Asymmetrical control of reciprocal inhibition at wrist level

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ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE MOTOR CORTEX INDUCES OPPOSITE MODULATION OF RECIPROCAL INHIBITION IN WRIST EXTENSOR AND FLEXOR

Asymmetrical control of reciprocal inhibition at wrist level

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Abbreviations: transcranial direct current stimulation (tDCS), extensor carpi radialis (ECR), flexor carpi radialis (FCR)
Abstract

Transcranial direct current stimulation (tDCS) is used as a non-invasive tool to modulate brain excitability in humans. Recently, several studies have demonstrated that tDCS applied over the motor cortex also modulates spinal neural network excitability and therefore, can be used to explore the corticospinal control acting on spinal neurones. Previously, we showed that reciprocal inhibition directed to wrist flexor motoneurones is enhanced during contralateral anodal tDCS, but it is likely that corticospinal control acting on spinal networks controlling wrist flexors and extensors is not similar. The primary aim of the study was to explore the effects of anodal tDCS on reciprocal inhibition directed to wrist extensor motoneurones. To further examine the supraspinal control acting on the reciprocal inhibition between wrist flexors and extensors, we also explored the effects of the tDCS applied to the ipsilateral hand motor area. In healthy volunteers, we tested the effects induced by sham and anodal tDCS on reciprocal inhibition pathways innervating wrist muscles. Reciprocal inhibition directed from flexor to extensor muscles and the reverse situation, i.e. reciprocal inhibition, directed from extensors to flexors were studied in parallel using the H reflex technique.

Our main finding was that contralateral anodal tDCS induces opposing effects on reciprocal inhibition: it decreases reciprocal inhibition directed from flexors to extensors but it increases reciprocal inhibition directed from extensors to flexors. The functional result of these opposite effects on reciprocal inhibition seems to favour wrist extension excitability suggesting an asymmetrical descending control onto the interneurones that mediate reciprocal inhibition.

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The control of neural transmission in pathways mediating reciprocal inhibition in antagonist muscles continues to raise questions ever since Sherrington (1906), who first introduced the concept of reciprocal innervation. Intracellular recordings in cat spinal cord reveal a striking similarity in the descending and segmental convergence on agonist α-motoneurones and Ia inhibitory interneurones of the antagonist α-motoneurones (Lundberg 1970, Hultborn 1976). Lundberg (1970) proposed that these connections from the brain to corresponding α-motoneurones and Ia interneurones were also used in parallel during voluntary movement in order to achieve a coordinated contraction and relaxation of the antagonist muscles. Consistent with animal data, it has been shown in humans that pathways mediating reciprocal inhibition in flexor and extensor motoneurones are disynaptic, and that motoneurones and inhibitory interneurones have received similar segmental and descending control (Day et al. 1984, Cavallari et al. 1984, Shindo et al. 1984, Rothwell et al. 1984, Cowan et al. 1986). At the level of the elbow and ankle, extensor and flexor muscles operate as real antagonists, so interneurones relaying reciprocal inhibition to flexor and to extensor motoneurones are identified as Ia inhibitory interneurones. At the wrist level, extensor carpi radialis (ECR) and flexor carpi radialis (FCR) not only operate as antagonists but also as agonists in wrist abduction so interneurons mediating reciprocal inhibition to α-motoneurons innervating extensor and flexor muscles differ from those mediating Ia inhibition at the ankle and elbow levels. The interneurones mediating reciprocal inhibition between FCR and ECR are not inhibited by Renshaw cells (Aymard et al. 1995) but receive input from both Ia and Ib afferent fibres (Wargon et al. 2006). It has been hypothesised that interneurones mediating reciprocal inhibition between wrist flexors and extensors, probably share more characteristics with Ib than Ia inhibitory interneurones. Regarding their descending control, Ib inhibitory
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interneurones receive a powerful controlling input from the reticulospinal tract, and thus, are
influenced by both contra- and ipsi-lateral descending control (Crosby et al. 1962). Moreover,
Illert et al. (1981) have shown that forelimb muscle motoneurones receive a concomitant
descending control from both cortices. In humans, the role of the ipsilateral motor cortex is
still under debate although recent studies (Bradnam et al. 2011, McCambridge et al. 2011)
suggest that ipsilateral tDCS influences arm motor control. In humans, reciprocal inhibition
directed from ECR to FCR and its descending control from the contralateral hand motor
cortex have been studied following changes in excitability of contralateral hand motor cortex
induced by Transcranial Magnetic Stimulation (TMS) (Rothwell et al. 1984; Cowan et al.
1986) and by Transcranial Direct Current Stimulation (tDCS) (Roche et al. 2009). To our
knowledge, the control of transmission of the reciprocal inhibition from FCR to ECR has not
yet been described in humans. This is mainly due to the difficulty of evoking an H reflex in
extensor muscles in humans. Previous results suggest that corticospinal control is
asymmetrical between flexor and extensor ankle motoneurones in humans (Crone et al. 1987).
Although the presence of an ECR H reflex is rarely seen, we were able to recruit a sample of
healthy subjects exhibiting an H reflex in ECR at rest with sizeable amplitude allowing the
study of reciprocal inhibition directed to ECR motoneurones. The aims of this study were
therefore primarily to explore the effects of contralateral anodal tDCS on the reciprocal
inhibition directed from FCR to ECR, in order to compare corticospinal control acting on
interneurones mediating reciprocal inhibition from flexors to extensors and vice versa and
secondly to explore the possible effects of anodal tDCS applied over the ipsilateral motor
cortex on pathways that mediate reciprocal inhibition in flexor and extensor wrist muscles.

Materials and Methods

Subjects
Thirty-two healthy subjects ranging from 22 to 60 years (mean 31.1 ± 9.9 years), 20 females and 12 males (9 left-handed and 23 right-handed), were included in this study. However not all the subjects participated in every experiment. Among them only 9 subjects had an H reflex in ECR stable enough at rest to explore reciprocal inhibition directed from ECR to FCR. All subjects gave written informed consent before participating in the experiments. This study was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki), and was approved by the local ethical committee (CPP Ile de France 6-Pitié-Salpêtrière).

**Transcranial direct current stimulation of the motor cortex**

tDCS was applied using a NEUROCONN DC-STIMULATOR (NEUROCONNGMBH COMPANY, Ilmenau, Germany) via two conductive rubber electrodes placed in saline-soaked sponges (5x7 cm). Transcranial magnetic stimulation (TMS) elicited by MAGSTIM 200 (MAGSTIM DYFED, UK), was used to determine the position of the anode positioned over the hand motor cortex. The cathode was placed over the supra-orbital region. Three conditions of tDCS were tested: i) the active contralateral condition: with the anode placed over the contralateral hand motor cortex and cathode positioned over the ipsilateral supra-orbital area; ii) the active ipsilateral condition; anode over the ipsilateral hand motor cortex and cathode over the contralateral supra-orbital area; iii) the sham condition: the electrodes were placed in the same position as in active conditions but, current was activated for only 120 seconds at the beginning and 30 seconds at the end of sham stimulation in order to mimic the sensations of ramp up and ramp down current perceived in the active conditions. In the experiments involving with the ECR H reflex, due to the difficulty of evoking a test H reflex in ECR, the sham condition was performed in only one configuration with anodal tDCS electrode placed over the contralateral motor cortex. We were careful to respect a minimum
delay of 48 hours between the different tDCS conditions and on average the delay between two recording sessions was about one week. Moreover, in the present study, active and sham contralateral tDCS was tested only on reciprocal inhibition directed from FCR to ECR. Effects induced by contralateral tDCS on reciprocal inhibition directed from ECR to FCR were obtained from our previous study (Roche et al. 2009).

In all conditions, current intensity was fixed at 1.75 mA. Current flowed continuously for 20 minutes for both active conditions, and for 150 seconds in the sham condition, since Nitsche and Paulus (2000) had previously reported that a duration of at least 3 minutes of tDCS was necessary to induce after-effects. The current was ramped up or down over the first and last 8 seconds of stimulation. The experimental procedure was identical to that used by Roche et al. (2009).

**Measurement of spinal network excitability**

**Electromyogram recordings**

Subjects were seated in a comfortable reclining armchair with the shoulder slightly abducted at about 60 degrees, the elbow semi-flexed and with slight pronation of the forearm. The distal part of the upper limb was supported by an armrest in order to exclude any active maintenance of wrist posture, and the subjects were asked to relax the arm. Electromyographic (EMG) activity was recorded from FCR and ECR muscles using bipolar surface electrodes positioned on the muscle belly. EMG activity was displayed in a wide analysis window beginning 100 ms before, ending 200 ms after the test stimulus. To ensure that subjects relaxed their wrist muscles, background EMG activity was measured a posteriori, in the 100 ms pre-trigger windows with rectified EMG activity. EMG activity was sampled at 2 kHz, amplified (x 5000 – 10000) and band-pass filtered (250 Hz–3 kHz) using a
Digitimer D360 amplifier (DIGITIMER LTD, WELWYN GARDEN CITY, Herts, UK. In all
subjects, experiments were performed on the dominant upper limb based on patient self-reports.

**Electrical stimuli**

Transcutaneous electrical stimulation (rectangular pulses of 1 ms duration every 3 s) were
applied to radial and median nerves, via 3 cm diameter hemi-spherical bipolar electrodes. The
electrodes were placed near the cubital fossa to stimulate the median nerve and at the spiral
groove to stimulate the radial nerve.

**Test stimuli**

**FCR H reflex**

The FCR H reflex was evoked by electrical stimuli applied to the median nerve. First, the
maximum direct motor response (Mmax) was first determined and the unconditioned H reflex
was adjusted to 10% – 20% of Mmax in each subject (mean value 14.17 ± 2.5% Mmax). The
amplitude of the unconditioned FCR H reflex corresponded to 50% of the maximum
amplitude of H reflex in the majority of cases. It was kept constant throughout the experiment,
since the H reflex sensitivity to facilitation or inhibition can vary with its unconditioned
amplitude (Crone et al. 1990).

**ECR H reflex**

The ECR H reflex was evoked by radial nerve stimulation. As mentioned previously, it is
difficult to elicit the H reflex in ECR (Pierrot-Deseilligny and Burke 2012). Thirty-two
subjects participated in this study, but only 9 subjects had an ECR H reflex large enough at
rest to show changes in reciprocal inhibition. As above, the Mmax response was determined
first and the unconditioned ECR H reflex was adjusted to 5%-15 % of Mmax in each subject
and was kept constant throughout the experiment (mean value 6.62 ± 1.4% Mmax).
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Conditioning stimuli

Conditioning stimuli were applied to the nerve innervating the antagonist muscle, i.e. that counteracting the muscle in which the test H reflex was evoked. The intensity of the conditioning stimuli was adjusted to activate group I fibres but was below the activation threshold of Renshaw cells in order to prevent recurrent inhibition (Aymard et al. 1997). This implies that the conditioning stimuli did not evoke either a direct motor response (which may have an influence by antidromic activation of Renshaw cells) or an H reflex (which may have influence by orthodromic activation of Renshaw cells). The motor threshold was determined by the oscilloscope display of EMG. The average intensity of conditioning stimuli was 0.88 ± 0.02 motor threshold (MT) for the radial nerve, and was 0.66 ± 0.02 MT for the median nerve (Table 1). The interstimulus interval (ISI) was the time interval between test and conditioning stimuli for which the level of reciprocal inhibition was maximal. By convention, a positive ISI corresponds to a conditioning stimulus preceding the test stimulus. The ISI was determined using 0.5 ms steps in the range –3 ms/+ 1 ms for reciprocal inhibition from ECR to FCR (Day et al. 1984) and -1 ms/+ 3 ms for reciprocal inhibition from FCR to ECR (Wargon et al. 2006). The mean ISI for reciprocal inhibition from ECR to FCR was 0.12 ± 0.6 ms and for reciprocal inhibition from FCR to ECR was 0.60 ± 0.8 ms. The ISI was kept constant throughout the experiments.

Experimental procedure

A randomised, sham-controlled tDCS study was performed. During the experiments, the subjects were blind to the conditions of tDCS. The active contralateral condition, the active ipsilateral condition, and the sham condition were randomly alternated. Each condition was performed on the subjects on different days to avoid carry-over effects.
Once all parameters (unconditioned H reflex amplitude, conditioning stimulation intensity and ISI) were set, the baseline inhibition (without tDCS) was determined over the first 10 minutes, being defined as the baseline period. Next, the tDCS electrodes were attached. The anode was placed over the hand motor cortex for 20 minutes for both active (ipsilateral and contralateral conditions) and sham tDCS. These 20 minutes were divided into two “10 minute” periods: period 1 and period 2. The tDCS electrodes were removed immediately after the end of the stimulation. The amount of reciprocal inhibition was also measured for 10 minutes following the end of stimulation in order to evaluate post–effects (see diagram on Fig. 1). In each period (baseline, period 1 tDCS, period 2 tDCS and post tDCS), the amount of inhibition was assessed with three series of 40 H reflexes (20 conditioned H reflexes and 20 unconditioned H reflexes). Conditioned and unconditioned H reflexes were evoked every 3 s and randomly alternated.

**Analysis**

**Parameter definitions**

The background EMG activity was evaluated by calculating the pre-trigger root mean square (rms) of rectified EMG activity in the 100 ms window preceding the test stimulation. The average H reflex size was determined from peak-to-peak amplitudes expressed as a percentage of the maximum motor response (Mmax). The amount of reciprocal inhibition was defined as \(((\text{unconditioned H value} - \text{conditioned H value})/\text{unconditioned H value}) \times 100\). The mean amount of reciprocal inhibition from each period was normalised as a percentage of the baseline inhibition measured over the baseline period (t₀) according to the equation: \(((\text{inhibition}_{t} - \text{inhibition}_{t₀})/\text{inhibition}_{t₀}) \times 100\). Therefore when amount of reciprocal inhibition was normalised to the baseline, a positive value means that inhibition was larger than the baseline and a negative value means the inhibition was weaker than the baseline.
The normalised amounts of reciprocal inhibition were only used in the graphics representing group data. Statistical analyses were performed on raw data, i.e. with amount of reciprocal inhibition expressed as a percentage of unconditioned H value.

Statistical analysis

For individual data, a two-way ANOVA was performed with time period as the first factor (baseline, period 1 tDCS, period 2 tDCS, and post tDCS) and tDCS condition (sham, active contralateral tDCS and active ipsilateral tDCS) as the second factor. When reciprocal inhibition from FCR to ECR was investigated as subjects were examined in all 3 conditions we first compared data from active controlateral tDCS to those obtained from sham tDCS and then we performed another analysis to compare data from active ipsilateral tDCS to those obtained from sham tDCS. To evaluate effects induced by active ipsilateral tDCS on reciprocal inhibition from ECR to FCR, we compared the modulations observed from sham and active ipsilateral tDCS conditions, only since active contralateral tDCS had already been tested on another group of subjects in our previous study (Roche et al. 2009).

A two-way ANOVA was performed on unconditioned H reflexes (with time period and condition as factors) to ensure that the modulations of reciprocal inhibition resulted from tDCS not from the variation of the H reflex over time. Moreover i) as amplitude of unconditioned H reflex may affect the conditioned H reflex (Crone et al. 1990) and ii) as the mean amplitude of unconditioned H reflex in ECR was smaller than that in FCR (mean value of unconditioned ECR H reflex was 6.62 ± 1.4% Mmax, compared to mean value of unconditioned FCR H reflex was 14.17 ± 2.5%, cf Table 1) a linear regression between the ratio ECR unconditioned H reflex/FCR unconditioned H reflex and the ratio of ECR conditioned H reflex/FCR conditioned H reflex was calculated in order to ensure that modulations induced by tDCS, were not affected by unconditioned H reflex amplitude.
Group data were analysed using two-way repeated-measures ANOVAs to determine effects of tDCS and time period on reciprocal inhibition. Moreover, to determine if modulations of reciprocal inhibition from ECR to FCR observed in left-handed subjects during active ipsilateral tDCS, were different to that observed in right-handed subjects, a two-way ANOVA was performed with period (baseline, period 1 tDCS, period 2 tDCS, post tDCS) as the first factor and handedness (left-handed subjects, right-handed subjects) as the second factor. Note both two way ANOVAs were performed on raw data using amount of reciprocal inhibition expressed as a percentage of unconditioned H reflex rather than on normalised data (reciprocal inhibition expressed as a percentage of baseline inhibition). To ensure that background EMG activity was constant all over the time, and whatever the tDCS condition a two-way ANOVA (testing tDCS condition and time period as factors) was performed on rms. When the $F$ value was significant, post hoc pairwise comparisons were performed using the Newman-Keuls test. Degrees of freedom calculated by statistical analyses are indicated in brackets after the F value. Significance was taken at $P < 0.05$. Mean data are shown as mean ± 1 Standard Error of the Mean (SEM). Statistical analysis was performed using the SigmaPlot software 11.0.

**Results**

Fig. 2 illustrates a representative example of unconditioned and conditioned reflexes obtained over the baseline period in the same subject. Note that reciprocal inhibition induced in the FCR H reflex (upper traces) is larger than that in the ECR H reflex lower traces. Table 1 summarises the mean unconditioned ECR and FCR H reflex amplitudes: for each tDCS condition (sham, contralateral, ipsilateral) and period (baseline, during tDCS, after tDCS), no significant change of unconditioned test reflex amplitude was observed.

**Background EMG activity**
To ensure that all experiments were conducted at rest we assessed the background EMG activity by calculating the rms of rectified EMG activity in the 100 ms pre-trigger window. The mean rms was calculated for experiments testing reciprocal inhibition directed from FCR to ECR (mean rms = 0.103 ± 0.025 mV) and for experiments testing reciprocal inhibition directed from ECR to FCR (mean rms = 0.109 ± 0.014 mV). Statistical analysis with tDCS condition as first factor (sham, active ipsilateral and active contralateral) and time period as second factors attested that background EMG activity was constant over time and that it was not affected by tDCS: experiments exploring reciprocal inhibition directed from ECR to FCR (F(2,88) = 1.868, \(P_{\text{condition}} = 0.177\); F(3,88) = 0.853, \(P_{\text{period}} = 0.471\); F(6,88) = 0.0198, \(P_{\text{condition x period}} = 0.996\)); experiments testing reciprocal inhibition directed from ECR to FCR: (F(1,152) = 0.00561, \(P_{\text{condition}} = 0.940\), F(3,152) = 0.350, \(P_{\text{period}} = 0.789\), F(3,152) = 0.00369, \(P_{\text{condition x period}} = 1.000\)).

**Sham conditions**

Fig. 3A shows individual data obtained in 9 subjects in whom it was possible to evoke a stable ECR H reflex at rest (5 right-handers, 4 left-handers). The amount of reciprocal inhibition directed from FCR to ECR was plotted against the four time periods (baseline, period 1 tDCS, period 2 tDCS and post tDCS). The amount of reciprocal inhibition did not change significantly over time. The mean level of inhibition as a percentage of unconditioned H reflex in ECR for each time period was: 17.80% ± 2.9 in baseline period; 15.32% ± 2.6 in period 1 tDCS; 14.43% ± 2.3 in period 2 tDCS and 14.16% ± 3.7 in post tDCS.

Fig. 3C shows individual data obtained in 20 subjects (17 right-handers, 3 left-handers). The amount of reciprocal inhibition directed from ECR to FCR did not change significantly over time: the mean level of inhibition as a percentage of unconditioned FCR H reflex for each time period was 34.63% ± 2.4 in baseline period; 35.44% ± 3.4 in period 1 tDCS; 37.59% ± 3.2 in period 2 tDCS and 34.63% ± 2.3 in post tDCS. These results confirm that whichever
reciprocal inhibition pathway explored (from FCR directed to ECR – Fig. 3A or from ECR
directed to FCR – Fig. 3C), sham tDCS never induced a significant change of reciprocal
inhibition.

**Active tDCS applied over the contralateral hand motor cortex**

**Reciprocal inhibition from FCR to ECR**

Fig. 3B shows individual data obtained from 9 subjects (5 right-handers, 4 left-handers). The
amount of inhibition of the ECR H reflex is plotted against the four time periods. In 9
subjects, the level of inhibition was lower in both periods 1 and 2, compared to baseline.
During the post tDCS period, the level of inhibition increased in 7 subjects compared to
period 2. The average reciprocal inhibition expressed as a percentage of unconditioned H
reflex in the 9 subjects was: 16.55% ± 1.7 in baseline period; 7.23% ± 3.1 in period 1 tDCS;
3.91% ± 3.1 in period 2 tDCS and 10.92% ± 2.4 in post tDCS

Fig. 4A shows group data with the amount of reciprocal inhibition from FCR to ECR
normalised to a percentage of its baseline value obtained from sham and active contralateral
tDCS conditions. The two-way repeated measures ANOVA showed an effect of time period
(baseline, period 1 tDCS, period 2 tDCS, post tDCS) and a significant interaction between
time period and tDCS condition (active contralateral and sham): $F_{(1,8)} = 0.537$, $P_{condition} =
0.485$; $F_{(3,24)} = 4.117$, $P_{period} = 0.017$; $F_{(3,24)} = 5.714$, $P_{condition \times period} = 0.004$. Post hoc analyses
confirmed that sham tDCS did not affect the amount of reciprocal inhibition directed from
FCR to ECR which remained constant over time (Newman and Keuls analysis, baseline vs
period 1 tDCS $P = 0.911$, baseline vs period 2 tDCS $P = 0.995$, baseline vs post tDCS $P =
0.944$). Post hoc analyses attested that the amount of reciprocal inhibition was significantly
depressed during both periods (period 1 tDCS and period 2) when active tDCS was applied
over the controlateral motor cortex: the mean values of inhibition evaluated in period 1 and
period 2 were lower than those obtained in the baseline period (Newman and Keuls analysis,
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Baseline vs period 1 tDCS $P = 0.001$, baseline vs period 2 tDCS $P < 0.001$). Moreover at the end of tDCS application the amount of inhibition increased but was not restored to its baseline value (baseline vs post tDCS $P = 0.028$).

Note that the mean levels of reciprocal inhibition recorded during the baseline period were similar in sham and active tDCS conditions. Mean inhibition as a percentage of H unconditioned reflex was 17.80% ± 3.6 in the sham condition compared to 16.55% ± 2.6 with contralateral stimulation. (Table 1). Moreover the mean values of unconditioned H reflex amplitudes were not affected by condition or time period ($F_{(1,8)} = 0.0487$, $P_{\text{condition}} = 0.831$; $F_{(3,24)} = 1.878$, $P_{\text{period}} = 0.160$; $F_{(3,24)} = 0.451$, $P_{\text{condition} \times \text{period}} = 0.719$). Mean values of unconditioned H reflex amplitude were similar during the baseline period (7.08 ± 1.5% Mmax in the sham condition compared to 7.46 ± 1.3% Mmax with contralateral stimulation) (Table 1).

Reciprocal inhibition from ECR to FCR

The effects of active contralateral tDCS on reciprocal inhibition directed from ECR to FCR were described in our previous study (Roche et al. 2009). The data presented in Fig. 4B were extracted from our previous findings for comparison with the results obtained from the present study of reciprocal inhibition directed from FCR to ECR (Fig. 4A). Reciprocal inhibition was enhanced in periods 1 and 2 compared to that observed in the baseline period and sham condition (Fig. 4B) (two-way repeated measures ANOVA (4 periods (baseline, period 1 tDCS, period 2 tDCS, post tDCS) and 2 conditions (sham, active contralateral tDCS)): $F_{(1,12)} = 2.085$, $P_{\text{condition}} = 0.174$; $F_{(3,36)} = 3.323$, $P_{\text{period}} = 0.03$; $F_{(3,36)} = 8.078$, $P_{\text{condition} \times \text{period}} < 0.001$). Reciprocal inhibition was restored to near baseline levels after the end of stimulation for the active tDCS condition: Newman and Keuls analysis; baseline vs period 1 tDCS $P = 0.04$, baseline vs period 2 tDCS $P < 0.001$, baseline vs post tDCS $P = 0.38$.  

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Influence of the unconditioned H reflex size on the amount of reciprocal inhibition.

It can be seen that the size of the unconditioned ECR H reflex was lower than that of the unconditioned FCR H reflex (cf Table 1). Therefore, to ensure that the size of the unconditioned H reflex did not impact on the results, two ratios; unconditioned ECR H reflex/unconditioned FCR H reflex and conditioned ECR reflex/conditioned FCR H reflex were calculated. A linear regression was performed to determine whether the difference between ECR and FCR reflexes altered the amount of reciprocal inhibition (figure not shown). The analysis revealed a significant linear correlation ($P < 0.001; R^2 = 0.957$) indicating that the level of reciprocal inhibition in ECR and FCR muscles would be equal if unconditioned H reflex evoked in ECR and FCR were similar.

Active tDCS applied over the ipsilateral motor cortex.

Reciprocal inhibition from FCR to ECR

Reciprocal inhibition directed from FCR to ECR was tested in 8 subjects as it was not possible to perform the experiment with active ipsilateral tDCS in one subject. The mean levels of inhibition, expressed as a percentage of unconditioned H test reflex were: $17.46\% \pm 3.9$ in baseline period; $15.65\% \pm 4.8$ in period 1 tDCS; $14.28\% \pm 5.1$ in period 2 tDCS and $14.13\% \pm 5.3$ in post tDCS. The group data illustrated in fig 5A show that the mean values of reciprocal inhibition evaluated in active ipsilateral tDCS condition and in sham condition. Statistical analyses showed that in both conditions (active ipsilateral tDCS and sham tDCS) the amount of reciprocal inhibition directed from FCR to ECR remained constant over time: two-way repeated measures $F_{(1,7)}=0.0291$, $P_{condition} = 0.869$; $F_{(3,21)}=1.042$, $P_{period} = 0.394$; $F_{(3,21)}= 0.0183$, $P_{condition \times period} = 0.997$). Here again the mean values of unconditioned H reflexes were constant over time whatever the tDCs conditions (active ipsilateral tDCS and sham tDCS): two-way repeated ANOVA , $F_{(1,7)}= 2.576$, $P_{condition} = 0.153$; $F_{(3,21)}=1.136$, $P_{period} = 0.357$; $F_{(3,21)}= 0.854$, $P_{condition \times period} = 0.480$. 
Reciprocal inhibition from ECR to FCR

First, reciprocal inhibition directed from ECR to FCR was compared during sham (Fig. 3C) and anodal ipsilateral stimulation (Fig. 3D) in 20 subjects. As a percentage of unconditioned test H reflex, the mean levels of inhibition were: 27.74 ± 2.7 in baseline period; 27.9 ± 3.1 in period 1 tDCS; 29.82 ± 3.4 in period 2 tDCS; 28.08 ± 3.0 in post tDCS. The level of inhibition for group data is illustrated in Fig. 5B which shows that ipsilateral tDCS did not induce any statistically significant modification. Results obtained with anodal stimulation strongly resemble those obtained with sham stimulation. This was confirmed by statistical analysis indicating that the time period had no effect on the amount of inhibition in sham and in active ipsilateral tDCS conditions (two-way ANOVA (2 conditions (sham, active ipsilateral tDCS)) X 4 time periods (baseline, period 1, period 2, post tDCS)), \( F_{(1,19)} = 2.954, P_{\text{condition}} = 0.104; F_{(3,57)} = 1.829, P_{\text{period}} = 0.152; F_{(3,57)} = 0.0868, P_{\text{condition} \times \text{period}} = 0.967 \). Moreover the mean values of unconditioned H reflex amplitudes were not affected by condition or time period \( F_{(1,19)} = 1.329, P_{\text{condition}} = 0.268; F_{(3,57)} = 0.589, P_{\text{period}} = 0.626; F_{(3,57)} = 0.128, P_{\text{condition} \times \text{period}} = 0.948 \). Mean values of unconditioned H reflex amplitude were similar during the baseline period (15.13± 2.3% Mmax in the sham condition compared to 13.00 ± 1.9% Mmax with ipsilateral stimulation) (Table 1).

Subsequently, the number of subjects was increased in order to compare results obtained in right-handed and left-handed subjects. Thirty-one subjects were included, of which 8 were left-handed (individuals data are not shown). In the 23 right-handed subjects we found that the level of inhibition was increased compared to baseline in 9 subjects and decreased in 14 subjects in period 1. In period 2, the values were increased compared to baseline in 15 subjects and decreased in 8 subjects. Mean levels of inhibition as a percentage of unconditioned test H reflex were 24.02 % ± 2.4 in baseline period 22.19 % ± 2.7 in period 1 tDCS; 23.94 % ± 2.7 in period 2 tDCS and 23.62 % ± 3.2 in post tDCS. Moreover for the 8
left-handed subjects included in this series of complementary experiments, we found that in 7
subjects, the values were decreased compared to baseline in period 1 and in 4 subjects in
period 2. Mean level of inhibition as a percentage of unconditioned test H reflex was 26.77 %
± 4.0 in baseline period, 22.01 % ± 5.4 in period 1 tDCS, 25.41 ± 6.6 in period 2 tDCS and
25.14 ± 4.9 in post tDCS. Group data are shown in Fig. 5C. Whatever the handedness, no
significant modification was seen during or after anodal ipsilateral tDCS (two-way ANOVA
F(3,116) = 0.252, \( P_{\text{period}} = 0.860 \); F(1,116) = 0.243, \( P_{\text{handedness}} = 0.623 \); F(3,116) = 0.044, \( P_{\text{period} \times \text{handedness}} = 0.987 \)).

Study limitations

ECR and FCR H reflex methodological considerations

Thirty-two healthy subjects were enrolled in this study. Among them, 32 had an FCR H reflex
and only 9 of them had an ECR H reflex. This finding is in accordance with previous results
(Day et al. 1984; Aymard et al. 1995; Wargon et al. 2006). Furthermore, the amplitude of
unconditioned reflexes is usually smaller in ECR than in FCR H. The conditioning stimulus,
when applied to the radial nerve, does not usually evoke an H reflex in the ECR, while the
conditioning stimulus applied to the median nerve, usually evokes an FCR H reflex. To avoid
evoking FCR H reflexes which may induce activation of Renshaw cells between FCR and
ECR motoneurones (Aymard et al. 1995), a lower average intensity conditioning stimulus was
applied to the median nerve than that applied to the radial nerve (cf. Table 1). This lower
median nerve conditioning stimulus intensity probably contributes to the lower baseline level
of reciprocal inhibition in ECR compared to FCR motoneurones. However, in 1995, Aymard
et al. were able to find a subject in which the conditioning stimuli applied to the radial nerve
and to the median nerve were identical. In this condition, the amounts of reciprocal inhibition
were similar in both ECR and FCR reflexes (Aymard et al. 1995; Fig. 1). However, Crone et
al. (1990) emphasised that the amount of inhibition also depends on the unconditioned H reflex amplitude, and the size of the unconditioned ECR H reflex was lower than the FCR H reflex. It could be argued that the differential effects of tDCS on reciprocal inhibition directed from ECR to FCR and from FCR to ECR could be at least partly due to differences in FCR and ECR unconditioned reflex amplitude. However, we found a significant linear correlation between the ratio of unconditioned ECR H reflex/unconditioned FCR H reflex and the ratio of conditioned ECR H reflex/conditioned FCR H reflex indicating that the level of reciprocal inhibition in ECR and FCR would be equal if unconditioned H reflexes evoked in ECR and FCR were similar. This confirms that the effects of anodal tDCS applied over the contralateral hand motor area cannot be explained by the difference in size of conditioned reflexes. Moreover, differences between unconditioned reflex amplitudes may impact on quantitative comparisons but would not influence the qualitative differences (facilitation vs inhibition). Therefore, it is more likely that the reciprocal inhibition behaviour following tDCS strongly reflects differences in the excitability of interneurones.

Among the 32 subjects having an FCR H reflex, 23 were right-handed and 9 left-handed, whereas among the 9 subjects having an ECR H reflex, only 4 were left-handed. Therefore, the comparison between left-handed and right-handed subjects, were restricted to reciprocal inhibition directed from ECR to FCR.

**Discussion**

The main finding of the present study is that anodal tDCS applied over the contralateral hand motor cortex increases reciprocal inhibition directed from wrist extensors to wrist flexors but decreases reciprocal inhibition from wrist flexors to wrist extensors.

**Opposite effects of active tDCS applied to the contralateral hand motor cortex**
Since the position and stimulation characteristics of the active tDCS electrode were identical, when we tested reciprocal inhibition from ECR to FCR and from FCR to ECR, hand motor cortex excitability was the same for both directions of reciprocal inhibitions. The most striking finding of the present series of experiments is that increasing the excitability of the same motor cortex area, induces an increase of reciprocal inhibition from ECR to FCR but a decrease in reciprocal inhibition from FCR to ECR. Evidence from both animal and human studies (Purpura and McMurtry 1965; Priori et al. 1998), shows that anodal tDCS applied over the motor cortex decreases the membrane resting potential of cortical cells, which are spontaneously active in M1 (Evarts 1981). In our previous study (Roche et al. 2009), we proposed that the enhancement of the reciprocal inhibition from ECR to FCR, following tDCS, was due to an increase in efficiency of the descending volley reaching the interneurones that mediate reciprocal inhibition from ECR to FCR. To understand the opposing effects of interneurones that mediate reciprocal inhibition from ECR to FCR and vice-versa, following the same changes in motor cortex excitability, we propose to take into account the mutual inhibition between opposite-side interneurones that mediate reciprocal inhibition, for example an FCR interneurone which mediates reciprocal inhibition from FCR to ECR also inhibits the interneurone which mediates reciprocal inhibition from ECR to FCR as depicted in Fig. 6. In animal studies, mutual inhibition between opposite-side interneurones has been identified as a general central nervous system mechanism. Baldissera et al. (1987) also demonstrated that mutual inhibition exists in humans at the wrist level. Thus, we could propose two hypothetical mechanisms: i) that the descending control acting on interneurones that mediate reciprocal inhibition is asymmetrical and is concentrated on interneurones that mediate reciprocal inhibition from ECR to FCR (Fig. 6A), ii) the reciprocal inhibition at spinal level between ECR and FCR is asymmetrical (Fig. 6B).
The first hypothesis is related to a study by Marteens de Noordhout et al. (1999), suggesting that the cortico-motoneuronal synaptic connections are stronger on wrist and finger extensor motoneurones than on flexor motoneurones. Lundberg and collaborators have shown in the cat that there is a corticospinal parallel control of motoneurones and of the corresponding reciprocal Ia interneurones, i.e. the interneurones that mediate reciprocal inhibition to antagonistic motoneurones (Lundberg 1970). Although the interneurone which mediates reciprocal inhibition at the wrist level exhibits characteristics different from that of Ia interneurones, it might thus be hypothesised that there is parallel descending control of ECR motoneurones and of interneurones that mediate reciprocal inhibition from ECR to FCR (and similarly from FCR motoneurones and interneurones that mediate inhibition from FCR to ECR). If the descending control acting on ECR and interneurones that mediate reciprocal inhibition from ECR to FCR, is stronger than the descending control acting on FCR, the excitability of the interneurones that mediate inhibition from ECR to FCR (the ECR interneurone in Fig. 6) is increased more than that of the interneurones that mediate reciprocal inhibition from FCR to ECR (the FCR interneurone in Fig 6). As a consequence, mutual inhibition between the two opposite-side interneurones is more strongly directed to the FCR interneurone than ECR interneurone. Thus, the net effect of the descending control and mutual inhibition is an increase in the excitability of the ECR interneurone. For the FCR interneurone, its descending control is weaker and leads to the reverse situation: the weaker facilitatory descending control is counteracted by greater mutual inhibition. Hence, this results in a decrease in FCR interneurone excitability.

The second hypothesis is shown in Fig. 6B. The descending control from the hand motor cortex projecting to the ECR and FCR interneurones is similar, but the reciprocal inhibition and the mutual inhibition at the spinal level are asymmetric. The reciprocal inhibition is more strongly directed from ECR interneurones to FCR motoneurones than in the reverse situation.
Asymmetrical control of reciprocal inhibition at wrist level

This hypothesis is supported by results observed at the lumbar level indicating that reciprocal inhibition is asymmetric: the reciprocal Ia inhibition from extensors to flexors is more powerful than the reciprocal Ia inhibition from flexors to extensors (R. Eccles and Lundberg 1958; Crone et al. 1987). Moreover, the activity of spinal circuits is often asymmetric with regard to target motoneurones, for example, the monosynaptic reflex in FCR is stronger than that in ECR. In this case, when the mutual inhibition is more powerful on FCR interneurones than on ECR interneurones, the net effect on FCR interneurones is inhibitory whereas the effect on ECR interneurones is facilitatory.

However, the indirect methods we used do not allow us to choose between these two hypotheses. Furthermore both asymmetrical descending control and asymmetrical reciprocal inhibition may coexist.

Effects of tDCS applied to the ipsilateral hand motor cortex

The possible effects of tDCS applied to ipsilateral hand motor cortex on spinal networks may originate i) from ipsilateral connections to spinal neurones; or ii) hemispheric connections from ipsilateral to contralateral homologous motor cortex areas.

Although the existence of uncrossed corticospinal tracts from motor cortex to spinal motoneurones has been established in healthy humans and higher primates (Kuypers 1981), the effects of activation of the ipsilateral cortex on spinal motoneurones are still under debate. A few papers have reported ipsilateral responses in distal muscles during strong voluntary contractions and high intensity TMS (Wassermann et al. 1991; Ziemann et al. 1999). Bawa et al. (2004) concluded that, in general, forearm and hand muscles in healthy subjects, did not show any ipsilateral motor evoked potentials. However, in post-stroke patients, ipsilateral responses have been recorded (Alagona et al. 2001).

Interhemispheric connections between homologous cortical areas are well known and generally considered to be inhibitory although the presence of excitatory interhemispheric
connections have also been proposed (Bloom and Hynd 2005). Furthermore, several studies (for example, Hervé et al. 2005) suggest that ipsilateral control may be different in left-handed and right-handed subjects. In the present study, we were unable to find significant effects with ipsilateral anodal tDCS. If anything, it seems that a small decrease of reciprocal inhibition from ECR to FCR may be occurring in the period 1, more marked in left-handed than in right-handed subjects.

Functional significance and possible therapeutic applications

Our findings have shown that an increase of excitability of contralateral hand motor cortex results in an increase of reciprocal inhibition to FCR motoneurones, and in contrast a decrease of the reciprocal inhibition to ECR motoneurones. In other words, it seems likely that the function of this descending control is to facilitate ECR motoneurone excitability by reducing inhibitory influences and to depress the excitability of FCR motoneurones by enhancing inhibitory influences. Fine motor hand movements in humans (grasping, writing, typing, etc.) require ECR contraction to stabilise the wrist joint. The descending control acting on reciprocal inhibition is likely to contribute to the facilitation of ECR contraction. In this case, anodal tDCS may be useful for the treatment of patients with cortical lesions who show wrist extensor deficit. It might also be used to facilitate ECR contraction and promote control of hand movements. This therapeutic approach is based on papers published since 2008 (for review see Ayache et al. 2012), that indicate that anodal tDCS applied to the lesioned hemisphere may improve motor performance.

Recent studies performed in stroke patients suggested that cathodal or dual tDCS may reduce spasticity in upper limb muscles (Vandermeeren et al. 2013, Wu et al. 2013). Cathodal tDCS was not tested in the present study but our findings that reveal an increase of reciprocal inhibition directed from ECR to FCR, suggest that contralateral anodal tDCS may be used to reduce flexor spasticity in stroke patients. Indeed, Nakashima et al. (1989) showed that
Asymmetrical control of reciprocal inhibition at wrist level

reciprocal inhibition between wrist muscles is decreased in spastic patients. Therefore, it may be hypothesised that a reinforcement of reciprocal inhibition directed to flexor motoneurones may limit the hyper-excitability of the FCR stretch reflex.

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Asymmetrical control of reciprocal inhibition at wrist level


Asymmetrical control of reciprocal inhibition at wrist level


Asymmetrical control of reciprocal inhibition at wrist level


Asymmetrical control of reciprocal inhibition at wrist level


Figure legends

Figure 1: diagram adapted from Roche et al. (2009) illustrating the experimental procedure.

Experiments lasted about 40 minutes divided in 4 periods of 10 minutes: 10 minutes before the beginning of tDCS baseline period, period 1 tDCS, period 2 tDCS and 10 minutes after the end of tDCS (post tDCS). Current flowed continuously for 20 minutes for both active conditions divided into two 10 minute periods (period 1 tDCS and period 2 tDCS), and for 120 s at the beginning of period 1 tDCS and 30 sec at the end of period 2 tDCS in the sham condition. Conditioned and unconditioned H reflexes were recorded continuously during each period of 10 minutes. Indeed a sequence of 40 H reflexes (20 conditioned H reflexes and 20 unconditioned H reflexes randomly alternated) lasted 3 minutes so 3 sequences of 40 H reflexes were done in each period.

Figure 2: representative example of unconditioned and conditioned H reflexes in ECR and FCR obtained in baseline period in the same subject.

Fig. 2 AB illustrates an unconditioned (A) and a conditioned H reflex (B) in ECR.

Fig. 2 CD illustrates an unconditioned (C) and a conditioned (D) H reflex in FCR. By convention the zero corresponds to the test stimulation represented by an artefact. Latency of the H reflex was symbolized by the dotted line. Peak-to-peak amplitude of the H reflex was expressed in mV.

Figure 3: Individual data showing modulation of the two types of reciprocal inhibition (from FCR to ECR and from ECR to FCR) induced by tDCS applied over the motor cortex.
Fig. 3AB: modulations of reciprocal inhibition from FCR to ECR when tDCS is applied to the contralateral motor cortex: with sham tDCS (A) and active contralateral tDCS (B).

Fig. 3CD: modulations of reciprocal inhibition from ECR to FCR when tDCS is applied over the ipsilateral motor cortex: with sham tDCS (C) and with active ipsilateral tDCS (D). The level of reciprocal inhibition is plotted against the four time periods (baseline, period 1 tDCS, period 2 tDCS and post tDCS). Reciprocal inhibition is expressed as a percentage of the unconditioned H reflex elicited in the ECR (3A and 3B) or in the FCR (3C and 3D) and then calculated as follows: (unconditioned H - H conditioned)/H test X 100. Variations observed in each subject are represented by different symbols (cf. drawing). The mean of amount of reciprocal inhibition obtained in all subjects, represented by the black line.

Figure 4: Group data representing modulations of the two types of reciprocal inhibition (from FCR to ECR and from ECR to FCR) induced by tDCS applied over the contralateral motor cortex.

Fig. 4A: modulations of reciprocal inhibition from FCR to ECR. Group data are calculated with reference to the amount of inhibition in the baseline period. Amounts of inhibition are plotted against time periods. Data obtained in the sham tDCS condition are represented by the symbol (--○--) whereas those obtained in active contralateral tDCS condition are represented by symbol (−●−). Vertical bars represent the standard error of the mean (± 1 SEM). Asterisks (*) indicate significant differences between level of inhibition in baseline compared to level of inhibition estimated over time (in period 1 tDCS, in period 2 tDCS and in post tDCS). The results were significant at (* P < 0.05, (** P < 0.01 and (*** P < 0.001.

Fig. 4B: modulations of reciprocal inhibition from FCR to ECR (taken from our previous paper (Roche et al. 2009). Amounts of inhibition are plotted against time periods. Data obtained in the sham tDCS condition are represented by symbol (--□--) whereas those
obtained in the active contralateral tDCS condition are represented by symbol (●). Vertical bars represent the standard error of the mean (± 1 SEM). Asterisks (*) indicate significant differences between level of inhibition in baseline compared to level of inhibition estimated over time (in period 1 tDCS, in period 2 tDCS and in post tDCS). The results were significant at (*) $P < 0.05$, (**) $P < 0.01$ and (***) $P < 0.001$.

**Figure 5:** Group data representing modulations of the two types of reciprocal inhibition (from FCR to ECR and from ECR to FCR) induced by tDCS applied over the ipsilateral motor cortex.

**Fig. 5A:** modulations of reciprocal inhibition from FCR to ECR. Group data are calculated with respect to the amount of inhibition observed in the baseline period. Amounts of inhibition are plotted against time periods. Data obtained in the sham tDCS condition are represented by the symbol (---O--) whereas those obtained in the active ipsilateral tDCS condition are represented by the symbol (●●●●). Vertical bars represent the standard error of the mean (± 1 SEM).

**Fig. 5B:** modulations of reciprocal inhibition from ECR to FCR. Amounts of inhibition are represented over time. Data obtained in sham tDCS condition are represented by the symbol (---□--) whereas those obtained in the active ipsilateral tDCS condition are represented by the symbol (●●●●). Vertical bars represent the standard error of the mean (± 1 SEM). Standard error of the mean is included in the symbol.

**Fig 5C:** Impact of handedness on effects induced by ipsilateral anodal tDCS on reciprocal inhibition directed from ECR to FCR. Group data comparing effects induced by active ipsilateral tDCS in right-handed subjects and in left-handed subjects. Group data are calculated with respect to the amount of inhibition observed in the baseline period. Amounts of inhibition are plotted against time periods. Data obtained in right-handed subjects are
represented by the symbol (\( \rightarrow \Delta \)) whereas those obtained in left-handed subjects condition are represented by the symbol (\( \rightarrow \ast \)). Vertical bars represent the standard error of the mean (± 1 SEM).

**Figure 6: schematic diagram of reciprocal inhibition between flexor and extensor:**

cortical control and mutual inhibition

Fig. 6A: asymmetric descending control from motor cortex projecting onto spinal neurons (interneurones and motoneurones) innervating ECR and FCR.

Fig. 6B: asymmetric reciprocal inhibition at the spinal level. The thicker the lines, the stronger the control. Black circles represent inhibitory interneurones (IN) of reciprocal inhibition with their collaterals projecting onto the opposite-side interneurones. Excitatory descending pathways from the motor cortex (contralateral and ipsilateral) projecting to motoneurones (MN) and interneurones (IN) are shown with Y-shape terminals. Motoneurones innervating ECR and FCR are star-like.

**Table 1:** Two ways repeated measures ANOVA were performed to compare effects of time period (baseline, period 1, period 2 and post tDCS) and effects of tDCS condition (sham, active contralateral and active ipsilateral) on amount of reciprocal inhibition and unconditioned H reflex amplitudes.
tDCS process

Sham tDCS

or

Active anodal tDCS

20 min

0 10 11 20 21 30 31 40

baseline per1 tDCS per2 tDCS post tDCS
time period (min)

Schema 1: adapted from Roche et al. 2009
Figure 2

Amplitude in mV

A & B

unconditioned ECR H reflex
conditioned ECR H reflex

C & D

unconditioned FCR H reflex
conditioned FCR H reflex

Figure 2
Figure 3

Reciprocal inhibition from FCR to ECR

A. tDCS sham

B. active tDCS contra

Reciprocal inhibition from ECR to FCR

C. tDCS sham

D. active tDCS ipsi

Amount of inhibition in % of unconditioned H reflex

Baseline per1 tDCS per2 tDCS post tDCS

Time period
Reciprocal inhibition from FCR to ECR

A

group data n= 9

- active tDCS contra
- tDCS sham

Reciprocal inhibition from ECR to FCR

B

group data n= 13

- active tDCS contra
- tDCS sham

Figure 4
Reciprocal inhibition from FCR to ECR

A

Reciprocal inhibition from ECR to FCR

B

- active tDCS ipsi
- tDCS sham

C

- right handed subjects
- left handed subjects

Figure 5
Asymmetric control from motor cortex

Asymmetric reciprocal inhibition at spinal level
### Table 1

Values presented in the table show the mean data obtained in baseline period in all subjects. Two ways repeated measures ANOVA were performed to compare effects of time period (baseline, period 1, period 2 and post tDCS) and effects of tDCS condition (sham, active contralateral and active ipsilateral) on amount of reciprocal inhibition and unconditioned H reflex amplitudes.