F_{2,11} = 6.83$, $P = 0.0118$) but no interaction between TIME and INTERVENED side ($F_{2,11} = 0.96$, $P = 0.4105$). These results indicate that the cathodal tDCS had an effect on MEP amplitudes and that the effect was the same when cathodal tDCS was applied over either the left or right hemisphere. Post hoc analyses showed that the cathodal tDCS produced a decrease of MEP amplitude immediately after current application ($P = 0.0174$) and that the amplitudes had returned to the baseline values 20 minutes later ($P = 0.5350$) (Figure 3).

Comparison of bilateral and unilateral tDCS of the motor cortex

Baseline MEP amplitudes were similar in all experiments ($F = 0.875$, $P = 0.530$).

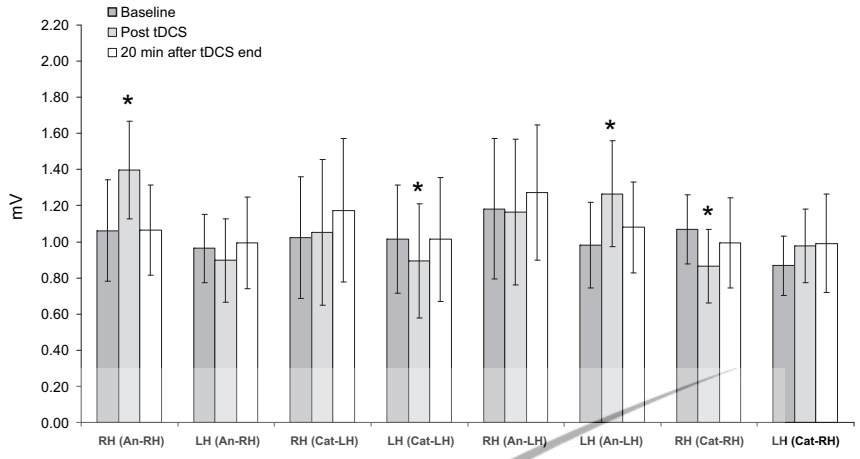

Figure 3 Effects of unilateral motor cortex tDCS. After 2 mA anodal tDCS of the right or left hemisphere (ipsilateral to the TMS), the mean MEP amplitude was significantly increased with respect to the baseline. MEP amplitude obtained by TMS stimulation of the contralateral hemispheres showed a trend of nonsignificant decreases in MEP amplitude. After 2 mA cathodal tDCS of the left or right hemisphere (ipsilateral to the stimulation), the mean MEP amplitude was significantly decreased relative to baseline. The MEP amplitude obtained by TMS stimulation of the contralateral hemispheres showed a trend of nonsignificant increases in MEP amplitude. These effects lasted for less than 20 minutes. The polarity of tDCS and the stimulated hemisphere are reported in parentheses. Error bars are standard deviations. $*P < 0.05$.

A three-way repeated measures MANOVA was used to analyze the MEP amplitudes when unilateral or bilateral motor cortex tDCS with a 2 mA intensity was applied (13 subjects evaluated), examining the factors TIME (three levels), INTERVENTION (two levels), and MONTAGE (two levels, unilateral or bilateral motor cortex tDCS). Because the previous experiments showed that there were no differences regarding the INTERVENED side, the results of the right- and left-stimulated hemispheres were combined in this MANOVA. There was a significant interaction between TIME and INTERVENTION ($F_{2,11} = 19.09$, $P = 0.0002$), confirming the previous analyses (Experiences 1 and 2). There was no significant interaction between TIME and MONTAGE, or between TIME, INTERVENTION, and MONTAGE ($P > 0.46$). There was a trend for anodal tDCS to produce a greater increase in the MEP amplitude obtained with the unilateral montage, but we demonstrated that unilateral and bilateral montages are similarly effective in modulating cortical excitability. Nevertheless, the intersubject variability of the induced changes was significantly higher for unilateral anodal motor cortex tDCS than for bilateral motor cortex tDCS when the anodal tDCS (anodal side in case of bilateral montage) was considered (Bartlett's test: $P = 0.0139$; right hemisphere F test: $P = 0.0138$; left hemisphere F test: $P = 0.0348$). There were no differences observed in intersubject variability (Bartlett's test: $P = 0.64$) of the induced changes between unilateral and bilateral montage when the cathodal effects were analyzed (Figure 4).

Discussion

The results of the current study confirm our a priori hypothesis that when using the simultaneous bilateral tDCS it is possible to obtain simultaneous modulation of cortical excitability in different directions in the two motor cortices, such that cortical excitability increases in one hemisphere while it decreases in the contralateral hemisphere. The application of a weak anodal electrical current to one hemisphere while a cathodal electrical current was simultaneously applied to the contralateral hemisphere enhanced excitability in the hemisphere stimulated with anodal tDCS and decreased excitability on the cathode-stimulated side. Excitability of both motor cortices (right

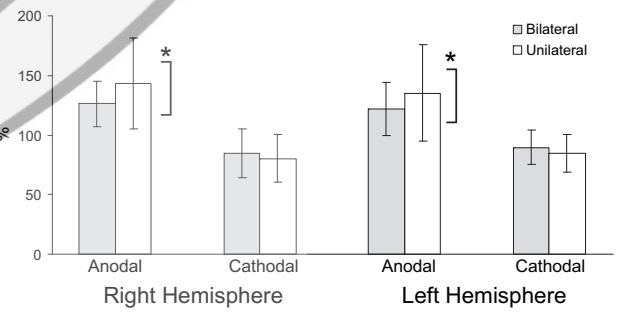

Figure 4 Effects of unilateral and bilateral motor cortex tDCS. Immediately after tDCS, the percentage of change in MEP amplitude with respect to the baseline was slightly higher when applying the unilateral anodal tDCS than when using bilateral tDCS over the anodal site. A similar decrease was found when using the unilateral cathodal tDCS or the bilateral tDCS over the cathodal site. Error bars are standard deviations. Intersubject variability of the percentage of change was similar between the unilateral and bilateral montage for cathodal tDCS. However, the intersubject variability of the percentage of change was higher in the unilateral compared with bilateral montage for anodal tDCS ($*P < 0.05$).

and left) was similarly modulated by bilateral tDCS. Moreover, these effects lasted for some minutes after the end of stimulation. This is in agreement with the tDCS data reported previously with different electrode locations–anodal stimulation of the motor cortex enhanced excitability, whereas it was decreased with cathodal stimulation.

As previously reported, the electrode position is critical for achieving cortical excitability changes of the motor cortex. The motor cortex-contralateral orbit placement is the most widely used arrangement.[5] Using this unilateral montage, the changes in MEP amplitude and the length of time the changes remain beyond the end of stimulation are current-intensity and stimulation-duration dependent.[5]

When evaluating the anodal tDCS side by grouping all subjects, on average the simultaneous bilateral tDCS tested in this study is a less robust electrode arrangement than the motor cortex-contralateral orbit montage. Using the simultaneous bilateral tDCS, we could obtain a mean excitability change of no more than 20% of the baseline MEP amplitude, which was less than the facilitation obtained with the unilateral montage (about 30%). Our data revealed facilitation, which is similar to previous studies.[15,17] Another interesting observation is that intersubject variability over the anodal side was significantly less when the bilateral montage was used. The different variabilities and, possibly, the different strengths of the effects of bilateral and unilateral anodal motor cortex tDCS may have at least two possible physiologic explanations. First, the current direction is different when the cathode is anterior (contralateral orbit) compared with when it is lateral (opposite motor cortex). Alternatively, the concomitant effects of the cathodal stimulation of the contralateral hemisphere, which is present with the bilateral but not with the unilateral montage, may promote the consistency of the increased excitability of the motor cortex stimulated by the anode.

On the cathode-stimulated side, the simultaneous bilateral tDCS tested here has similar effects when compared with the unilateral montage. We could obtain a mean excitability change of about 20% of the baseline MEP amplitude using both montages. In healthy subjects, it has been reported that dual-hemisphere tDCS stimulation of human motor cortex facilitated motor performance in the hemisphere stimulated with the anode much more than when the same hemisphere was stimulated using unilateral anodal tDCS.[13] It has been widely reported that there is not a linear relationship between neurophysiologic and behavioral changes. For example, antiepileptic drugs deeply modify the motor cortex excitability but the motor performances are only subtly affected. In any case, we might suggest that the differences between tDCS montages on motor behavior may be due to the reduced inter-subject variability for the anodal tDCS with the bilateral montage and/or to the concomitant effects of the cathodal stimulation of the contralateral hemisphere.

Repetitive TMS, tDCS, and other cerebral modulatory therapies have been proposed for use in stroke recovery therapies.[9,10,18] Different approaches have been proposed to facilitate recovery, with the main goal being to enhance excitability of the affected motor cortex and to reduce excitability of the spared one. Vines et al.[13] reported that when using bilateral simultaneous tDCS in healthy subjects, motor performance is facilitated in the anodal stimulated hemisphere much more than when the same hemisphere is stimulated using unilateral anodal motor cortex tDCS. In addition, Williams et al.[14] reported that this kind of stimulation enhances the effects of unilateral motor training and contralateral hand restraint on motor function. The possibility of achieving the two effects at the same time is intriguing. We confirmed that the simultaneous bilateral motor cortex tDCS could be a promising tool when the main goal is to obtain increases in cortical excitability in one hemisphere with simultaneous decreases in the cortical excitability in the contralateral hemisphere (e.g., stroke). Moreover, it appears that the bilateral electrode montage has the advantage of lower intersubject variability. However, further research has to be done to demonstrate that simultaneous bilateral motor cortex tDCS is effective enough to have a clinical impact. It will also be necessary to demonstrate that it is possible to prolong the changes in cortical excitability, probably by using longer stimulation sessions or by increasing the number of sessions.

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