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RESEARCH ARTICLE

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Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory

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Abstract Previous studies have claimed that weak transcranial direct current stimulation (tDCS) induces persisting excitability changes in the human motor cortex that can be more pronounced than cortical modulation induced by transcranial magnetic stimulation, but there are no studies that have evaluated the effects of tDCS on working memory. Our aim was to determine whether anodal transcranial direct current stimulation, which enhances brain cortical excitability and activity, would modify performance in a sequential-letter working memory task when administered to the dorsolateral prefrontal cortex (DLPFC). Fifteen subjects underwent a three-back working memory task based on letters. This task was performed during sham and anodal stimulation applied over the left DLPFC. Moreover seven of these subjects performed the same task, but with inverse polarity (cathodal stimulation of the left DLPFC) and anodal stimulation of the primary motor cortex (M1). Our results indicate that only anodal stimulation of the left prefrontal cortex, but not cathodal stimulation of left DLPFC or anodal stimulation of M1, increases the accuracy of the task performance when compared to sham stimulation of the same area. This accuracy enhancement during active stimulation cannot be accounted for by slowed responses, as response times were not changed by stimulation. Our results indicate that left prefrontal anodal stimulation leads to an enhancement of working memory performance. Furthermore, this effect depends on the stimulation polarity and is specific to the site of stimulation. This result may be helpful to develop future interventions aiming at clinical benefits.

Keywords Electrical stimulation · Prefrontal cortex · Transcranial magnetic stimulation · Working memory

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Introduction

Despite it being an old technique to stimulate the brain, not much is known about the behavioral effects of transcranial direct current stimulation (tDCS) in humans. Several animal studies carried out in the past (Bindman et al. 1964; Purpura and McMurtry 1965) showed that this method of brain stimulation has strong effects on brain activity and excitability. The recent development and the study of other methods of brain stimulation, particularly transcranial magnetic stimulation (TMS), have placed the tDCS in the research agenda of brain stimulation once more. Recently, a number of studies using tDCS in humans have been published (Nitsche and Paulus 2001; Nitsche et al. 2003a, b, 2004; Antal et al. 2004a). These studies have shown that this technique can be safely used in human beings.

In tDCS, the cerebral cortex is stimulated through a weak constant electric current in a non-invasive and painless manner. This weak current can induce focal changes of cortical excitability—increase or decrease depending on the electrode polarity—that lasts beyond the period of stimulation. Several studies have shown that this technique might modulate cortical excitability in the human motor cortex (Nitsche and Paulus 2000;

Rosenkranz et al. 2000; Baudewig et al. 2001) and visual cortex (Antal et al. 2001, 2004a). Recent studies have demonstrated a beneficial effect of excitability-enhancing anodal DC stimulation on simple reaction times and implicit motor learning when the primary motor cortex was stimulated (Nitsche et al. 2003c), as well as improved learning of a visuo-motor coordination task by stimulation of the primary motor area or the visual area V5 (Antal et al. 2004b). Moreover, frontopolar stimulation enhanced probabilistic classification learning (Kincses et al. 2004). Thus anodal tDCS appears to improve cognitive functions in humans, and it has been proposed that this cognition enhancement might be accomplished by its strengthening effects on glutamatergic synapses. The effects are particularly intriguing, given that subjects can indeed be blinded as to the nature of the stimulation, anodal, cathodal or sham, given the lack of associated perceptions. Therefore, the aim of the present investigation was to study the effects of tDCS on working memory, which can be considered a paradigmatic case of cognitive functioning.

Working memory refers to temporary storage and manipulation of the information necessary for complex tasks such as language comprehension, learning and reasoning. Neuroimaging studies have shown that prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) (Brodmann areas 9 and 46) plays a crucial role during working memory tasks (D'Esposito et al. 1998; Mottaghy et al. 2000). Studies using electroencephalogram (EEG) have demonstrated a theta coupling in the DLPFC during working memory tasks (Sauseng et al. 2004) and temporary disruption of the activity of the DLPFC by TMS that can lead to performance deterioration in different working memory tasks (Grafman et al. 1994; Pascual-Leone and Hallett 1994; Jahanshahi et al. 1998; Mottaghy et al. 2000; Mull and Seyal 2001). However, although these studies deliver convincing evidence that the DLPFC is involved in working memory, these techniques, in a strict sense, allow no definite conclusion about the specific involvement of this cortical area in these processes. For example, changes of brain activation and EEG modifications could be an epiphenomena and a disruption of cortical processing, as delivered by TMS, could diminish performance by disturbing working memory storage or just performance. Therefore, tDCS has an advantage over these techniques, as this method demonstrates a causal link between the stimulated area and behavior—which is deficient in neuroimaging studies—and does not disrupt cortical processing. Although tDCS does not have the same spatial resolution as TMS, the potential enhancement of cortical function by tDCS may provide further evidence of the association between the DLPFC and working memory, thus strengthening this relationship. In addition, an enhancement of working memory, although only short-lived and *on-line*, might provide insights that may lead to further studies of this technique exploring working memory function in healthy subjects and patients with disturbed working memory.

The aim of this study was to investigate the effects of anodal stimulation of the DLPFC on working memory. We postulated that the stimulation would improve task performance if the DLPFC is critically involved in working memory formation and a cortical activity enhancement is important for this process, as suggested by neuroimaging studies. Moreover, this study will be important to increase our knowledge about the behavioral effects induced by tDCS because this is the first study to test the effects of this stimulation technique on DLPFC function.

Materials and methods

Subjects

Fifteen healthy human subjects (11 females) were tested. The age range was 19–22 years (mean 20.2 years). All participants were right-handed. All subjects were college students, thus all shared the same level of education. Seven (six females) out of these 15 subjects participated in an additional control experiment. Subjects gave informed consent and the local Human Subjects Review Committee approved the study, which was conducted in strict adherence to the Declaration of Helsinki.

Direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. To stimulate the DLPFC, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrode placement. This method of DLPFC localization has been used before in TMS studies (Gerloff et al. 1997; Rossi et al. 2001), and has been confirmed as a relatively accurate method of localization by neuronavigation techniques (Herwig et al. 2003). The cathode was placed over the contralateral supraorbital area. Although neuroimaging (D'Esposito et al. 1998; Smith and Jonides 1999) and TMS studies (Mottaghy et al. 2000) have demonstrated that right and left DLPFC are involved in working memory paradigms, we decided to focus our investigation on the left DLPFC, as the modulation of this area by rapid repetitive transcranial magnetic stimulation (rTMS) (*off-line* rTMS) can cause an improvement in some aspects of the cognitive function in patients with major depression (Padberg et al. 1999; Moser et al. 2002; Martis et al. 2003) and Parkinson's disease (Boggio et al. 2005). Therefore, we planned to test if *on-line* tDCS can also improve one aspect of the cognition, working memory, in normal subjects. For the control experiment, the position of electrodes was changed (see "Control experiment"). A constant current of 1 mA intensity was applied for

10 min. Subjects felt the current as an itching sensation at both electrodes at the beginning of the stimulation. For sham stimulation, the electrodes were placed in the same position; however, the stimulator was turned off after 5 s as previously described (Siebner et al. 2004). Therefore, the subjects felt the initial itching sensation in the beginning, but received no current for the rest of the stimulation period. This procedure allowed to blind subjects for the respective stimulation condition (Nitsche et al. 2003a).

Working memory assessment

We used the three-back letter working memory paradigm described elsewhere (Mull and Seyal 2001). Subjects were presented with a pseudo-random set of ten letters (A–J). The stimuli were generated using the Superlab pro v2.0 software (Cedrus Corporation, San Pedro, Calif., USA). Each letter was displayed on computer monitor for 30 ms. A different letter was displayed every 2 s. Black letters were presented on a white background and subtended 2.4 cm (when viewed at 50 cm). Subjects were required to respond (key press) if the presented letter was the same as the letter presented three stimuli previously (Fig. 1). In this test, a total of 30 correct responses were possible. In each set of this task, the targets could be separated by three to five letters. Subjects were allowed to practice the task for 20 min or until they obtained an accuracy of ≥50%.

Experimental protocol (main experiment)

Following a first practice run, subjects were tested during sham and active stimulation. Since the test run lasted 5 min, it was delivered during the last 5 min of active and sham stimulation (Fig. 2). The two test runs differed in the order of the letters and were randomized across subjects to avoid difficulty bias. To avoid carryover effects, the order of active versus sham stimulation was fully counterbalanced across subjects, such that seven subjects received first active stimulation and eight subjects received first sham stimulation. In addition, each condition was separated by at least 1 h to washout the effects of the previous run. Subjects could not distinguish between real and sham stimulation as they felt the initial itching in both conditions.

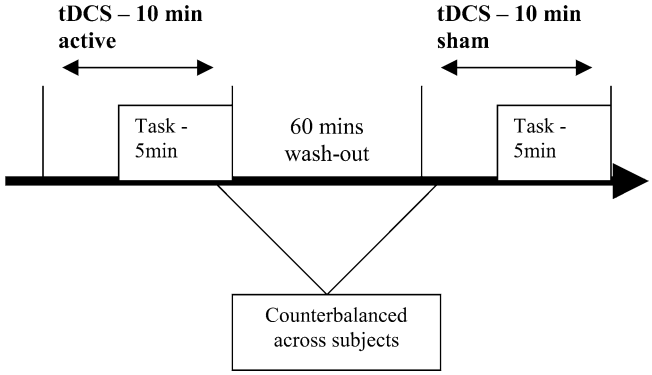

Fig. 2 The experimental protocol design. Each subject was tested during sham and active stimulation. The two tests runs were randomized within subject and the order (active versus sham stimulation) was counterbalanced across subjects

Control experiment

In order to test if the anodal stimulation of the left DLPFC was indeed responsible for the observed effects, seven out of the 15 subjects that participated in the main experiment were enrolled in a control experiment. This control experiment was carried out 6 months after the main experiment. In this control experiment, we tested: (1) whether the effects of the tDCS on DLPFC were focal and (2) whether the effects of tDCS on DLPFC were dependent on polarity (anodal versus cathodal stimulation).

To test aim (1) (focality of tDCS), subjects underwent an identical study protocol; however, with the anodal electrode placed over the primary motor cortex (M1)

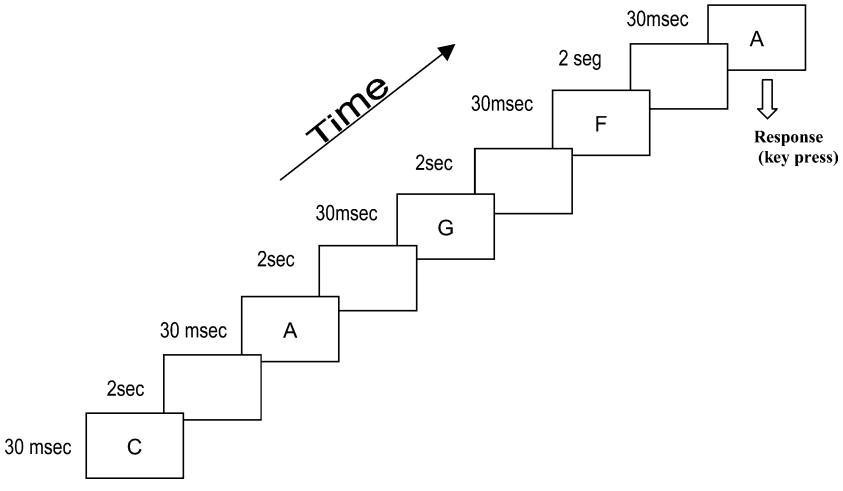

Fig. 1 The sequence of the 3-back letter working memory paradigm. Note that subjects were required to respond (*key press*) if the presented letter was the same as the letter presented three stimuli previously

rather than left DLPFC. The cathodal electrode was again placed on the right supraorbital area. To test aim (2) (polarity of tDCS), the same experimental design as in the main experiment was used, however, with inverted electrode polarity. The anode was placed over the right supraorbital area and the cathode over the left DLPFC.

These subjects also underwent sham tDCS. Therefore, in the control experiment, three different types of stimulation (anodal M1 stimulation, cathodal left DLPFC stimulation and sham stimulation) were applied. We used the same experimental design: 10 min of 1 mA of tDCS (*on-line* test in the final 5 min of stimulation). The order of these three conditions was randomized and counterbalanced across subjects. The washout period was 1 h.

Data analysis

The primary outcomes for this study were number of correct responses, false alarms (errors) and response time during active compared to sham stimulation. Analyses were done with SAS statistical software (version 8.0, Cary, N.C., USA). We used the Shapiro-Wilk test to evaluate whether the data were normally distributed. The results from this test for the data from reaction time ($W = 0.94$, $P = 0.39$), correct answers ($W = 0.89$, $P = 0.08$) and errors ($W = 0.91$, $P = 0.11$) show that the null hypothesis (sample is taken from a population with normal distribution) should not be rejected; therefore these data are normally distributed. Assuming normal distribution, paired Student's *t*-test was used to compare each pair of results (response time, number of errors and correct answers). Paired *t*-test, rather than two independent samples *t*-test, was used as data are dependent—each subject was measured after two different interventions (active and sham stimulation). Repeated measures of analysis of variance (ANOVA) was performed to investigate if there was an order effect between sham and active stimulation. This two-way ANOVA assessed the main effect of type of stimulation (active versus sham) and order of stimulation (active first or sham first). Statistical significance refers to a two-tailed *P*-value < 0.05.

Results

All subjects completed the entire experiment. One important observation is that there were no side effects observed throughout the experiment. All subjects tolerated the treatment well, and there was no complaint of pain or any uncomfortable symptom during the stimulation. All subjects reported that they could not feel the difference between the active and sham conditions and forced guessing was at chance level.

Correct responses (main experiment)

Subjects had significantly more correct answers during active condition when compared to the sham stimulation ($t = 3.4$, $df = 14$, $P = 0.0042$). The mean number of correct responses during the sham stimulation was 19.8 (± 5.8 SD) whereas the mean number of correct answers during active stimulation was 21.7 (± 5.0 SD), and the mean difference between these two types of stimulation was 1.92 (± 2.18 SD) (Fig. 3). In order to test if the order effect was significant, a two-way ANOVA (stimulation type versus order) was performed. This analysis disclosed that there was no order effect ($F = 1.77$, $df = 1,13$, $P = 0.21$), but only a stimulation effect ($F = 12.85$, $df = 1,13$; $P = 0.003$). This finding confirmed that the order of stimulation did not influence our results.

Errors (main experiment)

Subjects could make two types of errors when performing this task. They could either omit the correct response or press the response key at a wrong time. We used only this last variable—designated as false alarms—to compute total errors as omissions are implicitly analyzed under correct responses. This analysis showed that subjects made significantly more errors during sham condition when compared to the active stimulation ($t = 2.77$, $df = 14$, $P = 0.015$). The mean number of errors during the sham stimulation was 6.9 (± 6.1 SD), whereas

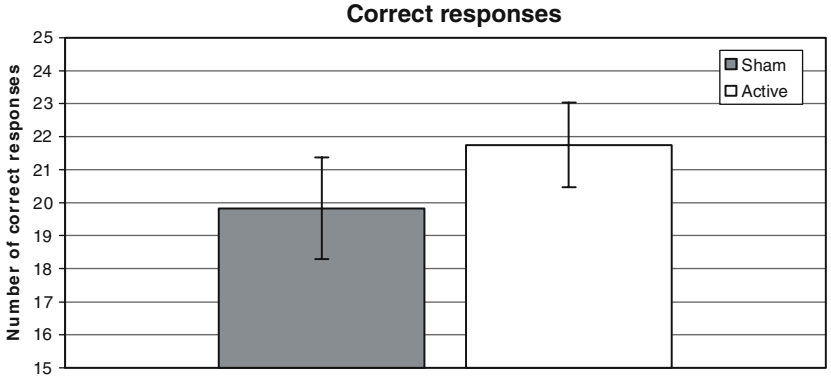

Fig. 3 Number of correct responses during each stimulation condition (active and sham). *Dark bar* indicates mean number of correct responses during sham stimulation. *White bar* represents mean number of correct responses during active stimulation. There was a significant difference in the mean number of correct response between sham and active stimulation. *Error bars* indicate $\pm$SEM (standard error of the mean)

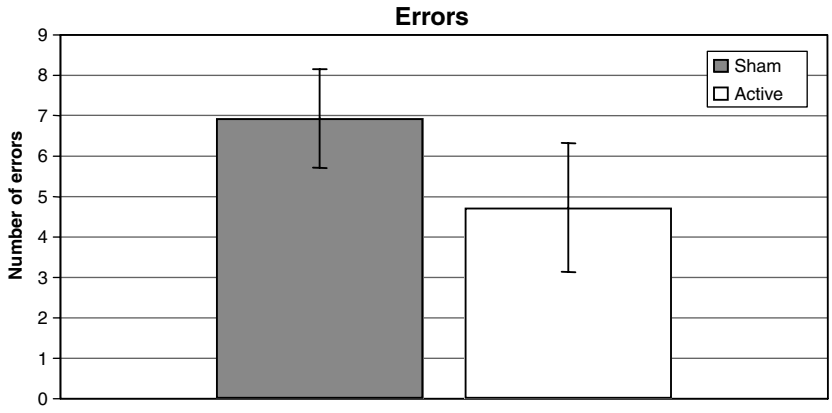

Fig. 4 Number of errors during each stimulation condition (active and sham). *Dark bar* indicates mean number of errors during sham stimulation. *White bar* represents mean number of errors during active stimulation. There was a significant difference in the mean number of errors between sham and active stimulation. *Error bars* indicate ±SEM (standard error of the mean)

the mean number of errors during active stimulation was 4.7 (±4.7 SD) and the mean difference between these two types of stimulation was 2.2 (±3.1 SD) (Fig. 4). In order to test if the order effect was significant, a two-way ANOVA (stimulation versus order) was performed. This analysis showed that there was no order effect ($F=0.88$, $df=1,13$, $P=0.36$), but only a stimulation effect ($F=7.93$, $df=1,13$; $P=0.014$). This finding confirmed that the order of stimulation did not influence our results. Indeed, Fig. 5 shows that subjects that received active stimulation first had larger improvement than subjects that received active stimulation second (although this difference was not significant). This result speaks against a carryover or learning effect.

Response time (main experiment)

There was no significant difference in the mean response time between the active and sham conditions ($t=0.04$; $df=14$; $P=0.97$). The mean response time during the active condition was 573.0 ms (±160.3 SD) whereas the mean response time during the sham condition was 572.4 ms (±126.7 SD) (Fig. 6).

Control experiment

To test if the effects of left DLPFC tDCS were focal, anodal stimulation of the primary motor cortex (M1) was performed. The results showed that there was no significant difference between anodal stimulation of the primary motor cortex and sham stimulation regarding number of correct response ($P=0.70$), errors ($P=0.46$) and reaction time ($P=0.71$) (Fig. 7).

In order to test if the effects of left DLPFC tDCS depend on polarity, we inverted the electrodes polarity: cathode electrode was placed over left DLPFC and anode electrode over the right supraorbital area. Similarly to the other control experiment, results from this stimulation revealed that there was no significant difference between cathodal stimulation of the left DLPFC and sham stimulation regarding number of correct response ($P=0.67$), errors ($P=0.64$) and reaction time ($P=0.72$) (Fig. 7).

Discussion

Our results indicate that anodal stimulation of the left prefrontal area increases the accuracy of the task

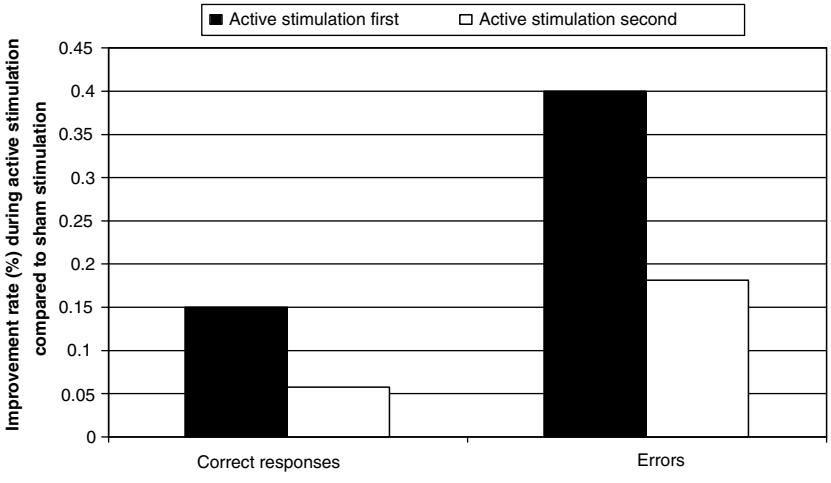

Fig. 5 This chart shows that subjects that received active stimulation first (*black column*) had larger improvement (compared to sham stimulation) than subjects that received active stimulation second (*white column*). However, this difference was not statistically significant

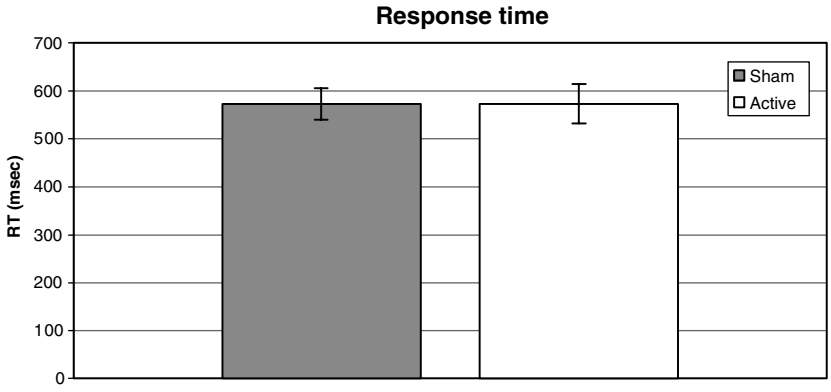

Fig. 6 Mean response time during each stimulation condition (active and sham). *Dark bar* indicates mean response time during sham stimulation. *White bar* represents mean response time during active stimulation. There was no significant difference in the mean response time between sham and active stimulation. *Error bars* indicate ±SEM (standard error of the mean)

performance when compared with sham stimulation of the same area. Furthermore, our control experiment showed that the effect of the anodal stimulation of the left DLPFC was relatively focal and depends on the polarity of stimulation. This accuracy enhancement during active stimulation cannot be accounted for by slowed responses, as response times were not changed by stimulation. These results showed that left prefrontal anodal stimulation leads to an enhancement of working memory performance.

It is interesting to note that opposite effects were demonstrated when the stimulation was performed with TMS. Although TMS can modulate the activity of a given cortical area, this technique transiently disrupts brain activity during the period of stimulation and hence creates a temporary "virtual lesion" (Pascual-Leone et al. 1999). Mull and Seyal (2001) and Mottaghy et al. (2000) showed that on-line single pulse TMS and 1 Hz-repetitive TMS, respectively, applied over the left DLPFC resulted in an increase of task errors compared to the control condition (Mottaghy et al. 2000; Mull and Seyal 2001). This degradation in task performance is likely related to transient disruption of the left DLPFC information processing caused by TMS. Opposed to these findings, the present study showed that tDCS causes no degradation in task performance during anodal stimulation. On the contrary, on-line anodal tDCS causes an enhancement in working memory. This observation is important as it might indicate that tDCS can stimulate the brain in a different way compared to TMS. The main characteristic that could underlay this difference is the amount of electric current involved in these two techniques. While TMS is likely to elicit neuronal depolarizations and induction of action potentials, tDCS as applied here only causes a slight change in the resting potential of the stimulated cells (Creutzfeldt et al. 1962), and thus may not disrupt but rather improve information processing by bringing neurons closer to depolarization thresholds in response to appropriate inputs.

The results of this study underscore the importance of cortical excitability and activity enhancements for working memory function, as suggested by previous functional imaging studies. Moreover, since accuracy, but not response times, differed between the stimulation conditions, the results are in accordance with a critical role of the DLPFC in working memory formation rather than simply task execution.

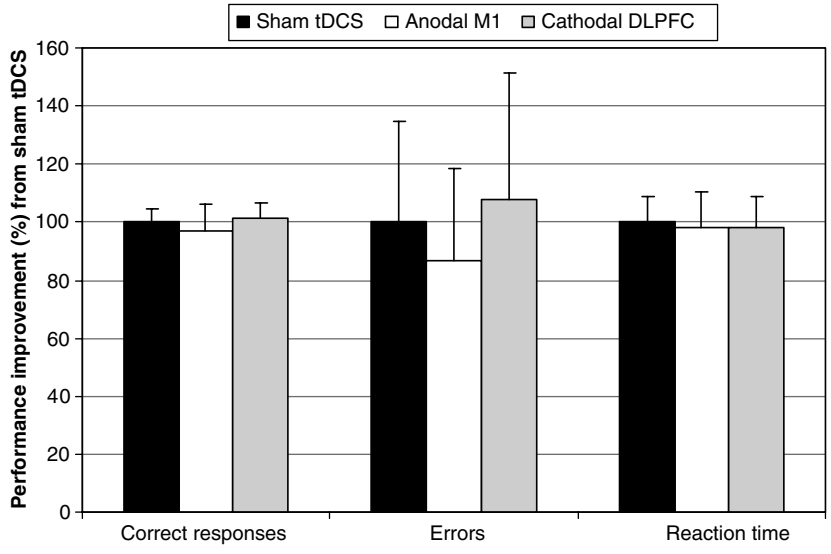

Fig. 7 Results from the two control experiments. Normalized average performance of working memory during sham, anodal primary motor cortex (*M1*) and cathodal left dorsolateral prefrontal cortex (*DLPFC*) stimulation with tDCS. Normalized values were obtained setting the performance during sham tDCS to 100((*black column*). There was no significant difference in working memory performance during either anodal M1 (*white column*) or cathodal DLPFC (*gray column*) stimulation when compared with sham stimulation (*black column*). *Error bars* indicate SEM (standard error of the mean)

The results of this study extend the findings of a previous investigation that showed a modification of implicit probabilistic classification learning by weak anodal tDCS (Kincses et al. 2004). It appears that tDCS may be an interesting tool to enhance some aspects of cognition. One important issue to consider is a possible carryover effect. It has been demonstrated that the effects of 11 min of 1.0 mA tDCS of the motor cortex can shift excitability for up to 60 min (Nitsche and Paulus 2001). We allowed for at least 1 h of washout period between test conditions, but the effects of tDCS on the prefrontal cortex might last longer than those on motor cortex. However, we counterbalanced stimulation conditions across subjects, and failed to observe order effects. In addition, subjects that received tDCS first had larger improvement, though not significant, compared to the group of subjects that received tDCS second, indicating that carryover and learning effects were not likely responsible for the results. If there was carryover or learning effect, we would expect an opposite effect: the task performance during sham tDCS when performed after active tDCS (active tDCS first) would have been similar or even larger than during active tDCS. Another important concern is a potential learning effect as the task was given repeatedly and a learning curve could distort the results. We addressed this issue allowing the subjects to practice the test. In addition, we compared the difference in the performance between sham and active stimulation. As these two conditions were counterbalanced, a learning effect would have affected both groups to a similar extent.

It has been shown that the effect of tDCS on brain activity seems to depend on the stimulation polarity, i.e. whereas anodal stimulation hyperpolarizes brain tissue, cathodal stimulation has the opposite effect (Nitsche et al. 2003a). Our control experiment confirms behaviorally that the effects of tDCS depend on polarity. While anodal stimulation of the DLPFC enhanced working memory, cathodal stimulation of the same area caused no changes. However, according to the anodal/cathodal opposite effects, we would expect worsening of working memory after cathodal stimulation. Nevertheless, we only observed a significant effect related to anodal stimulation. We speculate that the lack of effects of cathodal stimulation may be explained by two factors. First, the sample size of the control experiment was small, although there was not even a statistical trend that could suggest a possible effect masked by the small sample size. Second, our test may not have been adequate to detect behavior worsening.

Because the technique of tDCS uses large electrodes (35 cm^2) and the electric current passes throughout the brain, one can argue that the tDCS effects on the left DLPFC might be diffuse and involve a larger area of the left hemisphere. However, our control experiment revealed that the effects of tDCS were relatively focal. Anodal stimulation of the primary motor cortex did not cause any significant effect on working memory. Due to the fact that we maintained the cathodal electrode over the right supraorbital area, this finding also ruled out the alternative explanation that cathodal stimulation to the right frontopolar cortex accounts for the working memory improvement, unless the anodal stimulation of the left primary motor cortex was worsening working memory (and thus counterbalancing the effects of cathodal stimulation of supraorbital area); however, this explanation is improbable, because it is unclear how such an inhibition of neural activity of the motor area would lead to working memory impairment. This finding is also in accordance with the study of Uy and Ridding (2003). In this study, the effects of tDCS on the motor cortex had a remarkably good spatial resolution: anodal stimulation to the motor cortex representation of the FDI (first dorsal interosseous) muscle did not produce any effect in nearby muscles such as ADM (abductor Digiti Minimi) and FCU (Flexor Carpi Ulnaris) (Uy and Ridding 2003). However, this study shows the effects for the motor cortex, and thus the same specificity may not automatically be transferred to the dorsolateral prefrontal cortex.

One important methodological consideration should be entertained. Our findings could have been further validated by varying the working memory load (modifying the *n* in the *n*-back task). We decided to use a more challenging three-back task (Mull and Seyal 2001), because the degree of difficulty of a test is related to the likelihood to detect degradation or improvement in the brain function following tDCS. An easier task might not have detected subtle behavioral effects due to "ceiling" effect, while a more difficult version may have obscured performance disruption due to the "floor" effect. Testing different working memory load in the same task (as in a traditional Sternberg paradigm) would have increased the duration of the stimulation, possibly raising safety concerns. Safety studies to date have only evaluated the effects of less than 10 min of tDCS.

The results of the present study indicate that working memory performance, in a sequential-letter-matching task, is enhanced by anodal tDCS of the left prefrontal cortex. Although the aim of this study was not to explore the therapeutic effects of tDCS on working memory, these results should encourage further investigations for the use of tDCS in clinical applications.

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