Bidirectional Modulation of Primary Visual Cortex Excitability: A Combined tDCS and rTMS Study

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PURPOSE. In the motor cortex (M1), transcranial direct current stimulation (tDCS) can effectively prime excitability changes that are evoked by a subsequent train of repetitive transcranial magnetic stimulation (rTMS). The authors examined whether tDCS can also prime the cortical response to rTMS in the human visual cortex.

METHODS. In nine healthy subjects, the authors applied tDCS (10 minutes; ±1 mA) to the occipital cortex. After tDCS, they applied a 20-second train of 5 Hz rTMS at 90% of phosphene threshold (PT) intensity. A similar rTMS protocol had previously demonstrated a strong priming effect of tDCS on rTMS-induced excitability changes in M1. PTs were determined with single-pulse TMS before and immediately after tDCS and twice after rTMS.

RESULTS. Anodal tDCS led to a transient decrease in PT, and subsequent 5 Hz rTMS induced an earlier return of the PT back to baseline. Cathodal tDCS produced a short-lasting increase in PT, but 5 Hz rTMS did not influence the tDCS-induced increase in PT. In a control experiment on four subjects, a 20-second train of occipital 5 Hz rTMS left the PT unchanged, whereas a 60-second train produced a similar decrease in PT as anodal tDCS alone.

CONCLUSIONS. Compared with previous work on the M1, tDCS and rTMS of the visual cortex only produce short-lasting changes in cortical excitability. Moreover, the priming effects of tDCS on subsequent rTMS conditioning are relatively modest. These discrepancies point to substantial differences in the modifiability of human motor and visual cortex. (Invest Ophthalmol Vis Sci. 2007;48:5782–5787) DOI:10.1167/iovs.07-0706

Transcranial direct current stimulation (tDCS) applied through the skull can directly modulate the excitability of the human motor, somatosensory, and visual cortices. Usually, in the underlying cortex cathodal, stimulation induces excitability diminution while anodal stimulation results in excitability enhancement. If the direct current (DC) is applied long enough (more than 5 minutes), the effects can persist for up to hours after the current is switched off. Although the precise physiological mechanisms that cause these aftereffects are still relatively unclear, the tDCS-induced aftereffects have been shown to be affected by drugs that change neuronal membrane excitability or N-methyl-D-aspartate receptor efficacy.

Another method for noninvasive brain stimulation is transcranial magnetic stimulation (TMS), which has been widely used to explore neuronal plasticity in the human cerebral cortex. When trains of magnetic pulses are given to a cortical area, repetitive TMS (rTMS) can induce short-term functional reorganization. This has been shown for rTMS of the primary motor cortex (M1) by measuring the amplitude of the motor evoked potential (MEP) in contralateral hand muscles before and after rTMS conditioning. Low-frequency rTMS over the M1 at frequencies of approximately 1 Hz can produce a lasting inhibition of intracortical and corticospinal excitability, whereas high-frequency rTMS at 5 Hz or higher tends to induce facilitation. Focal TMS of the visual cortex can also induce changes in cortical excitability. These changes in excitability can be assessed by measuring the threshold for eliciting phosphenes or by measuring TMS-induced changes in visual perception. Low-frequency rTMS over the occipital cortex provokes an increase in phosphene threshold (PT) and contrast threshold. However, the aftereffects of high-frequency rTMS on PT and contrast threshold have not been systematically tested. When rTMS was given as a short train over the occipital cortex, the threshold current necessary to produce phosphene during the train decreased as frequency of stimulation increased. This suggests that high-frequency rTMS may also produce a decrease in PT beyond the stimulation itself.

The threshold and direction of excitability changes that can be induced by low- and high-frequency rTMS in the M1 can be effectively primed by a preceding session of tDCS. A 20-second train of 5 Hz rTMS given at an intensity of individual active motor threshold did not change corticospinal excitability as determined by TMS-evoked MEP but did reduce M1 excitability if it was preceded by facilitatory anodal tDCS, and it enhanced excitability if it was preceded by inhibitory cathodal tDCS. Similar effects could be observed with 1 Hz rTMS. It is thought that these effects occur on the cortical level because evidence suggests that neither tDCS nor rTMS of short duration, and given at subthreshold intensities, changes the excitability of subcortical or spinal structures. The pattern of excitability changes induced by combining tDCS and rTMS was interpreted in the context of homeostatic plasticity in the human cerebral cortex that keeps plastic changes within a physiologically useful range and allows for network stability.

In the visual cortex, a similar pattern has been demonstrated only in the context of light deprivation, where the modulatory effects of different rTMS frequencies on visual cortex critically depended on the preexisting excitability state. Using the same experimental design as in our previous study, the aim of the present study was to explore whether a preceding tDCS session can also prime the response of the...
human visual cortex to 5 Hz rTMS conditioning. To this end, we preconditioned the visual cortex with anodal or cathodal tDCS. tDCS was followed by a short train of 5 Hz rTMS to the visual cortex. Changes in PT were assessed with single-pulse TMS to probe stimulation-induced shifts in occipital excitability.

**Subjects and Methods**

**Subjects**

The study involved 13 healthy subjects (mean age, 28 years; range, 23–45; four men), all of whom were familiar with tDCS, rTMS, and the perception of phosphenes induced by TMS from previous experiments and who fulfilled the following criteria: no history of neurologic or psychiatric disorders, no metallic implants or electrical devices in the head, no medication, no substance abuse. Subjects were interviewed about their medical history and were clinically examined before participating in the experiments. All subjects gave their written informed consent in accordance with the Declarations of Helsinki, and the Ethics Committee of the University of Göttingen approved to the study.

**Main Experiment**

Nine subjects (mean age, 29 years; range, 23–45 years; three men) participated in the main experiment. Figure 1 illustrates the time line of the experimental procedures. The main experiment consisted of five sessions. In separate sessions, we applied different interventional protocols: anodal tDCS followed by real rTMS, cathodal tDCS followed by real rTMS, sham tDCS followed by real rTMS, anodal tDCS followed by sham rTMS, and cathodal tDCS followed by sham rTMS. Consecutive sessions were separated by at least 1 week, and the order of interventional protocols was pseudorandomized and balanced across subjects. Using single-pulse TMS, PT was determined before (baseline), immediately after tDCS, immediately after rTMS, and 5 and 15 minutes after rTMS.

**Determination of Phosgene Threshold**

PTs were determined using single-pulse TMS with biphasic pulses and a slightly bent standard figure-of-eight coil (MC-B70; Medtronic, Fridley, MN) connected to a stimulator (MagPro; Medtronic Functional Diagnostics, Skovlund, Denmark). The coil was placed over the occipital cortex, approximately 2 to 4 cm above the inion. The current direction in the coil was away from the handle, with the handle of the coil pointing upward (Fig. 1). At this orientation, the first phase of the transcranial stimulus induced a caudocranial current flow in the visual cortex. This orientation of the coil was maintained throughout the experiments. Single pulses were applied initially with 50% maximum stimulator output. If the subject did not perceive a phosphene in more than 5 of 10 trials at 50% of maximum stimulator output, the intensity was increased in increments of 5% until the subject perceived a phosphene, maximally up to 80% of maximum stimulator output. If the subject still did not perceive a phosphene, the coil was moved 1 cm up or 1 cm left or right and the procedure was repeated.

Once the participant reliably perceived a phosphene and the phosphenes appeared in the same form at the same location, stimulation intensity was reduced in increments of 5% of maximal stimulator output until the phosphenes were no longer perceived. Then stimulus intensity was increased in 1% increments of maximal stimulator output until the subject reliably perceived a phosphene that had the same form and appeared at a constant location within the visual field. This intensity was defined as PT. The position of the coil on the head was marked with a pen to ensure identical positioning throughout the session.

**Repetitive Transcranial Magnetic Stimulation**

Real rTMS consisted of 100 biphasic pulses given at a constant rate of 5 Hz (20 seconds). The intensity of real rTMS was set at 90% of the individual PT. The stimulating device, coil position, and pulse form were identical to those used for determining the PT with single-pulse TMS. Sham rTMS was applied through a specially designed sham coil from the same manufacturer, which produced auditory stimulation without inducing magnetoelectric stimulation.

**Transcranial Direct Current Stimulation**

We applied tDCS using a battery-driven constant current stimulator (Schneider Electronic, Gleichen, Germany) and a pair of electrodes in two 5 × 7-cm water-soaked synthetic sponges. For cathodal stimulation, the cathode was placed at Oz and the anode over Cz (according to the international 10–20 system). For anodal stimulation, the current flow was reversed. In the real tDCS conditions, direct current was transcranially applied for 10 minutes with an intensity of 1 mA, and constant current flow was measured by an amperemeter. For sham tDCS, the current was turned on for only 5 seconds at the beginning of the sham session and then was turned off in a ramp-shaped fashion. This induces skin sensations indistinguishable from real tDCS.

**Control Experiment**

In four subjects who had also participated in the main experiment (mean age, 31 years; range, 23–45 years; 1 man, 3 women), we examined the effect of a prolonged rTMS. In this control experiment, sham tDCS was followed by a 5 Hz rTMS train that consisted of 100 or 300 biphasic pulses at 90% of the individual PT. Apart from the modified tDCS protocol, experimental procedures were identical with the main experiment.

**Statistical Analysis**

Analysis of variance (ANOVA) was used to test for differences in PT. Individual PT values were normalized to baseline and entered into a two-factorial ANOVA with the factors type of stimulation (five levels: anodal tDCS followed by real rTMS, cathodal tDCS followed by real rTMS, sham tDCS followed by real rTMS, anodal tDCS followed by sham rTMS, cathodal tDCS followed by sham rTMS) and time (four levels: after tDCS, immediately after rTMS, 5 minutes after rTMS, and 15 minutes after rTMS). A two-factorial ANOVA was also used to assess changes in individual PT during the control experiment. This ANOVA model included the factor type of stimulation (two levels: sham tDCS and real tDCS).
followed by a 100-pulse train of real rTMS, sham tDCS followed by a 300-pulse train of real rTMS) and time (four levels as in the main experiment). Conditional on significant F values in the ANOVA, two-tailed paired-samples t-tests were used to characterize the main effects or interactions as revealed by the ANOVA. Pearson correlation coefficient was used to examine the relationship between the initial states of visual cortex excitability (baseline PT) and PT changes induced by tDCS and rTMS, respectively, and between PT changes induced by tDCS and subsequent rTMS. \( P < 0.05 \) was considered significant. Data are given as mean ± SEM.

**RESULTS**

None of the subjects reported any adverse effects during or after the experiments. Neither tDCS nor rTMS induced phosphene. Figures 2 and 3 illustrate the effects of tDCS and rTMS on mean PTs. For the main experiment, ANOVA revealed an interaction between type of stimulation and time (\( F(4, 29) = 2.964; \ P = 0.039 \)). Anodal tDCS produced a consistent decrease in mean PT (Fig. 2A). The decrease in PT was comparable in the two sessions during which anodal tDCS was given (9.9% in the condition anodal tDCS followed by real rTMS [\( P = 0.010 \)] and 11.7% in the condition anodal tDCS followed by sham rTMS [\( P = 0.014 \)]. If anodal tDCS was followed by sham rTMS, the decrease in PT was still present immediately after rTMS (\( P = 0.006 \)) but not at later time points. If real rTMS was applied after anodal tDCS, the decrease in PT was antagonized by rTMS. In contrast to sham rTMS, mean PT had already returned to baseline levels immediately after real rTMS. For the first measurement after rTMS, a post hoc comparison confirmed a difference in mean PT between the two sessions with anodal tDCS (Fig. 2C): immediately after rTMS, there was a relative increase in mean PT after anodal tDCS followed by real TMS compared with mean PT after anodal tDCS followed by sham rTMS (\( P = 0.038 \)).

After cathodal tDCS (Fig. 2B), mean PTs were increased by approximately 6% to 8% compared with baseline (6% in the condition cathodal tDCS followed by real rTMS [\( P = 0.016 \)] and 7.9% in the condition cathodal tDCS followed by sham rTMS [\( P = 0.038 \)].) This increase in PT was transient and had already returned to the baseline level immediately after the application of the 5 Hz rTMS, irrespective of whether cathodal tDCS was followed by real or sham rTMS. When real rTMS was given after sham tDCS, PTs were not influenced by real rTMS, and PTs remained stable throughout the session.

In the control experiment, ANOVA revealed a type of stimulation \( \times \) time interaction (\( F(2, 0.0) = 2.346; \ P = 0.014 \)). Real rTMS produced a consistent reduction in PT if 5 Hz rTMS was given for 60 seconds (300 pulses) but not after a short 20-second train (100 pulses) of rTMS (Fig. 3). Compared with the mean PT at baseline, post hoc t-tests revealed a mean decrease in PT of 8.5% immediately after rTMS (\( P = 0.029 \)) and of 5.4% 5 minutes after rTMS (\( P = 0.029 \)), whereas PT had returned back to baseline PT 15 minutes after rTMS.

Correlation analyses revealed no significant correlation between the initial states of visual cortex excitability, as indexed by the PT at baseline and changes induce by tDCS (main experiment) or rTMS (control experiment). Regarding PT changes induced by tDCS and subsequent rTMS, we found a weak trend for a significant inverse correlation in the anodal tDCS condition (Pearson correlation coefficient, \( r = -0.584; \ P = 0.099 \)) but not for the cathodal condition.

**DISCUSSION**

Using phosphene thresholds as an index of regional excitability, we found that tDCS and rTMS of the visual cortex only produced transient changes in the excitability of the occipital visual cortex. The priming effects of tDCS on rTMS conditioning were modest. Anodal tDCS primed the cortical response of the visual cortex to a short train of low-intensity 5 Hz rTMS. Anodal rTMS had a short-lasting increase in PT, whereas the same 20-second train after sham TMS produced no change in PT. No priming effect was observed after cathodal tDCS. We interpret the present findings in the context of previous work on the conditioning effects of tDCS and rTMS on motor cortex excitability and consider the implications of our results for experimental and therapeutic studies on visual cortex excitability in healthy subjects and patients.

When anodal tDCS was given alone, it reduced PTs for several minutes, indicating a transient increase in excitability of the visual cortex. Cathodal TDCS alone had the opposite effect because it reduced cortical excitability indicated by an increase in PT. These findings replicate previous findings that tDCS can have bidirectional effects on visual cortex excitability and that the sign of the excitability change critically depends on the polarity of stimulation. Of note, the conditioning effects of TDCS on PT quickly returned to the baseline level. Overall, the changes in excitability only lasted minutes. This is in contrast to the duration of the aftereffects on the MEP amplitude that can be observed after 10 minutes of tDCS to the M1, suggesting that, at least for tDCS, the persistence of the conditioning effects may differ across cortical areas.

A new finding was that 60 seconds of low-intensity 5 Hz rTMS induced a short-lasting decrease in PT after the end of stimulation, whereas a 20-second train had no consistent effects on PT. Given that low-frequency rTMS over the occipital cortex increases the PT\(^{25}\) and contrast threshold,\(^{19}\) we infer that rTMS of the occipital visual cortex can also produce a bidirectional change in regional excitability. Analogous to the response pattern found in the M1,\(^{13}\) the direction of the aftereffects appears to depend on the frequency of rTMS, with high-frequency rTMS causing an increase in excitability and low-frequency rTMS reducing it.

Our main interest, however, focused on those sessions during which tDCS was followed by rTMS. Here the critical question was whether tDCS would be able to prime the response to the subsequent rTMS session. In a previous study, we found that preconditioning with tDCS sensitized M1 to high-frequency rTMS and controlled the direction of the aftereffects on motor cortical excitability M1.\(^{23}\) A 20-second train of 5 Hz rTMS at active motor threshold to the left M1 was preconditioned by 10 minutes of anodal, cathodal, or sham TDCS. Single-pulse TMS revealed that 5 Hz rTMS given after sham TDCS failed to produce any aftereffect, whereas 5 Hz rTMS led to a marked shift in corticospinal excitability when given after effective TDCS. The direction of rTMS-induced excitability changes in M1 depend on the polarity of TDCS conditioning, counteracting the excitability shift induced by TDCS priming. These preconditioning effects of TDCS indicate the existence of a homeostatic mechanism in the human motor cortex that keeps corticospinal excitability within a physiologically useful range.\(^{23,24}\)

In contrast to our previous study,\(^{25}\) the same interventional protocols, if applied to the visual cortex, only indicated a modest priming effect of anodal TDCS, whereas we found no priming effect of cathodal TDCS on the threshold and direction of rTMS-induced aftereffects on mean PT. The 20-second train of 5 Hz rTMS induced a short-lasting increase in PT when rTMS was preceded by anodal TDCS. Though the priming effect of anodal TDCS was short-lasting and modest in size, the pattern was analogous to the homeostatic priming effect induced by anodal TDCS on 5 Hz rTMS in M1. First, anodal TDCS increased the efficacy of subsequent rTMS to change the PT because the
20-second train of 5 Hz rTMS, when preceded by sham tDCS, had no consistent effect on PTs. Second, the “normal” direction of a 5 Hz rTMS-induced PT change was flipped by priming with anodal tDCS. The control experiment revealed that a prolonged (60-second) train of 5 Hz rTMS without tDCS priming produced a decrease in PT. Despite the general facilitatory nature of 5 Hz rTMS, the 20-second train of 5 Hz rTMS exerted an inhibitory effect after preconditioning with anodal tDCS. In other words, when given at an enhanced level of cortical excitability (i.e., after anodal tDCS), 5 Hz rTMS now antagonizes the recently induced enhancement in excitability and shortens the duration of the facilitatory aftereffect induced by anodal tDCS. A notable difference between the response pattern found in M1 and visual cortex is that, in contrast to the excitability changes found in the M1, 5 Hz rTMS to the visual cortex only normalized the tDCS-induced increase in excitability but did not reduce visual cortex excitability below the baseline level.

At first glance, the absence of any priming effect after cathodal tDCS and the weak priming induced by anodal tDCS seem to indicate that the homeostatic mechanisms regulating cortical excitability in the motor and visual cortex are substantially different. For instance, it is conceivable that in the visual cortex, homeostatic priming effects have a higher threshold than in M1. An alternative interpretation is that the homeostatic mechanisms are rather similar but the tDCS priming protocol was less effective in the visual cortex to produce a shift in excitability that was sufficiently long enough to invoke homeostatic plasticity. Two pieces of evidence favor the latter hypothesis. First, 10 minutes of tDCS to visual cortex only produced a transient change in PT, whereas the same protocol given to M1 induced long-lasting shifts in cortical excitability. Therefore, it is conceivable that a stronger or longer tDCS

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**FIGURE 2.** Main experiment: stimulation-induced changes of phosphenal thresholds (PTs). The study design used a 5 × 4 model with the factors type of stimulation (five levels: anodal tDCS followed by real rTMS, cathodal tDCS followed by real rTMS, sham tDCS followed by real rTMS, anodal tDCS followed by sham rTMS, cathodal tDCS followed by sham rTMS) and time (four levels: after tDCS, immediately after rTMS, 5 minutes after rTMS, and 15 minutes after rTMS). The upper two panels show mean PT values (±SEM) after anodal or sham (A) and cathodal or sham (B) tDCS and rTMS as a percentage of baseline values. Significant differences compared with baseline are indicated by filled symbols (post hoc t-tests, P < 0.05). (C) PT value differences between conditions with real or sham rTMS for anodal and cathodal tDCS, respectively (normalized to the time point after tDCS). *Significant difference for anodal tDCS at time point after rTMS (post hoc t-test, P < 0.05).

**FIGURE 3.** Control experiment: decrease of mean PTs after prolonged 5 Hz rTMS with 300 pulses (60 seconds) but not after 100 pulses (20 seconds). Significant differences compared with baseline are indicated by filled symbols (post hoc t-test, P < 0.05).
protocol may be more effective in revealing a homeostatic priming pattern in the occipital cortex. Second, “facilitatory” 5 Hz rTMS did produce an inhibitory effect on visual cortex excitability when the excitability level was previously raised by anodal tDCS. This finding would be compatible with the hypothesis that the visual cortex can respond with a homeostatic-like response pattern, but the pattern was only mildly expressed because of the weak priming effect of tDCS. Hence, a useful approach for further experiments could be to optimize the tDCS conditioning protocol or to use different conditioning methods, such as voluntary system deactivation or another stimulation method such as rTMS.

Taken together, the occipital response patterns to tDCS and rTMS suggest that it is more difficult to induce stable changes in cortical excitability that resemble mechanisms similar to long-term potentiation (LTP) and long-term inhibition (LTD) in the visual cortex than in the M1. Anatomic and physiological differences between the two cortices may account for this discrepancy because the motor and visual cortices contain partly different types of neurons and neurotransmitters.30 Moreover, the primary visual cortex, which probably is the critical area for phosphene perception,31 is located in the depth of the interhemispheric fissure, whereas the primary motor hand area is situated at the surface of the hemispheric convexity. Therefore, the relative distance and orientation of intracortical and cortico-cortical axons with respect to the stimulating coil differ for the M1 and visual cortex, resulting in site-specific preferences to excite different neuronal populations within the cortical target area. Accordingly, it has been shown that TMS thresholds of visual cortex show no correlation with cortical motor thresholds obtained over the M1.32,33

Another important aspect that must be taken into account is that transcranial stimulation studies of M1 use the amplitude of the transcranially evoked motor potentials in the contralateral target muscle to probe changes in cortical excitability. MEP amplitude is an electrophysiological measure of the intracortical (mainly transsynaptic) excitability of corticospinal output neurons (i.e., pyramidal cells) provided that the excitability at the spinal level is not modulated by tDCS or rTMS. In contrast, the excitability of the visual cortex can only be probed psychophysically using the threshold for eliciting phosphenes with TMS. For this measure, it is unclear which cortical neurons must be excited to elicit a phosphene. It may be that TMS-induced action potentials in cortical afferents to the visual cortex and intracortical interneurons in the visual cortex are the primary neuronal substrate generating the percept of phosphenes rather than stimulation of output neurons. Of note, studies in the M1 usually failed to demonstrate marked conditioning effects after tDCS or rTMS if the cortical motor threshold is used as a marker of excitability.15,23 This begs the question whether the mean MEP amplitude might be a more sensitive measure to probe the priming effects of transcranial cortex stimulation than measurements of perceptive thresholds.

Finally, a substantial difference in the cortical activity level before, during, and after tDCS and rTMS might also contribute to the different functional responses of the M1 and visual cortex to transcranial conditioning. In previous studies that combined tDCS with rTMS of the M1,23,24 subjects were seated in a comfortable chair and the motor system was completely at rest. Thus, the level of intrinsic neuronal activity of the M1 was in a relative idling state at the time of transcranial conditioning. This was markedly different in the present study because, apart from the measurements of the PT, participants were studied with their eyes opened, indicating that the visual cortex was in an activated state during transcranial conditioning. We argue that the intrinsic neuronal activity in occipital cortex caused by the visual signals from the retina might have attenuated the efficacy of transcranial stimulation to induce LTP- or LTD-like plasticity in the visual cortex. Although rTMS acts on neuronal networks by directly inducing action potentials in cortical neurons, continuous tDCS is thought to cause a tonic shift in the intrinsic membrane potential of cortical axons. Therefore, the level of ongoing intrinsic neuronal activity in the stimulated neuronal networks may be more relevant to the conditioning effects of tDCS than of rTMS. Further studies are needed to explore in more detail how intrinsic neuronal processing in cortical systems shapes the responsiveness to tDCS and rTMS.

In conclusion, our results have important implications for the use of transcranial cortex stimulation to induce changes in cortical excitability in the human brain. The response pattern found in cortical area A may not apply to area B or area C. Intrinsic factors such as the level of neuronal activity at the time of stimulation or the presence of a specific neuropsychiatric disease and extrinsic factors such as the protocol used for tDCS and rTMS shape the regional responsiveness of a given cortical target area to rTMS and tDCS conditioning. A priming approach that probes the preconditioning effect of a first intervention on the functional aftereffects of a subsequent intervention is a powerful tool to probe metaplasticity34 in the intact human cortex, and it can promote understanding of how distinct areas control their regional level of excitability.

References


