Excitability Changes Induced in the Human Primary Visual Cortex by Transcranial Direct Current Stimulation: Direct Electrophysiological Evidence

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PURPOSE. Transcranial direct current stimulation (tDCS) has been shown to modify the perception threshold of phosphenes elicited by transcranial magnetic stimulation (TMS). The current study was undertaken to examine whether tDCS, when applied over the occipital cortex, is also able to affect visual-evoked potentials (VEPs), which characterize occipital activation in response to visual stimulation, in a polarity-specific way.

METHOD. For this purpose, VEPs evoked by sinusoidal luminance grating in an on/off mode were recorded before, immediately after, and 10, 20, and 30 minutes after the end of 5, 10, or 15 minutes of anodal or cathodal tDCS of the primary visual cortex.

RESULTS. Significant effects were observed only when low-contrast visual stimuli were applied. Cathodal stimulation decreased, whereas anodal stimulation increased the amplitude of the N70 component. The effect of cathodal stimulation was significant immediately after and 10 minutes after the end of stimulation, if the stimulation duration was sufficiently long (i.e., 10–15 minutes). An increase of N70 amplitude by anodal stimulation was significant only 10 minutes after the end of the 15 minutes tDCS. Cathodal stimulation tended also to affect the amplitude of the P100 component; however, the effect of stimulation was inverse. The amplitude increased immediately after the end of cathodal stimulation. In contrast, anodal stimulation did not affect the P100. The latencies of the N70 and the P100 were not affected by tDCS.

CONCLUSIONS. tDCS appears to be a suitable method of inducing reversible excitability changes in a polarity-specific way, not only in the motor but also in the primary visual cortex. The duration of the induced aftereffects depends not only on stimulation duration but also on stimulation polarity. Cathodal stimulation seems to be more effective, in line with previous reports on the motor cortex. (Invest Ophthalmol Vis Sci. 2004; 45:702–707) DOI:10.1167/iovs.03-0688

The use of visual evoked potentials (VEPs) has occupied the electrophysiological mainstream for evaluating visual cortical functions in humans. Pattern VEPs even became a routine diagnostic method in neurology setups, because its intraindividual stability allows the detection of several neurologic diseases affecting the visual pathway. The purpose of the present study was to test transcranial direct-current (tDCS)–generated visual excitability changes by recording VEPs in healthy humans.

Weak DC stimulation is a noninvasive method that offers the possibility of inducing prolonged excitability changes in the motor and visual cortices, as has been shown in several animal studies.1–3 These early studies revealed that cathodal tDCS reduces spontaneous firing rates of cortical cells, most likely by hyperpolarizing cortical neurons, whereas anodal stimulation results in a reverse effect.

Transcranial application of weak direct current in humans has been shown to modify motor cortex excitability in a polarity-specific way. Cathodal tDCS diminishes the amplitude of transcranial magnetic stimulation (TMS) elicited motor-evoked potentials (MEPs), whereas anodal stimulation increases it. These effects are in the range of 30% to 40% compared with baseline and not restricted to the duration of stimulation itself, outlasting it for up to an hour, given a sufficient stimulation intensity and duration.4–8

The number of studies applying tDCS over the human visual cortex is still limited; however, the modification of visual processing by tDCS is of particular importance, in that animal studies have demonstrated that tDCS could affect visual perception and discrimination9,10 and therefore tDCS could be a new tool for manipulating human visual cortical processing. In a previous study in humans it has been observed that tDCS modulates phosphene thresholds (PTs) evoked by short trains of TMS,11 which are indexes of visual cortex excitability. Reduced PTs were detected immediately and 10 minutes after the end of 10 minutes anodal stimulation, whereas cathodal stimulation resulted in the opposite effect.

Moreover, tDCS changes visual perceptual functions, as was shown by a study measuring static and dynamic contrast sensitivities (sCS and dCS, respectively).12 Significant sCS and dCS loss was found during and immediately after 7 minutes of cathodal stimulation, whereas anodal stimulation had no significant effect. These results reveal that elementary visual functions, such as contrast detection and phosphene perception, can be transiently altered by tDCS, most probably by modulating neural excitability, as has already been shown in the motor cortex. However, the duration of induced aftereffects was, so far, somewhat shorter than those measured by previous human studies stimulating the motor cortex. As a possible reason, the difference in methods should be considered. The measurements of CS and PT depend more on subjective parameters, such as the compliance of subjects and adaptation processes, than measurements of MEPs. The purpose of the present study was to measure the effects of tDCS on VEPs, and thus study the effects of tDCS on a more direct electrophysiological level, independent of psychophysical parameters. First, for exploring the most effective stimulation electrode position over the occipital areas, three different stimulating electrode positions were applied. It was found that the electrode position is critical in inducing tDCS-generated effects over the motor cortex.4–8 Second, we applied three different stimulation durations to determine whether the induced aftereffects depend on stimula-
literation duration, as was observed in the motor cortex.\textsuperscript{4–6} Third, we used low- and high-contrast visual stimuli to test whether the effect of tDCS depends on the kind of stimuli applied.

**METHOD**

**Subjects**

Altogether 20 healthy subjects participated in the study (mean age, 28.9 years; range, 20 - 43 ± 6.89 years; nine men). Ten of the subjects underwent repeated measurements and took part in all the experiments. They all fulfilled the following conditions: visual acuity better than 0.9, no metallic implants, and no prior history of any neurologic or psychiatric disorders, drug abuse, or alcoholism. The subjects were interviewed about their state of health and were not taking any medication at the time of the experiment. All the subjects gave their written informed consent. The study protocol conformed to the Declaration of Helsinki, and the Ethics Committee of the University of Göttingen approved the study.

**Stimuli**

Stimuli were generated with a VisionWorks (Durham, NH) system and presented on a high-resolution monitor (Sony, Tokyo, Japan). The stimuli were 4-cyc/deg sinusoidal luminance gratings presented at on-off mode on a display size of 784 × 1024 pixels. The stimulus presentation time was 333 ms followed by a 1000-ms interstimulus interval. During the off-phase the screen was blank at the mean luminance level. Two different contrast levels were used, a high (100%) and a low (50%) contrast pattern. The absolute luminance of the screen was 60 cd/m\textsuperscript{2}, and the background luminance was 8 cd/m\textsuperscript{2}. In each trial 50 high- and 50 low-contrast patterns were presented.

**VEP Recording**

VEPs were recorded on three channels (Oz, O1, and O2, according to the international 10-20 system), with a scanning system (Neuroscan SynAmp; NeuroSoft, Sterling, VA). The reference electrode was positioned at Fz, and the ground was placed on the forehead. The resistance of the electrodes was held constant below 10 kΩ. A 50 Hz notch filter, 0.05 Hz high-pass filter, and 70 Hz low-pass filter were used to control for 50 Hz, low- and high-frequency interference. Data were collected continuously and analyzed offline.

**Transcranial Direct Current Stimulation**

tDCS was delivered by a battery-driven constant-current stimulator (Schneider Electronic, Gleichen, Germany) using a pair of conductive rubber electrodes in a 5 × 7-cm water-soaked synthetic sponge. In experiment I, three different electrode montages were used: (1) One of the electrodes was placed over Oz, the other over Cz, and the polarity refers to Oz (Oz–Cz montage); (2) one of the electrodes was placed over O1 (left side), the other over O2 (right side), and the polarity refers to O2 (L01–RO2 montage); (3) one of the electrodes was placed over Oz and the other one over the left mastoid, and polarity refers to Oz (Oz–LM montage). Anodal and cathodal stimulations were applied for 10 minutes with an intensity of 1.0 mA in different experimental sessions in randomized order. In experiment II using only the Oz–Cz montage (which had been shown to be the effective one in experiment I), two additional stimulation durations were applied: the anodal and cathodal stimulation was given for 5 or 15 minutes. Constant current flow was measured by a voltmeter and controlled by the experimenter. Between each experimental session there was an interval of at least 1 week.

**Experimental Procedures**

The subjects were seated in a comfortable armchair in front of the stimulator monitor. The distance between the subject’s eyes and the monitor was 0.75 m. First the recording electrodes were placed on the scalp of the subject and the first trial was initiated. Baseline VEPs were recorded for 50 low- and 50 high-contrast stimuli. The tDCS electrodes were attached, and cathodal or anodal tDCS was performed. The stimulating electrodes were removed immediately after the end of stimulation. VEPs were measured immediately after and 10, 20, and 30 minutes after the end of 5 to 10 minutes of stimulation and additionally 60 minutes after the end of 15 minutes of stimulation. First, for 10 minutes of stimulation, three different electrode positions were tested to identify the optimal electrode position (experiment I). In a subsequent block of experiments, the dependency of the effects on stimulation duration was studied by applying 5 and 15 minutes of tDCS at only the optimal electrode position (experiment II). The different experiments were performed on the subjects on different days.

**Measurement and Analysis of the Data**

The raw data were baseline corrected (based on the 50-ms prestimulus interval) and averaged in the 100-ms prestimulus and the 1000-ms poststimulus intervals. The baseline-to-peak amplitudes and peak latencies of the on response N70 and P100 were analyzed. The negative peak in the 60- to 110-ms time window was defined as N70. The first positive wave after the N70 peak was defined as the P100. The parameters of the off responses were not taken into account in this study.

Concerning the analysis, first the responses evoked by low- and high-contrast stimuli were baseline corrected, averaged, and measured separately in each subject for each trial and time point. Post-tDCS baseline-to-peak amplitudes and peak latencies in all subjects were normalized to the before-stimulation values and were entered in a repeated-measures ANOVA, comprising the 2 × (anodal-cathodal tDCS) × (recording electrode position: Oz, O1, O2) × (5–6 (time course). Separate ANOVAs were applied for the analysis of low- and high-contrast elicited VEPs, for the different stimulation durations and, with regard to the 10-minute stimulation, for the different tDCS electrode montages. For post-hoc analysis, the Tukey honest significant difference test was used.

**RESULTS**

Figure 1 shows averaged primary evoked potentials for 50 low-contrast stimuli in one representative subject.

**Experiment I**

This experiment was conducted to identify the optimal electrode arrangement to achieve current-driven cerebral excitability changes. Sixteen subjects participated in the study. Using three electrode montages and a 10-minute stimulation duration (Oz–Cz, L01–RO2, Oz–LM montages), tDCS was effective only through the Oz–Cz electrode position. Using the L01–RO2 and Oz–LM montages resulted in no significant main effects of stimulation or time course, and none of the interactions was significant (F < 1.0, P > 0.2), regardless of whether high- or low-contrast visual stimuli were applied.

With regard to the N70 component with the Oz–Cz montage using low-contrast stimuli, the ANOVA revealed a significant main effect of recording-electrode position (F\textsubscript{(2,50)} = 92.70, P < 0.0005), a significant interaction between electrode position and time course (F\textsubscript{(8,200)} = 3.51, P < 0.005), a significant interaction between electrode position and tDCS polarity (F\textsubscript{(2,50)} = 5.77, P < 0.03), and a significant interaction between tDCS polarity and time course (F\textsubscript{(4,100)} = 5.81, P < 0.0005). The Tukey HSD test revealed significantly smaller amplitudes for cathodal stimulation immediately and 10 minutes after the end of cathodal stimulation at the Oz electrode position and immediately after the end of stimulation at the O1 electrode location. Anodal tDCS induced nonsignificant changes (Fig. 2). The P100 amplitude tended to increase immediately after...
cathodal stimulation. In this case, the interactions between time course and tDCS polarity (\( F(4,100) = 5.29, P < 0.005 \)) and between electrode position and time course (\( F_{(8,200)} = 5.66, P < 0.005 \)) were significant. However, the Tukey HSD test revealed no significant amplitude changes (see Fig. 4).

For high-contrast stimuli, concerning the N70 amplitude there was a significant main effect of recording-electrode position (\( F(2,50) = 91.87, P < 0.0005 \)), a significant interaction between electrode position and time course (\( F_{(8,200)} = 5.17, P < 0.005 \)), and a significant interaction between electrode position and tDCS polarity (\( F_{(2,50)} = 3.28, P = 0.05 \)). Tukey’s HSD test showed that cathodal stimulation decreased the N70 amplitude immediately after the end of cathodal stimulation at the Oz, O1 electrode locations. Anodal stimulation was not effective (Fig. 3). The P100 amplitude was not affected by tDCS (\( F < 2.05, P > 0.1 \); Fig. 4).

**Experiment II**

For the Oz-Cz montage, 5 and 15 minutes of stimulation durations were tested in addition, to study the dependency of the aftereffects on stimulation duration. Twelve subjects participated in this study.

**Effect of 5 Minutes of tDCS.** Concerning the N70 amplitude, the interaction between tDCS polarity and time course (\( F_{(4,100)} = 3.24, P < 0.05 \)) was significant when low-contrast stimuli were applied. The Tukey HSD test revealed significantly lower amplitudes immediately after the end of cathodal stimulation at the Oz and O1 electrode positions (Fig. 2). Again, the P100 amplitude tended to increase after cathodal stimulation; however, the effect was not significant (\( P > 0.05 \)).

Five minutes of tDCS resulted in no main effect of tDCS or time course, and none of the interactions was significant when high-contrast stimuli were used (\( F < 1.57, P > 0.1 \) for the N70 and P100 components (Fig. 3). The P100 amplitude tended to increase immediately after cathodal stimulation; however, the effect was not significant (\( P > 0.05 \)).

**Effect of 15 Minutes of tDCS.** When low-contrast stimuli were used, the ANOVA revealed a significant effect of tDCS polarity (\( F_{(1,122)} = 9.56, P < 0.05 \)), a significant main effect of recording-electrode position (\( F_{(2,24)} = 8.23, P < 0.005 \)), and a significant effect of time course (\( F_{(5,60)} = 2.89, P < 0.05 \)).
Effect of tDCS on VEP

DISCUSSION

In this study, we have demonstrated that (1) tDCS can modify the amplitude of the N70 component. Anodal stimulation increased the amplitude; cathodal stimulation decreased it. (2) Cathodal stimulation was more effective in reducing the N70 amplitude than anodal stimulation was in increasing it. (3) With 10 minutes of stimulation, the effect of tDCS was elicited only with the Oz–Cz stimulating electrode position (optimal stimulating electrode position). (4) The observed effects were more pronounced when low-contrast stimuli were used, compared with high-contrast stimuli. (5) The induced aftereffects depended on stimulation duration. (6) The effects were largely restricted to the N70 component; however, a tendency for P100 amplitude to increase was observed after cathodal stimulation.

In agreement with previous studies on the motor cortex,4–6 we show in the current study that the amplitude of cortical VEPs can be modified by tDCS in a polarity-dependent way. Cathodal stimulation decreased the amplitude of the N70 component and anodal stimulation increased it. The observation that cathodal stimulation was more effective than anodal stimulation is noteworthy. A previous human visual tDCS study has described a similar result. Although cathodal tDCS impaired the contrast perception at threshold, anodal stimulation had no effect.9 However, this does not mean that anodal stimulation is inefficient when the visual cortex is stimulated. First, probably the visual system is optimally tuned and thus the excitatory enhancement induced by anodal tDCS cannot improve the perception of visual stimuli. A recent study has shown that anodal stimulation effectively modifies PTs.8 However, phosphenes are evoked by direct cortical stimulation, and therefore anodal tDCS probably can modify their perception.

Second, the data are in agreement with other observations of DCS used in animal studies,1,5 showing that the effect of cathodal stimulation is stronger than the effect of anodal stimulation if identical stimulation parameters are used. This is in line with the general observation that in the central nervous system the inducibility of neuroplastic effects seems to be asymmetrical. It is easier to elicit excitatory diminutions than excitatory elevations, as shown in animals in vivo.10 In our study, the effect of anodal stimulation was significant only when the 15 minutes of tDCS was applied; therefore a further increase of the stimulation duration or the intensity of stimulation may increase its effectiveness. However, we did not

Interaction between stimulation type and time course ($F_{(5,60)} = 2.76, P < 0.05$) was also significant. The Tukey HSD test revealed significantly smaller amplitudes immediately and 10 minutes after the end of cathodal stimulation at each electrode position, whereas anodal stimulation caused significantly higher amplitudes only 10 minutes after the end of the stimulation (Figs. 1, 2). The P100 amplitude tended to increase after cathodal stimulation; however, the effect was not significant ($F < 1.775, P > 0.1$).

For the N70 component, the ANOVA revealed no significant main effect of tDCS polarity or time course ($F < 2.00, P > 0.05$), and only the main effect of the recording-electrode position was significant ($F_{(2,24)} = 13.88, P < 0.0005$) when high-contrast stimuli were used. The interaction between tDCS polarity and time course was marginally significant ($F_{(5,60)} = 2.17, P = 0.07$). Tukey’s HSD test showed significantly lower amplitudes 10 minutes after the end of cathodal stimulation at each electrode location, and the effect of anodal stimulation was significant only at the O2 electrode position 20 minutes after the end of stimulation (Fig. 3). The P100 amplitude tended to increase after cathodal stimulation, but the effect was not significant ($F < 3.062, P > 0.067$).

Latency of the VEP Components

The ANOVAs revealed no significant main effects of tDCS polarity or time course and none of the interactions were significant when high- or low-contrast stimuli were used ($F < 2.00; P > 0.1$).

The figure shows the means of the N70 peak amplitude for 50 low- and 50 high-contrast stimuli recorded at the Oz position in all tested subjects. Significant amplitude decreases were observed only after 10 and 15 minutes of cathodal stimulation. Anodal stimulation yielded no significant VEP amplitude changes at this electrode position. Bars, SE; *significant changes.

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The figure shows the means of the P100 peak amplitude for 50 low- and 50 high-contrast stimuli recorded at the Oz position in all the tested subjects. Bars, SE.

FIGURE 3. Effects of 5 to 10 to 15 minutes of tDCS on N70 amplitude. The figure shows the means of the N70 peak amplitude for 50 high-contrast stimuli recorded at the Oz position in all tested subjects. Significant amplitude decreases were observed only after 10 and 15 minutes of cathodal stimulation. Anodal stimulation yielded no significant VEP amplitude changes at this electrode position. Bars, SE; *significant changes.

FIGURE 4. Effects of 10 minutes of tDCS on P100 amplitude. The figure shows the means of P100 amplitude for 50 low- and 50 high-contrast stimuli recorded at the Oz position in all the tested subjects. Bars, SE.
perform longer stimulation durations so as to remain in accordance with currently available safety criteria. Using several electrode montages, only the Oz-Cz stimulating electrode position was effective, suggesting that the stimulation efficacy of tDCS over the visual cortex depends on current flow direction. This mirrors the situation of the effect of tDCS observed in the motor cortex.

The N70 amplitude modification was more pronounced when low-contrast stimuli were used than with high-contrast stimuli. This effect may be due to a ceiling effect. High-contrast stimuli may activate the respective visual cortical areas maximally (especially because we used 4 cyc/deg). Therefore a relatively weak subthreshold excitability modulation induced by tDCS may not be sufficient to produce a clear change in the VEP in this case. Further studies using a range of different SFs are necessary to clarify this observation.

Previous studies on the motor cortex determined that by varying the duration of tDCS, the duration of the aftereffects could be changed. Motor cortical tDCS of 2 to 5 minutes was effective in eliciting aftereffects; however, in our visual study flow was the case only for cathodal stimulation. It is minutes of stimulation resulted in a 10-minute aftereffect, 15 minutes of stimulation produced longer (20-minute) after-effects from cathodal stimulation. However, this duration is relatively short-lasting compared with the 30- to 60-minute aftereffects elicited by motor cortical tDCS using the same stimulation durations. Possible reasons for this may be anatomical differences: (1) The motor hand area is located on the cortical surface, whereas the greater part of the visual cortex is buried deep in the calcarine fissure. Therefore, the effects of tDCS on the visual cortex may be restricted to the surface and thus reach fewer neurons, compared with the situation in the motor cortex. (2) As was shown in the motor cortex, the current flow direction to neuronal populations modulates the cortical response to thalamic stimulation in a similar way. Anodal stimulation enhanced the positive and reduced the negative component of the respective cortical potentials, whereas cathodal stimulation resulted in opposite changes. These results may be caused by the different effects of tDCS on different types of neurons which are located in different cortical layers and generate the N70 and P100 components. In addition, in animal studies it has been shown that beyond the dominant excitability shift, some neurons are modulated conversely or are not modulated at all. Thus, in the feline motor cortex, neurons situated in deep cortical layers are often deactivated by anodal and activated by cathodal stimulation. The same was found for superficially situated motor cortical nonpyramidal tract neurons. This may depend on the special spatial arrangement of these neurons, causing a different current flow. Alternatively, the effect could be caused by evolving virtual electrodes” in the vicinity of the stimulating electrode, which would be of opposite polarity and would have influenced V2/V3 areas in which P100 is generated. It has already been shown that cathodal stimulation of the supplementary motor area might result in an additional slight anodal stimulation of the primary motor cortex. Similar to this, the cathodal stimulation of V1 may result in an additional anodal stimulation of V2-V3 cortical areas, causing a P100 amplitude increase.

According to our previous and present studies, tDCS seems to be a promising method to induce acute as well as prolonged cortical excitability and activity modulations, and therefore it could evolve as a potential new tool in the field of neuroplasticity research. For example, it can be used as a complementary tool to neuroimaging studies. Although functional magnetic resonance imaging (fMRI) shows which areas are activated during a given task, tDCS, by changing the excitability level of a stimulated cortical area, can deliver information about the specific impact of a given area with regard to a specific task. However, to make this tool relevant, not only for basic research purposes but also for clinical applications, additional studies are necessary, especially studies to enhance the duration of the effects and accompanying safety studies. In principal, the application of tDCS could be beneficial in conditions and diseases accompanied by pathologic changes in the cortical excitability of the visual areas—for example, in amblyopia, migraine, photosensitive epilepsy, and neglect. Our results also raise the possibility of using tDCS in the rehabilitation of brain injuries where visuomotor coordination is impaired because of deficient visual processing.

In summary, previous animal studies have already shown that anodal and cathodal tDCS over the primary visual cortex can modify the amplitude of EPs. In this study we have shown that tDCS can modify the amplitude of the N70 component of the VEP when it is applied over the human primary visual cortex. The effect depends on the stimulation polarity, the electrode positions, and the duration of stimulation. However, the different duration of the induced aftereffects compared with the motor cortex suggests that the effect of tDCS may be quantitatively different with regard to different cortical areas.

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References


