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How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain?

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Abstract

Transcranial direct current stimulation (tDCS) of the primary motor hand area (M1) can produce lasting polarity-specific effects on corticospinal excitability and motor learning in humans. In 16 healthy volunteers, $H_2^{15}O$ positron emission tomography (PET) of regional cerebral blood flow (rCBF) at rest and during finger movements was used to map lasting changes in regional synaptic activity following 10 min of tDCS (± 1 mA). Bipolar tDCS was given through electrodes placed over the left M1 and right frontopolar cortex. Eight subjects received anodal or cathodal tDCS of the left M1, respectively. When compared to sham tDCS, anodal and cathodal tDCS induced widespread increases and decreases in rCBF in cortical and subcortical areas. These changes in rCBF were of the same magnitude as task-related rCBF changes during finger movements and remained stable throughout the 50-min period of PET scanning. Relative increases in rCBF after real tDCS compared to sham tDCS were found in the left M1, right frontal pole, right primary sensorimotor cortex and posterior brain regions irrespective of polarity. With the exception of some posterior and ventral areas, anodal tDCS increased rCBF in many cortical and subcortical regions compared to cathodal tDCS. Only the left dorsal premotor cortex demonstrated an increase in movement related activity after cathodal tDCS, however, modest compared with the relatively strong movement-independent effects of tDCS. Otherwise, movement related activity was unaffected by tDCS. Our results indicate that tDCS is an effective means of provoking sustained and widespread changes in regional neuronal activity. The extensive spatial and temporal effects of tDCS need to be taken into account when tDCS is used to modify brain function.

Keywords

finger movements; human motor cortex; positron emission tomography; regional cerebral blood flow; transcranial direct current stimulation

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Introduction

Neuronal activity can be modulated by direct current (DC) stimulation. Surface-positive polarization of rat and cat cerebral cortex raises the mean firing rate of neurons recorded in deep cortical layers, whereas surface-negative polarization reduces spontaneous firing (Creutzfeldt *et al.*, 1962; Bindman *et al.*, 1964; Purpura & McMurtry, 1965). The conditioning effects of DC stimulation on firing rates have been attributed to shifts in the resting membrane potential of cortical neurons (Purpura & McMurtry, 1965). If DC is continuously applied for 5 min or more, it can provoke sustained changes in neuronal firing rates that last for many hours after the current is switched off (Bindman *et al.*, 1962).

Recently, transcranial DC stimulation (tDCS) was reintroduced as a non-invasive means of stimulating the intact human cortex (Nitsche & Paulus, 2000). tDCS induces lasting changes in corticospinal excitability when it is given through two electrodes above the primary motor cortex (M1) and the contralateral frontal pole. The direction of excitability change depends on the polarity of tDCS (Lang *et al.*, 2004a): Corticospinal excitability increases when the anode is placed over the motor cortex and the cathode over the frontal pole (hereafter referred to as anodal tDCS) but decreases when current flow is reversed (hereafter referred to as cathodal tDCS). Consistent with animal data, these changes in excitability persist beyond the time of stimulation if tDCS is given for more than 3 min (Nitsche & Paulus, 2000) and remain stable for at least an hour if tDCS is given for ≥10 min (Nitsche & Paulus, 2001; Nitsche *et al.*, 2003a). The conditioning effects of tDCS on corticospinal excitability are affected by drugs that change neuronal membrane excitability and are blocked by the NMDA-receptor antagonist dextromethorphan (Liebetanz *et al.*, 2002). These physiological properties are compatible with the notion that activity-dependent synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), mediate the effects induced by tDCS.

tDCS can also cause changes in human brain function. For example, tDCS given to M1 can facilitate implicit learning (Nitsche *et al.*, 2003b) and tDCS over the occipital cortex can facilitate visuo-motor learning (Antal *et al.*, 2004). Due to its conditioning effects, tDCS holds promise as a means of studying human brain function (Lang *et al.*, 2004b; Siebner *et al.*, 2004) and improving impaired brain function in neuropsychiatric diseases, e.g. in stroke (Hummel *et al.*, 2005).

Baudewig *et al.* (2001) performed functional magnetic resonance imaging (fMRI) before and after five minutes of tDCS of the left M1 to investigate movement-related changes in blood oxygenation level dependent (BOLD) signal during a sequential finger opposition task. Five minutes of cathodal tDCS caused a lasting decrease in the mean number of activated pixels in the supplementary motor area (SMA). BOLD fMRI is a sensitive imaging modality for assessing relative changes in task-related regional synaptic activity, but in contrast to perfusion MRI or $H_2^{15}O$ positron emission tomography (PET) of regional cerebral blood flow (rCBF), it cannot detect task-independent 'tonic' regional shifts in activity associated with tDCS.

We used $H_2^{15}O$ PET measurements of rCBF in humans to explore the lasting effects of anodal and cathodal tDCS over M1. To this end, consecutive PET measurements were performed after real (anodal or cathodal) and sham tDCS while participants were either at rest or performing finger movements with the right hand. This study design enabled us to assess the magnitude, duration and regional distribution of changes in rCBF after tDCS conditioning. In particular, we were interested to clarify whether changes in rCBF were dependent on the functional state of the motor system (rest vs. movement) and polarity (anodal vs. cathodal tDCS) by examination of interactions between the two.

Materials and methods

Study design

The experimental design was identical to recent PET studies that explored the lasting effects of repetitive transcranial magnetic stimulation (rTMS) given to the dorsal premotor cortex (Siebner *et al.*, 2003) or primary motor cortex (Lee *et al.*, 2003; Rounis *et al.* 2005). An identical study design was chosen to allow for a comparison between the lasting effects of tDCS and rTMS on rCBF. The study had a 2 × 2 × 2 factorial design (Fig. 1A), with two levels per factor: 'intervention' (real-tDCS vs. sham-tDCS), 'polarity' (anodal vs. cathodal tDCS) and 'task' (movement vs. rest). Real-tDCS and sham-tDCS were given on two separate days, at least 1 week apart. The 16 participants were divided into two groups of eight, receiving either anodal or cathodal tDCS in the real-tDCS condition. The order of intervention was counterbalanced across subjects. The after-effects of tDCS were assessed by consecutive $H_2^{15}O$ PET measurements of regional rCBF in the first hour after tDCS. Within each scanning session rest and movement tasks were alternated. The order of tasks was kept constant within a subject between sessions but was counterbalanced across subjects.

Subjects

Sixteen healthy, right-handed male volunteers aged 22–55 years (mean age 36 ± 9.7 years) with no history of neurological or psychiatric disorders or head trauma participated in the experiments. All subjects were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from all participants. The study was approved by the joint ethics committee for the National Hospital for Neurology and Neurosurgery (UCLH NHS Trust) and the Institute of Neurology (UCL), Queen Square, London, UK, and was performed according to the ethical standards laid down in the Declaration of Helsinki. Permission to administer radioactive $H_2^{15}O$ was given by the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK.

Transcranial DC stimulation

Subjects were blinded for tDCS conditions. After the second scanning session they were asked if they had noticed any differences regarding tDCS between the two sessions.

Bipolar tDCS was delivered by a battery-driven stimulator (Schneider Electronic, Gleichen, Germany) via two conductive-rubber electrodes, placed in saline-soaked sponges (5 × 7 cm), positioned over the left M1 [optimal M1 representation of the right first dorsal interosseus muscle (FDI) as revealed by TMS] and right frontopolar cortex (above the eyebrow; Fig. 1B). To reduce skin resistance and to minimize sensory effects we prepared the skin at the site where the electrodes were placed prior to tDCS. The electrodes were orientated approximately parallel to the central sulcus and the eyebrow. This montage has been shown to be most effective in modulating corticospinal excitability from M1 in a polarity-specific fashion (Nitsche & Paulus, 2000). tDCS polarity refers to the electrode over the left M1.

For real tDCS a constant current flow of 1 mA was applied for 10 min. The current was always ramped up or down over the first and last 5 s of stimulation, respectively. During tDCS, voltages of more than approximately 10 V can induce a mild tingling sensation in the skin under the scalp electrodes whereas tDCS at lower voltages is usually not associated with sensory stimulation even in experienced subjects. Skin resistance gradually declines after the first few seconds of current application. In consequence, the voltage needed to hold constant current decreases and becomes subthreshold for evoking peripheral sensations. In

this experiment the voltages needed to hold 1 mA for real tDCS always fell below 10 V within 10–20 s of commencing stimulation. Using an identical protocol, our previous work on tDCS-induced changes in corticospinal excitability has shown that 10 min of tDCS to the left M1 (1 mA) never induced muscle twitches or changed the muscle tone (Nitsche & Paulus, 2001; Nitsche *et al.*, 2003a; Lang *et al.*, 2004a; Lang *et al.*, 2004b; Siebner *et al.*, 2004).

For sham tDCS, placement of the electrodes was identical to real tDCS. DC was first switched on in a ramp-up fashion over 5 s. Current intensity (ramp down) was gradually reduced (over 5 s) as soon as DC had reached a current flow of 1 mA. Hence, sham tDCS only lasted 10 s. The rationale behind this sham procedure was to mimic the transient skin sensation at the beginning of real tDCS without producing any conditioning effects on the brain (Lang *et al.*, 2004b; Siebner *et al.*, 2004; Hummel *et al.*, 2005; Iyer *et al.*, 2005).

Movement task

All subjects underwent six sequential $H_2^{15}O$ PET scans on each of the two days. All scans were acquired during the first hour after tDCS conditioning. Normalized rCBF-dependent radiotracer uptake (referred to as rCBF) was used as an index of regional synaptic activity in two experimental conditions: rest (referred to as condition ‘R’) and random selection of finger movements (referred to as condition ‘M’). Three PET scans were acquired for each of the experimental conditions in an alternating order (R–M–R–M–R–M or M–R–M–R–M–R). Subjects were required to keep their eyes open and to fixate a cross on the centre of a screen located 0.7 m in front of their face. A pacing tone sounded every 2 s during both conditions. During the movement task, subjects were required to freely select from a set of four previously practised movements and execute brisk flexion movements with the index, middle, ring, or little finger of their right hand. They were asked to make a fresh choice on each trial, regardless of previous moves, so as to produce a random sequence (Lee *et al.*, 2003; Siebner *et al.*, 2003). Subjects were told to actively prepare the forthcoming movement and execute it as soon as they heard the pacing tone. To ensure a stable level of task performance, the random selection task started ≈20 s before the onset of the PET scan and lasted for the entire 90-s period of data acquisition. During the baseline condition, subjects were instructed to watch the fixation point and listen to the tones. Subjects practised the task beforehand to avoid learning effects during scanning. Subjects’ responses were made on four buttons, set under their fingertips on a moulded wrist splint (Fig. 1C). All responses were recorded by computer (Apple Macintosh 7300) using COGENT Cognitive Interface Software (Wellcome Department of Imaging Neuroscience, London, UK). The data were subsequently analysed using Matlab 6.0 (Mathworks Inc., Natick, USA) and SPSS 8.0 (SPSS Inc., Chicago, USA).

Behavioural assessment

In addition to the random selection task during scanning subjects performed two finger-tapping tasks with their right hand before PET scanning and after the first, third and fifth PET scans. These tasks served as additional controls to detect any behavioural effects of tDCS. In the simple tapping task, subjects tapped their right index finger as many times as possible during a 10 s interval. In the sequential tapping task, subjects were asked to repeat an ascending sequence (index, middle, ring, little finger) as quickly as possible for 10 s. Having familiarized the subjects with the tasks outside the PET scanner each task was performed twice in the PET scanner before tDCS on both scanning sessions. This was carried out to reduce learning effects during sequential PET scans. For each task the mean interval between responses and the mean duration of button presses were calculated as indices of motor performance. These values were entered into a repeated measures analysis of variance (ANOVA) with ‘intervention’ (real-tDCS vs. sham-tDCS) and ‘polarity’ (anodal vs.

cathodal tDCS) as factors. The free selection movement task during scanning was paced; therefore only the mean duration of button presses was considered as a kinematic variable of interest. Simpson's equitability index (Simpson, 1949) was calculated for sequential response pairs and taken as a measure of the randomness of the sequence. Data from the three repetitions of this task during each scan were analysed to provide two values of randomness for each subject: one after sham-tDCS and one after real-tDCS. These values were entered into a repeated measures ANOVA with 'intervention' (real-tDCS vs. sham-tDCS) and 'polarity' (anodal vs. cathodal tDCS) as factors. Significance was set at $P < 0.05$.

Positron emission tomography

PET was performed using a CTI ECAT HR+ scanner (CTI, Knoxville, USA) in three-dimensional mode with interdetector collimating septa removed. The axial field of view was 155 mm, providing whole-brain coverage including cerebellum. The subjects lay supine in the scanner. A padded helmet with a chinstrap, fixed to the headrest, reduced head movement. A TV monitor was adjusted to give subjects an unrestricted view of the instructions and fixation point.

Regional cerebral blood flow was assessed using $H_2^{15}O$. Background activity was counted over 30 s prior to each image. Six to 10 mCi (mean 8.9 mCi) were delivered intravenously over 20 s to the left arm. Image acquisition began 5 s before the rising phase of the count curve, ≈25 s after injection, and continued for 90 s. Correction for tissue and helmet attenuation was made using a transmission scan from $^{68}Ga/^{68}Ge$ sources at the start of each scanning session. The interscan interval was 8 min. Corrected data were reconstructed by three-dimensional filtered back-projection (Hanning filter, cut-o frequency 0.5 cycles per pixel) and scatter correction. Sixty-three transverse planes were obtained with a 128 × 128 pixel image matrix, with a pixel size of 2.4 × 2.1 × 2.1 mm and a resolution of ≈6 mm at full-width half-maximum.

In all subjects, the position of the centre of the TMS coil that had been used to determine the optimal representation of the right FDI muscle ('motor hot spot') was marked on the skull with a capsule containing cod liver oil. Anatomic structural images were acquired before tDCS with the surface markers in place using a VISION MR scanner at 2 tesla (Siemens, Erlangen, Germany) and a T1 MPRAGE sequence (echo time 4 ms; repetition time 9.5 s; inversion time 600 ms; resolution 1 × 1 × 1.5 mm; 108 axial slices). This structural image also excluded asymptomatic structural brain abnormalities. In all subjects the cod liver oil capsule marking the motor hot spot was located over the central sulcus.

Image analysis

All image analysis was performed using Statistical Parametric Mapping software, SPM99 (Wellcome Department of Imaging Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) in the MATLAB 6.0 environment (Mathworks Inc., Natick, USA). For each subject, images were realigned to the first image by rigid body correction for head movements between scans and change of position between sessions (Friston *et al.*, 1995a). All images were then normalized to a standardized anatomic space (Talairach & Tournoux, 1988) by matching to a standardized PET template using linear and nonlinear spatial transformations (Friston *et al.*, 1995a). Each image was smoothed with an isotropic Gaussian kernel of 12 mm full-width at half-maximum to accommodate intersubject differences in anatomy and enable the application of Gaussian field corrections during inference (Friston *et al.*, 1995a).

Statistical analysis was performed using a multigroup fixed effects model. The two groups comprised data from subjects following (i) real and sham anodal tDCS and (ii) real and

sham cathodal tDCS. Within each group, rest and move conditions during both real and sham tDCS were modelled as separate covariates. Thus eight covariates were modelled separately. In addition, the effect of global differences in cerebral blood flow between scans was modelled as a covariate of no interest by subject specific ancova scaling of activity to a nominal mean global activity of 50 mL/100 g/min (Friston *et al.*, 1990). The resulting covariates were used to specify the general linear model (Friston *et al.*, 1995b). The parameter estimates for each covariate resulting from the least mean squares fit of the model to the data were calculated. Statistical parametric maps of the *t* statistic [SPM(*t*)] resulting from linear contrasts of covariates were generated and stored as separate images. In this way we were able to generate SPMs representing (i) the main effects of both anodal and cathodal tDCS separately; (ii) the differences between anodal and cathodal tDCS and (iii) the shared main effects of anodal and cathodal tDCS. The shared effects were determined by performing a conjunction analysis between the two main effects. Conjunction analysis relies on the conjoint testing of multiple effects such that the null hypotheses that there is no effect of anodal tDCS and no effect of cathodal tDCS can be jointly rejected (Price & Friston, 1997). In addition we were able to examine for the main effects of task (i.e. movement) and for the interaction between task and tDCS. We were specifically interested in whether modulation of movement related activity by tDCS would be seen in M1 and premotor regions of either hemisphere. Thus we performed this analysis on restricted search volumes covering the M1 and dorsal premotor cortex (PMd) of each hemisphere. Recent studies have combined rTMS and PET using the same behavioural task (Lee *et al.*, 2003; Siebner *et al.*, 2003; Rounis *et al.* 2005). When 1800 stimuli of low-frequency (1 Hz) rTMS were given to the left M1, PET disclosed lasting changes in movement-related activity within the left M1 as well as the right PMd (Lee *et al.*, 2003; Rounis *et al.* 2005). In addition, there were changes in intraregional coupling within the M1 and interregional coupling between premotor cortex and left M1. As rTMS and tDCS produce similar after effects on corticospinal excitability we expected that tDCS, by analogy to rTMS, would influence movement-related activity in M1 and PMd. The search volume was defined by 20 mm radius spheres that were centred on stereotactic coordinates $x = -36$, $y = -16$, $z = +60$ (i.e. midpoints between coordinates for PMd and M1 from Fink *et al.*, 1997) and corrected for multiple comparisons within these volumes.

All SPM(*t*)s were transformed to the unit normal Z-distribution to create a statistical parametric map [SPM(*Z*)]. All *t*-tests carried out within SPM were one-tailed. All results are reported at $P < 0.05$ corrected for multiple nonindependent comparisons over the whole brain. Anatomical identification was performed by superimposing the maxima of activation foci both on the Montreal Neurological Institute (MNI) reference brain and on the normalized structural images of each subject and identifying areas with the aid of the atlas of Duvernoy (1991).

Results

None of the participants reported any adverse effects during or after the experiments. Real tDCS was always subthreshold for evoking a motor response in the right upper limb. Participants reported no difference between the two tDCS sessions (i.e. sham and real tDCS) in an interview at the end of the second experiment.

Behavioural data

All participants performed the random finger movement task in the scanner with little difficulty. For each task, Table 1 lists the mean values of each measure of motor performance. Two-way repeated ANOVAs with ‘intervention’ (real-tDCS vs. sham-tDCS) as a within-subject factor and ‘polarity’ (anodal vs. cathodal tDCS) as a between-subject factor revealed no significant interaction ‘intervention’ by ‘polarity’ for any of the kinematic

measures. ANOVAS showed marginal significant main effects for 'intervention' on the measures duration of button presses ($P = 0.05$) in the index finger tapping task and on interval between responses in the sequential finger tapping task ($P = 0.05$). All other P-values for 'intervention' or 'polarity' were > 0.1. This suggests that motor performance was matched between groups and was widely unaffected by tDCS.

PET measurements of regional cerebral blood flow

Movement related regional neuronal activity—In accordance with previous PET studies that used the same motor task (Lee *et al.*, 2003; Siebner *et al.*, 2003) selected finger movements led to a relative increase in rCBF in a well-defined motor network that is engaged in the generation of right hand movements. This included primary sensorimotor cortex (SM1), PMd, caudal supplementary motor area (SMA), adjacent anterior cingulate cortex and inferior parietal lobule contralateral to the moving hand. Additional activations were located in left anterior insula, right inferior parietal cortex, right frontal operculum and the cerebellum, particularly on the right.

tDCS effects on regional neuronal activity—Both anodal and cathodal tDCS led to widespread changes in rCBF relative to sham tDCS. The magnitude of tDCS induced changes was similar to the magnitude of task related changes seen during finger movements and remained stable throughout the 50-min period covered by the six PET measurements. Because real tDCS had a similar effect on rCBF levels at rest and during movement, the amount of movement related activity did not change in most motor areas. The only significant task by intervention interaction was seen in the left PMd (Fig. 2). In the left PMd, cathodal but not anodal tDCS led to a relative increase in movement related activity (peak voxel at $x = -22$, $y = -6$, $z = 70$ mm; Z-score = 3.67; $P = 0.038$ corrected using restricted search volume, see Materials and methods). Outside the predefined regions-of-interest no brain region showed a change in movement-related activity following real tDCS at $P < 0.05$ corrected for whole brain volume.

Main effects of anodal or cathodal tDCS: Brain regions in which a relative change in rCBF was seen during anodal tDCS compared to sham tDCS are listed in Table 2. Overall, cortical areas that increased rCBF in response to anodal tDCS outweighed those areas that showed a decrease in rCBF (Fig. 3, left panel). The area of the left central sulcus underlying the M1 electrode showed a sustained increase in rCBF after anodal tDCS relative to sham-tDCS. Brain regions in which cathodal tDCS induced a persistent change in rCBF are shown in Table 3. Cathodal tDCS predominately resulted in widespread decreases of rCBF in the cortex. Only a limited number of cortical areas showed an increase in rCBF (Table 3; Fig. 3, right panel).

Differences in rCBF changes induced by anodal and cathodal tDCS: A direct comparison of rCBF changes induced by anodal and cathodal tDCS revealed no polarity-specific differences in those cortical regions directly under the electrodes. By contrast, tDCS produced marked polarity-specific rCBF differences in multiple remote brain regions (Table 4; Fig. 4, left panel). Overall, anodal compared with cathodal tDCS induced a more widespread increase of rCBF in cortical areas. In addition, a distinct pattern emerged with respect to polarity-specific effects of tDCS on cerebral cortex. Almost all cortical foci that demonstrated a polarity-specific increase in rCBF after anodal tDCS were found in dorsal parts of the cerebral hemisphere (dorsal to the axial plane at $z = 17$ mm). Conversely, cortical areas which exhibited a polarity-specific increase in rCBF after cathodal tDCS were exclusively located in ventral regions of the cerebral hemisphere (ventral to the axial plane at $z = 25$ mm).

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Changes in rCBF common to anodal and cathodal tDCS: We performed a conjunction analysis to test for brain regions in which real tDCS produced a similar change in rCBF regardless of polarity. Compared to sham tDCS, anodal and cathodal tDCS induced a relative increase in rCBF in the cortex underlying both electrodes (Fig. 5). The regional maxima of increased activity in the left M1 (at $x, y, z = -56, -12, 52$ in mm) was located approximately 2 cm laterally to the average location of the left M1 hand area ($x, y, z = -31, -22, 52$ in mm) as revealed by a meta-analysis of motor activation studies (Paus *et al.*, 1998). The contralateral right M1 also showed a relative increase in rCBF after both anodal and cathodal tDCS. In contrast to the left side, this focal increase in rCBF was located in the hand representation of M1 (regional maxima at $x, y, z = 30, -26, 58$). Several remote cortical areas showed lasting changes (increase or decrease) in rCBF in response to both anodal and cathodal tDCS (Table 5; Fig. 4, right panel).

Discussion

To our knowledge, this is the first neuroimaging study to have explored the effects of tDCS on regional neuronal activity in the human brain at rest and during a task. When electrodes were placed over left primary motor and right frontopolar cortex, tDCS induced widespread bi-directional changes in regional neuronal activity. tDCS induced changes in rCBF were similar in magnitude to the effects of finger movement on rCBF in motor areas and remained stable throughout the ≈50-min period covered by PET scanning. These results indicate that tDCS can produce marked and persistent effects on regional neuronal activity in the human brain.

Methodological considerations

It is known from animal experiments that electric currents can influence vascular tone in isolated cerebral arteries, leading to vasoconstriction, vasodilatation or bi-model responses (Lee *et al.*, 1975; Toda, 1981). Though we can not exclude that lasting changes in vascular tone might have contributed to the observed changes in rCBF following real tDCS, a substantial contribution by this mechanism seems unlikely for the following reasons. (i) Changes in vascular tone should also be present in the skin and subcutaneous tissue underlying the electrodes, which was not observed in the present study. (ii) The scattered distribution of rCBF changes is not readily compatible with effects on vascular tone, as the strength of the electric field diminishes exponentially with distance from the electrode (Rush & Driscoll, 1968). Also, this is not a probable explanation for effects in regions away from the electrodes. (iii) Contrary to our observation, a tonic change in vascular tone should reduce the magnitude of neurovascular coupling and thus attenuate relative differences in rCBF between the rest and movement condition, especially at the sites under the electrodes.

Regional effects on the cortex underlying the electrodes

The superficial aspects of primary motor and frontopolar cortices under the electrodes were activated after anodal and cathodal tDCS. On the basis of experimental and theoretical data it is estimated that approximately 45% of the total current applied to the scalp passes through the cranial cavity and that the maximum current density is found in the cortices directly under the electrodes (Rush & Driscoll, 1968). Our data are in accordance with these simulations indicating that prolonged tDCS results in effective modulation of regional neuronal activity in the targeted cortex.

Regardless of the polarity of tDCS we found increased rCBF in the frontopolar and motor cortex under the electrodes. Hence, there is no clear relationship between the direction of rCBF changes in the left M1 and the bi-directional changes in corticospinal excitability reported previously following anodal and cathodal tDCS (Nitsche & Paulus, 2000; Lang *et*

al., 2004a). The common activation after both types of tDCS means that 10 min of tDCS results in a net increase in regional synaptic activity that may be excitatory or inhibitory. This does not preclude polarity-specific effects of tDCS on the excitability of different subpopulations of cortical neurons or membrane excitability of pyramidal cells (Lang *et al.*, 2004a). It implies only that the after effects of tDCS on cortical excitability when averaged result in similar changes in rCBF. Differential changes in the excitability and output from M1 are both compatible with a local activation of M1 because rCBF mainly reflects local levels of synaptic activity in intracortical neurons and inputs to those areas, rather than the activity of output neurons (Logothetis *et al.*, 2001; Logothetis, 2002). This interpretation is in concordance with recent rTMS-PET studies (Lee *et al.*, 2003; Rounis *et al.* 2005) showing increased rCBF in the stimulated left M1 after prolonged slow-frequency (1 Hz) and high-frequency (5 Hz) stimulation despite the fact that 1 Hz and 5 Hz rTMS have opposite after effects on corticospinal excitability. rCBF and electrophysiological measurements of motor evoked responses probe different aspects of cortical function and therefore provide complementary information about the conditioning effects of tDCS.

Remote changes in rCBF

Other brain areas activated by both types of tDCS include several motor areas such as the right M1, the caudal portion of the anterior cingulate cortex, right parieto-occipital junction, superior temporal sulcus and cerebellum. This may in part be due to a modulation of the functional interaction between M1 and these areas via cortico–cortical and cortico–subcortical connections. For example, both types of tDCS increased rCBF in contralateral right M1. A rCBF increase in homologous contralateral M1 was also found after rTMS to left M1 (Siebner *et al.*, 2000; Lee *et al.*, 2003) and may represent a lasting reduction in left-to-right transcallosal inhibition between the two cortices (Gilio *et al.*, 2003; Plewnia *et al.*, 2003; Schambra *et al.*, 2003).

We found substantial polarity specific differences in stimulation-induced regional activations. Anodal tDCS induced more widespread increases in rCBF in remote brain regions whereas cathodal tDCS induced more decreases. Brain areas showing polarity-specific increases in rCBF after anodal tDCS seemed to be clustered in dorsal parts of the cerebral hemispheres (dorsal to the axial plane at $z = 17$ mm). Conversely, cortical areas showing polarity-specific increases in rCBF after cathodal tDCS were exclusively located in ventral regions of the cerebral hemispheres (ventral to the axial plane at $z = 25$ mm). This raises the possibility that the complex geometry of the brain, and regional differences in the conductance, caused a distinct spatial distribution of current flow through the brain, resulting in a clustering of rCBF changes at distinct cortical and subcortical sites, independent of anatomical connections. Though the functional relevance of these distant changes in rCBF needs to be proven, the widespread effects of tDCS on rCBF needs to be taken into account when tDCS of a specific cortical area is used to interfere with cognitive functions.

Changes in movement related activity

The magnitude of tDCS-induced changes in rCBF at rest was similar to changes seen during finger movements. The one exception was left PMd, which showed a task-related increase in rCBF after cathodal but not anodal tDCS. As most motor regions did not show a change in task related activation between tDCS conditioned and unconditioned brain it seems likely that the effects of conditioning are mainly nonspecific and that in most areas task related activity was additive to that caused by conditioning. By analogy to the present findings, prolonged trains of 1 Hz or 5 Hz rTMS to the left M1 produced relatively modest and regionally restricted changes in movement related activity compared with marked and widespread nonspecific changes in rCBF (Lee *et al.*, 2003; Rounis *et al.* 2005). We conclude

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that both methods of transcranial cortex stimulation can have profound effects on the overall level of regional activity in many brain regions, but without having major effects on task-related gains in activity.

Baudewig *et al.* (2001) used fMRI to investigate lasting effects of a 5-min session of anodal and cathodal tDCS on movement related changes in the BOLD signal. In accordance with our study, only cathodal tDCS had a lasting effect on movement related activity in premotor cortex. In the fMRI study, cathodal tDCS provoked a decrease in BOLD signal in the supplementary motor area during a sequential finger opposition task, whereas our study found an increase in rCBF in left PMd during freely selected finger movements. We suggest that cathodal tDCS is more effective at interfering with motor execution than anodal tDCS. The inhibitory effects of cathodal tDCS at the site of stimulation may result in compensatory activity in premotor areas in order to maintain motor performance during self-generated finger movements.

Using the same experimental design, recent studies have shown that focal rTMS to the left M1 modifies the magnitude of movement-related activity in the caudal portion of the left M1 depending on the frequency of stimulation. 'Inhibitory' 1 Hz rTMS increased movement-related activity; 'facilitatory' 5 Hz rTMS had the opposite effect (Lee *et al.*, 2003; Rounis *et al.* 2005). Together, the PET data demonstrate that both interventions, tDCS and rTMS, can produce polarity-specific effects on movement-related activity in the targeted cortex. Because tDCS and rTMS altered movement-related activity in different motor areas (i.e. PMd or caudal M1), we infer that tDCS and rTMS interact differently with the brain and seem to induce different compensatory mechanisms.

Concluding remarks

Taken together, our study confirms the feasibility of assessing the lasting effects of tDCS at a systems level in the human brain using functional neuroimaging. We show that tDCS is an effective method of inducing lasting changes in synaptic excitability, but the spatial pattern of induced functional interactions may be more complex than previously thought. The specific patterns of regional effects may depend critically on the placement of electrodes over the scalp and on inhomogeneities of electrical conductivity of the skull, cerebrospinal fluid and brain tissue.

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Abbreviations

BOLD	blood oxygenation level dependent
DC	direct current
FDI	first dorsal interosseus muscle
fMRI	functional magnetic resonance imaging
M1	primary motor hand area
PET	positron emission tomography
PMd	dorsal premotor cortex

rCBF	regional cerebral blood flow
rTMS	repetitive transcranial magnetic stimulation
SMA	supplementary motor area
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation

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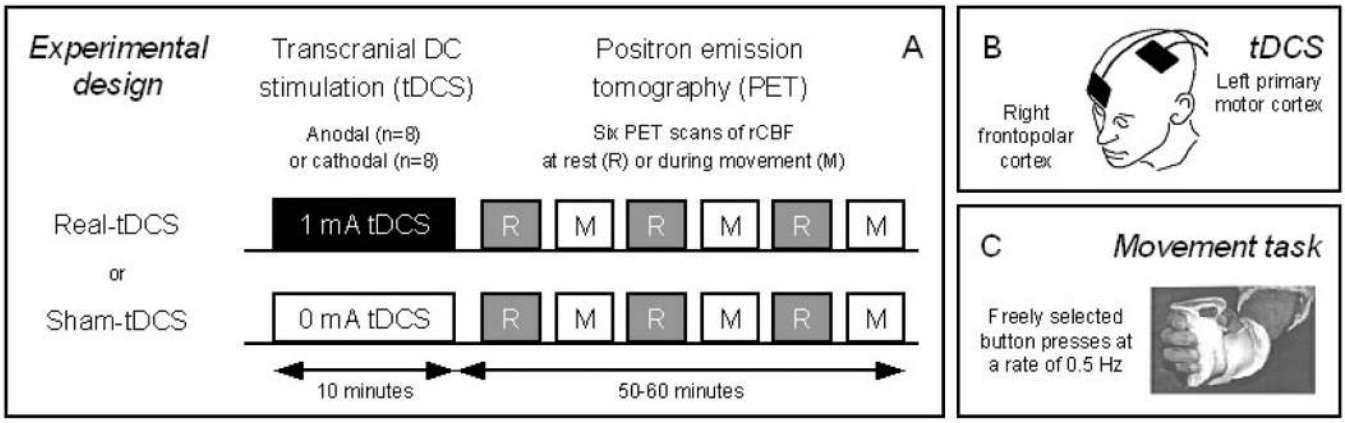

Fig. 1.

Panel A illustrates the experimental design. Subjects were divided into two groups of eight and received Real-tDCS (anodal or cathodal) and Sham-tDCS on separate days.

Immediately afterwards six sequential $H_2^{15}O$-PET scans were acquired at rest (R) or during finger movements (M). The order of intervention (Real-tDCS vs. Sham-tDCS) and experimental conditions (R vs. M) were counterbalanced across subjects. Panel B illustrates the technique used for tDCS. Weak direct current (1 mA) was applied between two large (35 cm^2), wet sponge-electrodes placed over left M1 (optimal representation of right FDI as assessed with TMS) and right frontopolar cortex (above the eyebrow). Polarity of tDCS refers to the M1 electrode. Panel C illustrates the motor task performed by the subjects during PET scanning. Subjects were required to freely select from a set of four previously practised movements and execute brisk flexion movements with fingers II–V of their right hand. They were asked to make a fresh choice on each trial, regardless of previous moves. Movements were paced every 2 s to ensure a constant movement rate across scans.

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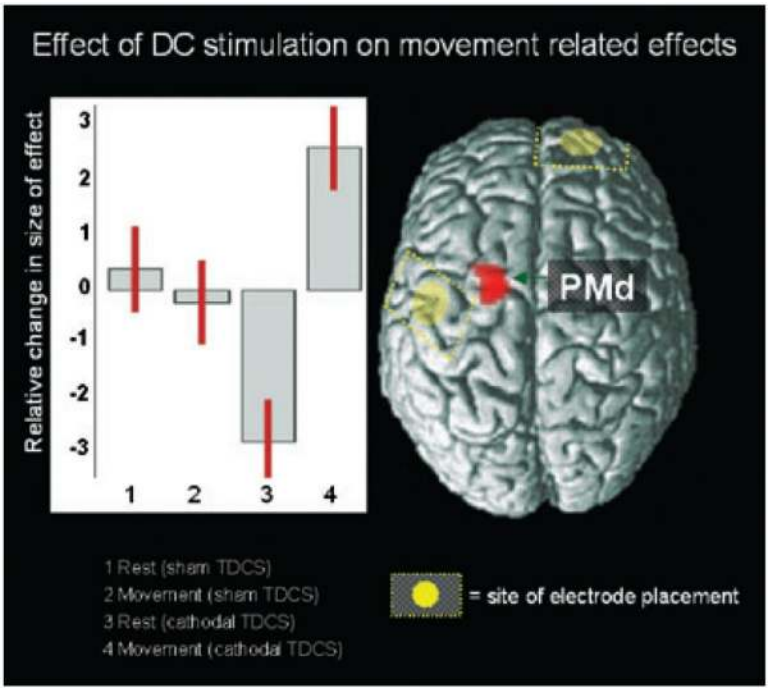

Fig. 2.

Changes in movement related activity. Surface rendering of those voxels showing enhanced movement related activity in left dorsal premotor cortex (PMd) after cathodal tDCS (red area; $P < 0.001$; uncorrected). The yellow areas indicate the motor and frontopolar site of electrode placement during tDCS. The graph (left panel) plots the relative changes in rCBF among the four experimental conditions regarding after effects of cathodal tDCS. Error bars equal SEM.

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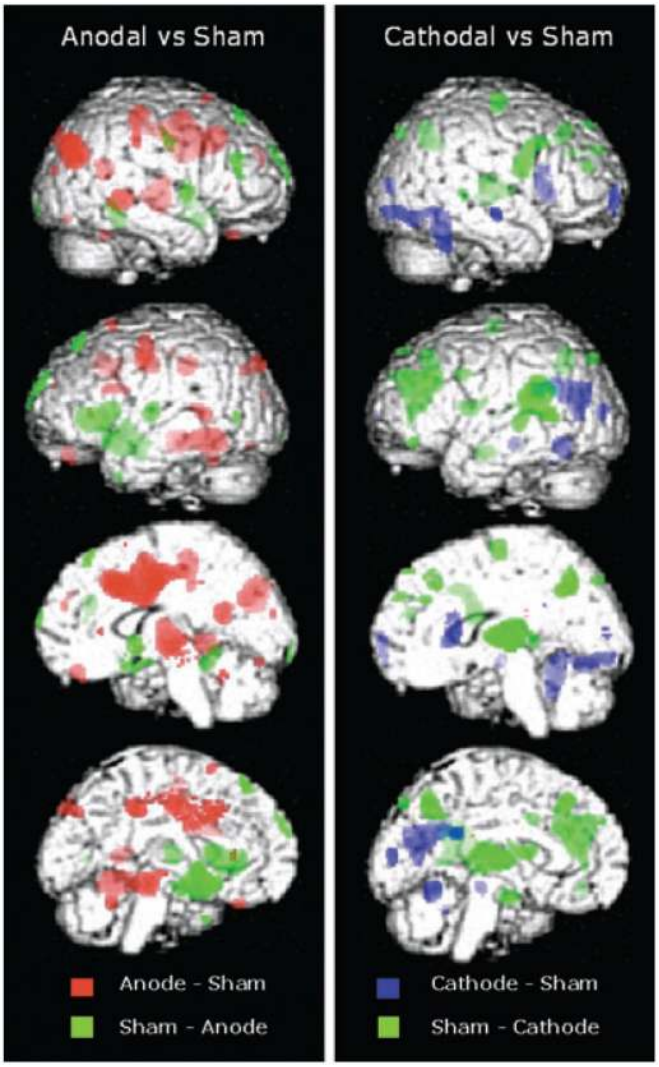

Fig. 3.

Main effect of anodal and cathodal tDCS compared to sham. Surface rendering of brain regions showing a relative increase or decrease rCBF after real-tDCS compared to sham tDCS ($P < 0.05$, whole-brain corrected). Images show (from the top) right lateral surface, left lateral surface, right medial surface, and left medial surface.

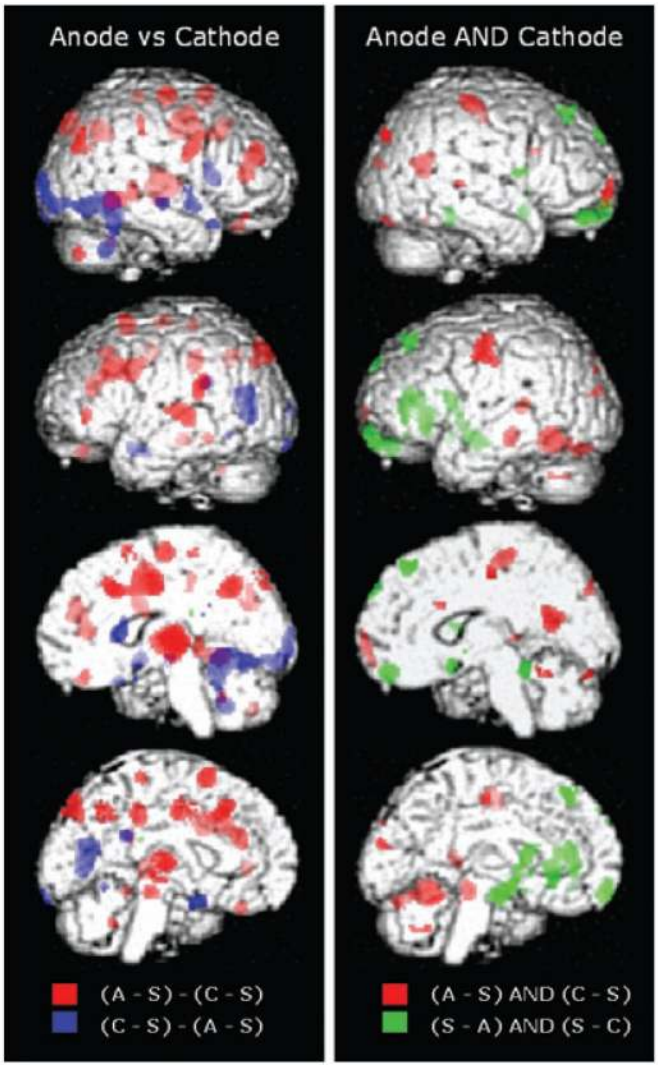

Fig. 4.

Differences and commonalities in rCBF changes induced by anodal and cathodal tDCS. Surface rendered statistical parametric maps showing brain regions in which anodal and cathodal tDCS had a differential (left panel) or similar (right panel) effect in terms of lasting changes in rCBF ($P < 0.05$, whole-brain corrected). Images show (from the top) right lateral surface, left lateral surface, right medial surface, and left medial surface.

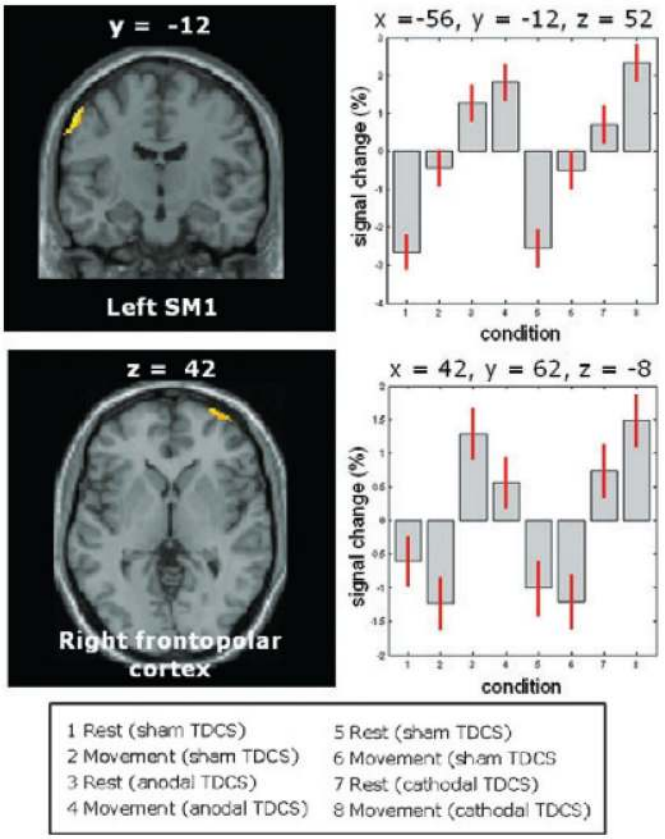

Fig. 5.

Increases in rCBF in the cortex underlying the electrodes. The left panels highlights those voxels in left SM1 (coronal slice) and right frontopolar cortex (axial slice) showing an increase in rCBF both during anodal and cathodal tDCS ($P < 0.05$, whole-brain corrected). The graphs (right panels) plot the relative changes in rCBF in the voxel showing peak increases in rCBF during tDCS regardless of polarity. Each column represents mean normalized rCBF for the eight experimental conditions. Error bars equal SEM.

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Table 1

Kinematic measures of motor performance during the index finger tapping, sequential finger tapping and random movement selection after real (anodal and cathodal) or sham tDCS

	Anodal tDCS		Cathodal tDCS		ANOVA	
	Sham	**Real**	**Sham**	**Real**	***F*-value**	***P*-value**
Index finger tapping						
Movement duration (ms)	117 ± 21	125 ± 30	104 ± 17	98 ± 12	3.236	0.122
Inter-movement interval (ms)	206 ± 38	220 ± 68	186 ± 15	181 ± 14	1.469	0.271
Sequential finger tapping						
Movement duration (ms)	263 ± 118	245 ± 71	172 ± 65	147 ± 58	0.1	0.764
Inter-movement interval (ms)	350 ± 73	326 ± 60	250 ± 101	238 ± 85	0.225	0.655
Random selection						
Movement duration (ms)	234 ± 30	244 ± 49	214 ±30	232 ± 38	0.235	0.649
Simpson's equitability index	0.78 ±0.11	0.79 ± 0.06	0.77 ± 0.09	0.75 ± 0.07	1.449	0.274

All values correspond to the mean ± SD. The mean data after anodal and cathodal tDCS were obtained from different groups. *F*- and *P*-values result from ANOVAs with 'intervention' (real-tDCS vs. sham-tDCS) and 'polarity' (anodal vs. cathodal tDCS) as factors.

Table 2

Brain regions showing a significant change in rCBF after anodal tDCS relative to sham tDCS

		Talairach coordinates in MNI space			
Region	**Side**	***x***	***y***	***z***	***Z*-value**
Anodal tDCS > sham tDCS					
Central sulcus	L	−54	−6	52	6.08
	L	−50	−10	58	5.21
	L	−34	−12	42	5.35
Postcentral sulcus	L	−8	−38	42	5.65
	R	40	−32	46	5.39
Ventral premotor cortex	L	−40	16	24	4.89
Pre-SMA	L	−6	14	68	5.2
Caudal cingulate sulcus	R	8	−8	42	7.4
Posterior parietal cortex	R	46	−76	32	6.74
Superior frontal sulcus	R	22	52	24	4.72
Superior temporal sulcus	R	50	−42	2	5.55
Parieto-occipital sulcus	R	20	−52	18	6.37
Superior occipital gyrus	L	−8	−86	42	5.71
Fusiform gyrus	L	−30	−54	−12	7.75
Cerebellar vermis (VI)		−2	−54	−24	5.5
Thalamus (vpl)	R	16	−18	4	5.99
Sham tDCS > anodal tDCS					
Superior temporal gyrus	R	68	2	2	6.81
Insular cortex	L	−28	18	6	6.75
	L	−34	−10	8	6.2
Anterior prefrontal cortex	L	−16	66	24	6.01
	R	12	70	16	5.49
Lateral prefrontal cortex	R	56	36	24	5.35
Fusiform gyrus	R	24	−46	−10	5.39
Globus pallidus	L	−10	2	−8	6.04
Nucleus accumbens	L	−12	14	−12	5.79

All co-ordinates (in standard stereotactic space) refer to maximally activated foci as indicated by the highest *Z*-score within a cluster of activations. *x*, distance (mm) to right (+) or left (−) of mid-sagital line; *y*, distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; *z*, distance above (+) or below (−) the intercommissural (AC–PC) line. The AC–PC line is the horizontal line between the anterior and posterior commissures. All voxels are significant at $P < 0.05$ (corrected for multiple comparisons across the whole brain). R, right; L, left; SMA, supplementary motor area; vpl, ventral poster-olateral.

Table 3

Changes in neuronal activity induced by cathodal tDCS relative to sham tDCS

		Talairach coordinates in MNI space			
Region	**Side**	***x***	***y***	***z***	***Z*-value**
Cathodal tDCS > sham tDCS					
Frontal pole	R	36	66	2	5.9
Superior temporal sulcus	R	62	−16	−8	5.69
Lateral occipital sulcus	L	−32	−72	18	6.69
Cerebellum (VI)	L	−26	−58	−16	5.76
	R	36	−52	−22	5.49
Cerebellar vermis		−4	−56	−12	5.12
Caudate	R	18	16	10	6.32
Sham tDCS > cathodal tDCS					
Deep central sulcus	R	50	2	26	5.97
Dorsal premotor cortex	R	20	−14	66	6.71
Ventral premotor cortex	R	50	12	38	5.15
	L	−34	8	34	5.11
Pre-SMA	R	8	48	52	5.08
	L	−4	30	46	6.05
Rostral cingulate sulcus	R	4	36	32	4.91
Superior frontal sulcus	L	−24	44	32	5.78
Prefrontal cortex	R	38	46	22	5.07
Medial parietal cortex	R	2	−60	42	5.6
Superior temporal gyrus	L	−60	−36	20	5.95
Superior temporal sulcus	L	−54	−30	2	5.79
Parieto-occipital sulcus	L	−2	−80	46	5.27
Thalamus (mediodorsal)	R	6	−20	8	> 8.0
Putamen	L	−20	2	12	5.92
Caudate	L	−16	0	16	6.88

All co-ordinates (in standard stereotactic space) refer to maximally activated foci as indicated by the highest *Z*-score within a cluster of activations. *x*, distance (mm) to right (+) or left (−) of midsagital line; *y*, distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; *z*, distance above (+) or below (−) the intercommissural (AC–PC) line. The AC–PC line is the horizontal line between the anterior and posterior commissures. All voxels are significant at $P < 0.05$ (corrected for multiple comparisons across whole brain). R, right; L, left; SMA, supplementary motor area.

Table 4

Subtraction analysis of differently activated areas after anodal and cathodal tDCS

		Talairach coordinates in MNI space			
Region	**Side**	***x***	***y***	***z***	***Z*-value**
(Anodal – sham) > (cathodal – sham)					
Post-central sulcus	R	40	−32	44	5.01
Dorsal premotor cortex	R	20	−14	64	6.48
Ventral premotor cortex	R	50	2	28	5.85
	L	−34	10	32	5.95
Cingulate sulcus	R	6	−8	42	6.51
Pre-SMA	L	−4	12	66	6.09
Prefrontal cortex	R	38	46	22	5.45
	L	−44	38	2	4.88
Inferior parietal cortex	R	52	−74	34	5.37
Intraparietal cortex	R	34	−70	28	4.88
Precuneus	R	10	−60	40	5.86
Superior temporal gyrus	L	−62	−36	22	5.31
Superior temporal sulcus	L	−56	−28	4	6.4
Inferior temporal sulcus	R	50	−50	−6	6.32
Superior occipital sulcus	L	−6	−82	44	6.16
Cerebellum (Crl)	R	50	−74	−42	5.29
Thalamus	R	12	−20	2	7.57
(Cathodal – sham) > (anodal – sham)					
Superior temporal gyrus	R	68	0	0	5.13
Superior temporal sulcus	R	62	−16	−8	5.5
	R	56	18	−22	4.95
Insula	R	44	2	−8	5.39
	R	12	70	16	5.49
Posterior cingulate gyrus	L	−8	−44	24	5.87
Inferior occipital lobe	R	30	−52	−8	6.18

All voxels are significant at $P < 0.05$ (corrected for multiple comparisons across whole brain). L, left; R, right; SMA, supplementary motor area.

Table 5

Conjunction analysis of commonly activated areas after anodal and cathodal tDCS

		Talairach coordinates in MNI space			
Region	**Side**	***x***	***y***	***z***	***Z*-value**
(Cathodal – sham) and (anodal – sham)					
Post-central gyrus	L	−56	−12	52	6.7
Deep central sulcus	R	30	−26	58	6.35
Frontopolar cortex	R	42	62	−8	7.01
Caudal cingulate sulcus	R	2	−18	48	5.89
Superior temporal sulcus	R	50	−32	4	5.09
Intraparietal sulcus	R	36	−84	40	6.01
Cuneus	L	−8	−86	18	5.56
Cerebellum (VI)	L	−22	−74	−20	5.07
	R	12	−82	−20	5.56
Cerebellar vermis		−2	−52	−18	5.75
(Sham – cathodal) and (sham – anodal)					
Medial prefrontal cortex	L	−2	36	50	6.45
	R	8	60	36	5.58
Anterior orbitofrontal cortex	L	−16	62	−14	5.92
	R	18	50	−18	5.62
Ventral premotor cortex	R	50	6	12	5.55
Cerebellum (IV)	R	16	−40	−16	5.76
Putamen	L	−22	8	10	6.08
Caudate head	L	−4	12	0	4.96

Voxels which are significant for the conjunction of (anodal vs. sham) and (cathodal vs. sham). All voxels are significant at $P < 0.05$ (corrected for multiple comparisons across whole brain). L, left; R, right.