

Transcranial direct current stimulation as a new method for changing the accommodative response of the eye

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The aim of the present study was to test if the exposure to transcranial direct current stimulation (tDCS) would change the excitability of the visual cortex and influence an accommodative response of the ocular lens. Twenty four subjects were divided into two groups: real-stimulation of the occipital cortex in which participants were exposed to real stimulation (1 mA for 12 min), and sham in which subjects were tested with placebo stimulation. The results showed that tDCS might indeed influence accommodative response. The strongest and most evident effect was observed when a 3.0 D accommodative stimulus was used: anodal tDCS increased but cathodal tDCS – decreased the accommodative response. The second finding was that the effect of stimulation was dependent on the examined eye. The right eye with slightly lower visual acuity and weaker accommodative response in pre-test, responded more strongly than the left eye. The short-time tDCS might modulate excitability of the neurons in visual cortex and eye sensitivity, reflected in the change of accommodative response. The tDCS method may be considered a technique that could reinforce conventional active visual training to improve accommodative functions.

Keywords: transcranial direct current stimulation (tDCS), accommodative response, visual training, visual cortex.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive method to modulate cortical excitability [1, 2]. This modulation arises from shifting neuronal resting membrane potential [3]. The tDCS is able to induce prolonged polarity-dependent cortical excitability alterations [4–6]. Cathodal stimulation usually reduces neuronal firing

rates but anodal stimulation produces the opposite effect. It was demonstrated that tDCS anodal stimulation affects γ -aminobutyric acid (GABA) which plays inhibitory role in the nervous system [1]. The reduction in the level of GABA then improves plasticity within the brain, resulting in a faster motor learning [7, 8]. Disinhibition (tDCS-induced reduction of GABA level) may result in exposing hidden connections within the brain [9] and may induce long-term potentiation due to enhancement of the transmission signal from neuron to neuron [10]. However, cathodal stimulation causes a reduction in glutamate levels [11] that is an excitatory neurotransmitter.

Andrea Antal's group published the first direct evidence for the efficacy of tDCS to alter excitability of the human primary visual cortex [12]. They have shown that tDCS modulates the amplitude of visual evoked potentials. It was reflected in the enhancement of the N70 component amplitude after anodal stimulation and diminished after cathodal tDCS. Another electrophysiological study, using different visual stimuli (pattern-reversal checkerboard), found an opposite polarity effect of tDCS on P100 amplitude [13]. The tDCS also modulates contrast sensitivity [14] in the same way that anodal stimulation of the occipital cortex increases the contrast sensitivity within the center (8°) of the visual field [15] as well as the motion detection threshold decrease [12]. Moreover, tDCS might also affect the perception of phosphenes [16, 17].

Transcranial stimulation looks to be also a promising method in neurorehabilitation of visual functions. For example, hemianopia (half-vision), caused by stroke or cerebral trauma, can be treated today by tDCS to enhance inherent mechanisms of plasticity associated with training [18]. Anodal stimulation of the visual cortex may result in a shift in the visual field border of persons after suffering a stroke [18]. Additionally, recent studies showed that short-time tDCS applied during visual training may improve visual acuity and stereopsis, possibly by reducing intracortical inhibition [19]. As tDCS might change excitability (sensitivity) of the neurons in visual cortex and is able to affect contrast sensitivity, we wonder if this change may also affect a visuomotor response as an accommodative response (AR) of the crystalline lens. AR is a change of optical power to maintain focus objects at various distances on the retina. So, AR is a measure of the actual accommodation that is present at a given time. In the current study, visual stimuli were presented with a changeable accommodative stimulus (different levels of focus/blur), and the AR was measured before and after a short-period of tDCS.

The aim of the current study was to examine whether short-time tDCS of the occipital cortex area may modulate AR. To the best of our knowledge, the effect of tDCS on the AR has never been investigated.

2. Material and methods

The study was approved by the local Ethics Committee of Adam Mickiewicz University in Poznań and was performed in accordance with the Declaration of Helsinki. All participants were asked to sign a written consent before the experiment started.

Twenty four students of Faculty of Physics participated in the study (6 males, 18 females, 23 ± 2 years). Only students who passed ophthalmological examination in the past year, and who had no ocular pathology, could participate in the study. An optometric vision examination was performed by an optometrist (one of the authors of the study) on each individual before the experiment started, and included: refractive error measurement, monocular visual acuity at near and far distance (Snellen chart) with and without optical correction, ocular dominance (fixating via a hole task), amplitude of accommodation (negative lenses test), and monocular and binocular accommodative facility (accommodative flipper ± 2.0 D). Binocular vision was evaluated by the following tests: alternating cover test, Titmus stereotest and Worth 4-dot. The detailed instructions of procedures listed above are included in the subject literature [20].

The participants enrolled in the study had no refractive error or were corrected with appropriate optical correction. None of them demonstrated manifest strabismus or amblyopia. Accommodative parameters were in normal range (mean 12.2 D, max. 16.2 D, min. 9.5 D for amplitude of accommodation and 16 cpm for monocular flipper and 9 cpm for binocular flipper). No eyes misalignment (orthophoria) or small heterophoria in normal range (value of exophoria 3.0 ± 1.5 PD at near and 1.0 ± 1.5 PD far distance) was noticed. Each of them had full stereovision (at least 40").

The tDCS method does not induce seizures and is well tolerated in patients with refractory epilepsy [21]. Adverse effects of tDCS method do not occur if a strict security protocol is followed [22]. However, to avoid any possible complication, only participants without any neurological diseases, including epilepsy could participate into the study. It was assessed based on the medical history, and neurological consultation if necessary (one of the authors of the current paper is a neurologist).

Participants were divided into 2 groups: 1) with real-stimulation (R-tDCS) where the subjects were exposed to real current stimulation, and 2) sham group (S-tDCS) in which the subjects were administered placebo stimulation. Each participant participated in two sessions: cathodal and anodal. During anodal stimulation the anode electrode was located over inion (Oz position according to the 10/20 system), but cathode electrode was placed over the vertex (Cz). In cathodal stimulation, electrodes were placed in opposite locations.

Research was carried out in the Vision and Neuroscience Laboratory of NanoBio-Medical Center, Adam Mickiewicz University in Poznań.

Accommodative response was tested using autorefractometer Righton Speedy-i K-model in a continuous mode of accommodative microfluctuation (AMF) measurement. This device measured refraction of each eye separately, when stimulus to the accommodation was changing from zero to -5.0 D, in steps of 0.5 D. The visual stimuli were presented on the monitor of the device, and the distance of the monitor was fixed. The device changed stimulus to accommodation automatically by changing image focus. The visual stimulus was a firework (~ 110 lx) and the participant had an instruction to fixate on the stimulus and keep the image as clear as possible.

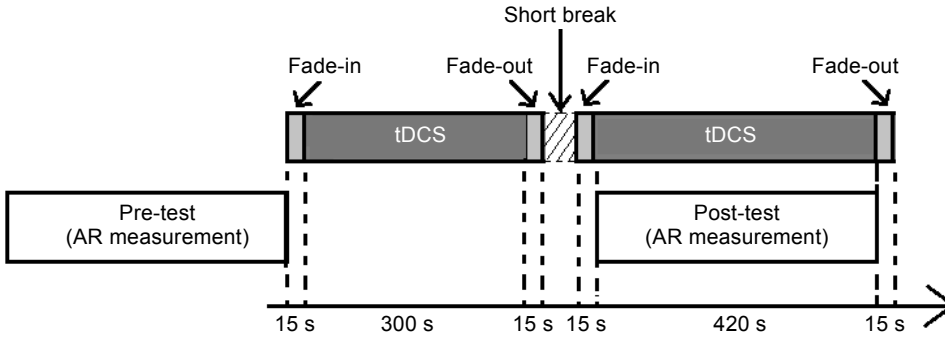


Fig. 1. The timing scheme of measurement.

Visual cortex was stimulated using DC-STIMULATOR PLUS (neuroConn Technology, Germany), which allows to use direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). In the current study, the tDCS method was used with the current intensity of 1 mA, which was flowing through a pair of sponge electrodes (size 25 cm²) slightly moistened with NaCl solution. The electrodes were placed with the elastic bands. Dimension of sponges was optimized to combine precise stimulation and safe current density. The tDCS was delivered at 1 mA current to the brain and this corresponds to the current density of about 0.04 mA/cm² (when 25 cm² electrodes were used). This value is safe since in the reported studies performed with rats, the brain lesions occurred at a current density of 14.29 mA/cm² for durations greater than 10 min [23].

Stimulation and AR measurement protocol is presented in Fig. 1. Before stimulation, AR was measured which gave us a baseline value for further calculations (pre-test). During R-tDCS, the current had a ramp-up time of 15 s and the stimulation was then held at level of 1 mA (300 s), after that the current faded out for 15 s. Short break (70 s) was introduced to prepare a subject for second AR measurement (post-test). After the break, when subject was seated by autorefractometer, tDCS was continued. Post-tests were carried out during tDCS in a 420-second time window (longer than the first, to be sure that the current will not expire before all measurements have been recorded). Stimulation in the sham group was very similar to the real stimulation, with differences in durations of stimulation (only 30 s).

The AR measurement in pre- and post-tests consisted of 11 steps, each lasting 10 s. Steps were separated by 3 s rest. Right and left eyes were measured separately. The effect of stimulation (EFS) was calculated as AR difference in post- and pre-test, according to the equation: $EFS = AR_{\text{post-test}} - AR_{\text{pre-test}}$. The obtained data were analyzed in the Statistica 10 software (StatSoft), using the analyses of variance (ANOVAs) for repeated measurements for 2 groups (R-tDCS vs. S-tDCS) with three within-subject factors: *i*) polarity – 2 levels (anodal vs. cathodal stimulation), *ii*) eye – 2 levels (right (RE) vs. left (LE)), *iii*) accommodative stimulus – 11 levels (0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 D). As a post-hoc, Tukey test was used. Differences were considered significant with a *p*-value equal or less than 0.05.

3. Results

As can be seen in Fig. 2, tDCS affected AR in two experimental groups in a different way. ANOVA showed that EFS was dependent on the eye and group (*eye* × *group* interaction, $F(1, 22) = 15.29, p < 0.001, \eta^2 = 0.41$). In R-tDCS group EFS with the RE was positive (facilitation), but negative (inhibition) with the LE ($p = 0.004$). Opposite trends occurred in S-tDCS group, but here this difference was not significant statistically ($p = 0.572$).

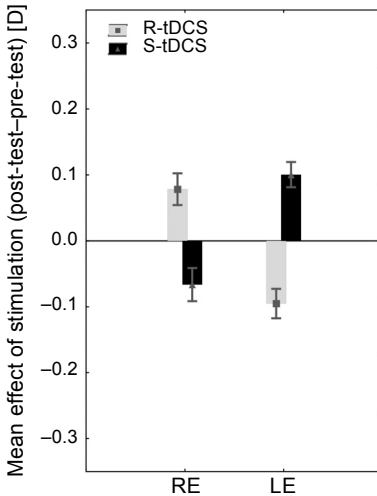


Fig. 2. Mean effect of stimulation for RE and LE in R-tDCS and S-tDCS groups. The vertical bars indicate the standard error.

The EFS depended also on the accommodative stimulus and polarity (cathodal or anodal stimulation), what was confirmed by a significant *eye* × *group* × *stimulus* interaction ($F(10, 220) = 2.84, p = 0.012, \eta^2 = 0.11$) and *polarity* × *eye* × *group* × *stimulus* interaction ($F(10, 220) = 2.12, p = 0.024, \eta^2 = 0.10$). To explain this interaction, additional ANOVA was performed for each stimulus, separately. Figure 3 shows the influence of the tDCS on the EFS for each accommodative stimulus. Some influence of tDCS can be observed starting from 1.0 D until 5.0 D stimulus. However, statistical analyses showed that for the lowest stimuli (from 0.0 to 1.0 D), as well as for the highest ones (from 4.5 to 5.0 D), no significant difference between R-tDCS and S-tDCS groups was found ($p > 0.050$).

More pronounced effects were obtained for the middle stimuli: starting from 2.5 D until 4.0 D, where the R-tDCS method influenced EFS in comparison to the sham stimulation. The strongest effect was found with accommodative stimulus set at 3.0 D. First of all, anodal stimulation induced a facilitatory response but cathodal had an inhibitory effect on the AR (see Fig. 4a), confirmed by significant *polarity* × *group* interaction ($F(1, 22) = 6.87, p = 0.016, \eta^2 = 0.24$). Post-hoc test showed this effect was found with the R-tDCS group ($p = 0.024$) but not with the S-tDCS ($p = 0.937$). Moreover, tDCS

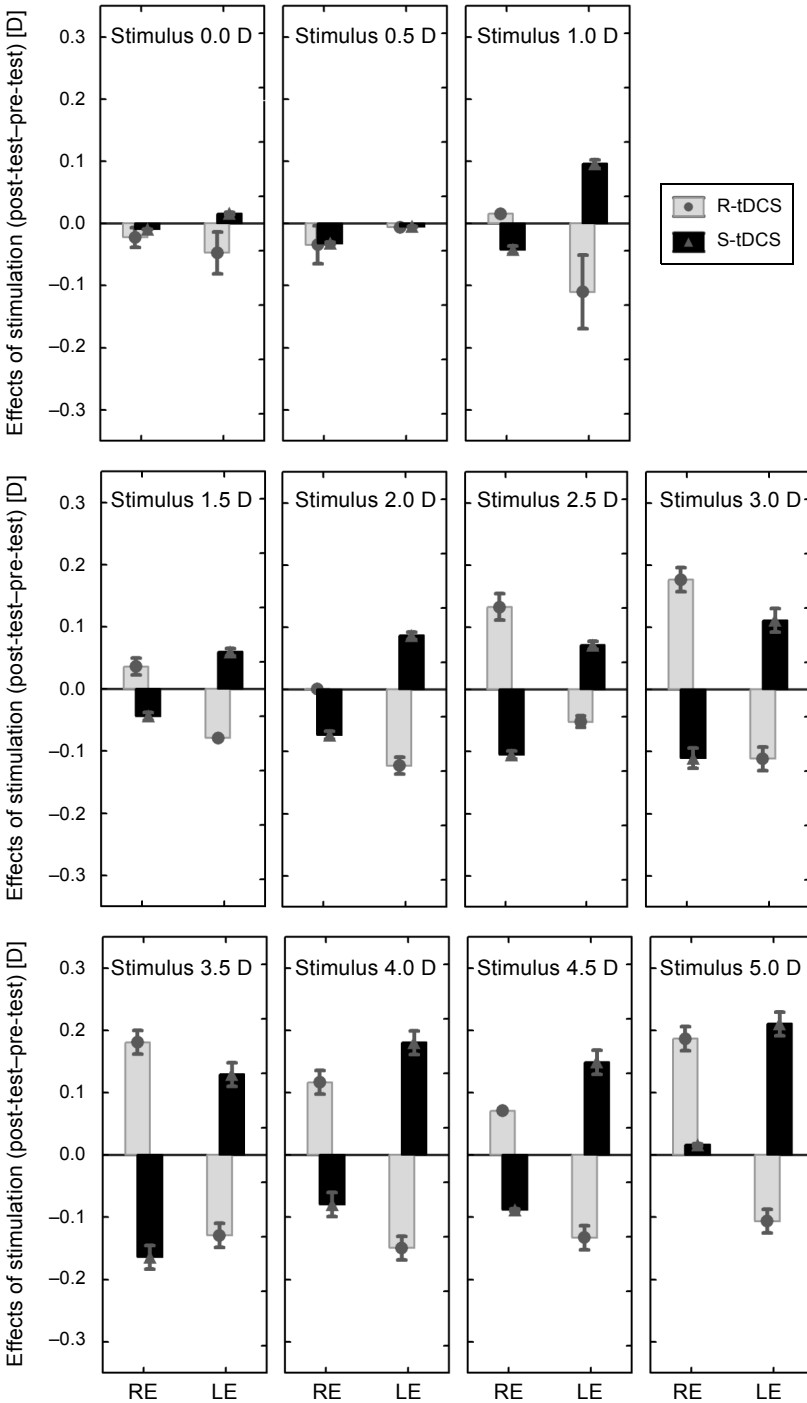


Fig. 3. Mean effect of stimulation depends on the eye (RE and LE), accommodative stimulus (from 0.0 to 5.0 D) and group: R-tDCS and S-tDCS. The vertical bars indicate the standard error.

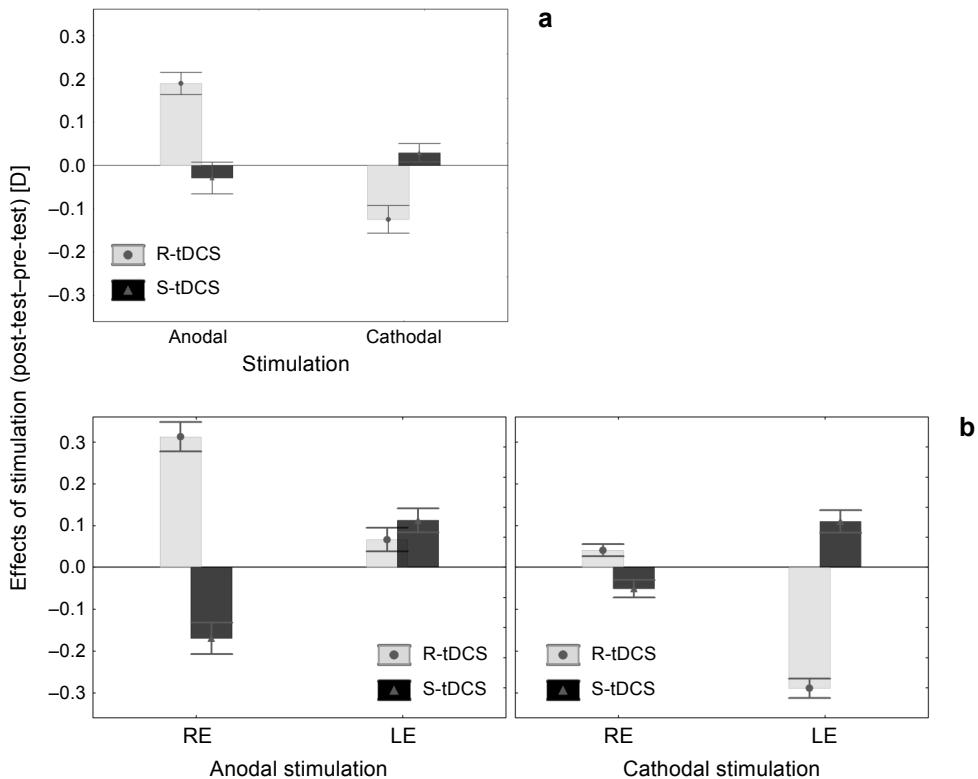


Fig. 4. Effect of stimulation with accommodative stimulus set at 3.0 D for RE and LE due to R-tDCS and S-tDCS. The vertical bars indicate the standard error.

affected the RE and LE in a different way (significant $group \times eye$ interaction ($F(1, 22) = 14.71, p < 0.001, \eta^2 = 0.40$)). As can be seen in Fig. 4b, real anodal stimulation caused an increase in AR (positive EFS) when viewing with RE, but no significant change was found when viewing with the LE ($p = 0.027$). Reversed effect was observed for the sham stimulation but here no significant difference in EFS between the eyes occurred ($p = 0.115$).

Similar influence of the tDCS on the RE and LE was found with 3.5 and 4.0 D stimuli ($F(1, 22) > 11.31, p < 0.003, \eta^2 > 0.34$), however here, EFS was not dependent on polarity ($polarity \times group \times eye$ interaction $F(1, 22) < 1.24, p > 0.277, \eta^2 < 0.05$). This indicates that both anodal and cathodal stimulation modulated AR in a similar way. Here, R-tDCS induced stronger AR on the RE (positive EFS) ($p < 0.024$) but no significant changes were obtained with the LE ($p > 0.125$). In the S-tDCS, the tendency seems reversed, but analyses showed that it was not statistically significant ($p > 0.050$). With the smallest (0.0 and 0.5 D) and the highest (5.0 D) stimuli no significant effect or interaction was observed ($p > 0.050$).

ANOVA showed that mean AR in pre-test was dependent on the eye and the group ($F(1, 22) = 8.34, p < 0.008, \eta^2 = 0.27$). In the R-tDCS group, AR of the RE was a little

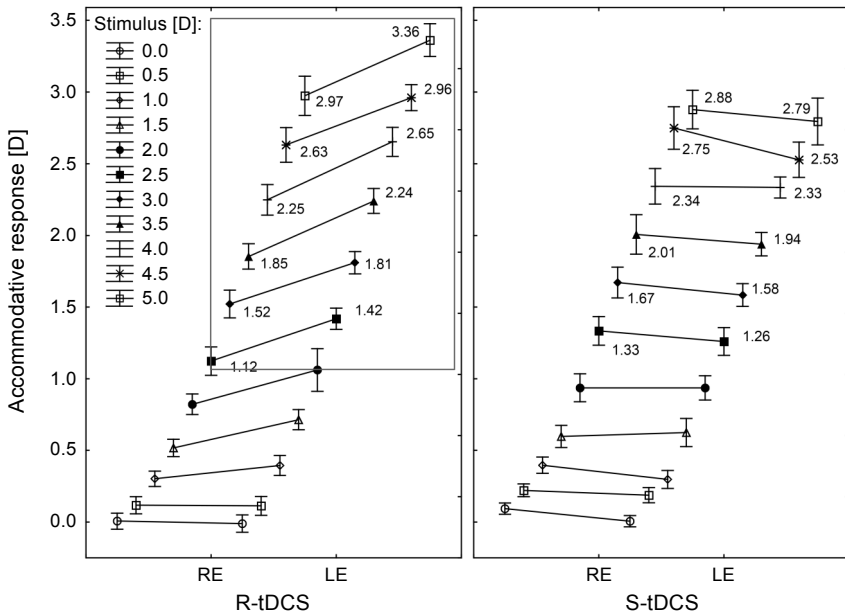


Fig. 5. Accommodative response (AR) in pre-test for the RE and LE for R-tDCS and S-tDCS groups.

lower than that of the LE (1.28 vs. 1.52 D for the RE and LE, respectively) and this difference was statistically significant (post-hoc, $p = 0.021$), but in the S-tDCS group was not significant (1.38 vs. 1.32 D for the RE and LE, respectively, $p = 0.804$). Moreover, the difference increased with the stimulus, what was revealed in the $eye \times group \times stimulus$ interaction ($F(10, 220) = 3.21$, $p = 0.007$, $\eta^2 = 0.13$). As can be seen in Fig. 5, in the S-tDCS group no significant difference in AR between the eyes was observed (post-hoc $p > 0.350$). However, in the R-tDCS, the difference increased with the stimulus. Post-hoc test showed that for 2.5 and 3.0 D stimulus, the difference was equal to 0.3 D, but for 3.5 until 5.0 D, it was even higher with mean difference equal to 0.39 D ($p < 0.001$).

Lower sensitivity of the RE could be partially reflected also in the visual acuity differences, so a separate ANOVA of the visual acuity was performed. Results showed that in the R-tDCS group, visual acuity for the RE (median logMAR -0.14) tends to be lower than for the LE (median logMAR -0.18) and the difference was close to significant ($Z = 1.75$, $p = 0.080$). While in the S-tDCS group, median logMAR visual acuity for both eyes was the same: -0.18 ($Z = 0.84$, $p = 0.402$).

4. Discussion

The results obtained in the current study showed that tDCS is able to change AR and this effect was dependent on the eye and partially on the polarity of the electrodes. Effect of stimulation was the most evident for accommodative stimulus set at 3.0 D. Here, anodal tDCS evoked increase, but cathodal tDCS decreased AR. This effect was ob-

served only in R-tDCS group but not in S-tDCS one. The polarity influence of tDCS is in agreement with previous studies involving both the motor and visual cortex. For example, NITSCHKE and PAULUS [5, 6] have shown, that anodal stimulation increases motor evoked potential response by enhancing excitability of the motor cortex, while cathodal stimulation tends to decrease. A similar polarity effect of tDCS was observed after stimulation of visual cortex. It is reasonable to think that excitability changes of the neurons in visual cortex after tDCS, could influence the detection of the blurred retinal image, influencing motor commands sent from the cerebral cortex to the ciliary muscles. A sudden change in target blur induces a signal transmitted to the visual cortex (and the Edinger–Westphal nucleus in the midbrain) from the retina [24, 25]. Then, proper motor commands from the brain are sent through the oculomotor nerve (III) to the ciliary ganglion and muscles [25, 26] to produce a clear image on the retina.

Why was the polarity effect of tDCS observed mainly with 3.0 D accommodative stimulus? AR is usually less than the stimulus required because of an increased depth of field due to constriction of the pupil. Accommodative lag related to depth of field is usually between 0.5 and 0.75 D. In the device used in the experiment (autorefractometer) the changes of the AR were done by changes in the power of the optical system of the instrument. Under natural conditions, proximal accommodation takes place when the object is moving closer to the eyes. In the experiment, all accommodative stimuli were displayed at the same distance, so the proximal component of the accommodation was weak. The mean AR for the stimulus 3.0 D was equal to 1.65 D in pre-test (measured before tDCS). Their difference, known as the accommodative lag, can be explained by ~ 0.75 D resulting from the depth of field and ~ 0.5 D from the absence of proximal accommodation. Everyday working distance for adults' population is 40 cm, what is equal to 2.5 D of accommodative stimulus. Due to the depth of field, 1.75 or 2.00 D, the AR is enough to make the image clear. In our studies the mean measured accommodative response for 3.0 D stimulus was 1.65 D. Thus 3.0 D stimulus evoked level of AR similar to that present in daily near work distance. One can expect that such frequent and long-standing accommodative state exhibits the highest sensitivity to tDCS. Smaller accommodative stimuli results in weak AR, thus changes after tDCS are expected to be less evident. On the other hand, larger stimuli result in higher accommodative lag (for example in our study with 5.0 D accommodative stimulus, the accommodative lag was 2.0 D). When the stimulus and the accommodative lag are too large, small changes in AR after tDCS could be difficult to detect.

The second finding of the present study was that tDCS influenced the right and left eye in a different way: the right eye indicated excitatory and the left eye inhibitory effect. Deeper analysis revealed that tDCS affected the AR mostly in the right eye. How should one interpret the different effects of tDCS between the eyes? All measurements were carried out with a counterbalanced order between the left and right eyes, so attention degree or fatigue factors could not be responsible for this effect. This effect was not expected in the study, but some explanation might be found in differences between sensitivity of the eyes. All participants demonstrated good visual acuity in each eye but we found that the left eye had slightly better visual acuity than the right one

(difference was close to significant). It was possible that tDCS method could increase the excitability of the visual cortex of the eye with the lower visual acuity (RE). An increase in excitability could improve detection of the image blur on the retina and could result in a better lens adaptation to the stimulus (better AR after the stimulation). This would mean tDCS does not selectively affect the eyes, but affects the balance between the eyes, equalizing the detection capabilities of both eyes. The phenomenon of continuous rivalry between information coming from both eyes is called retinal rivalry [27, 28]. In addition, the phenomenon of tonic interocular suppression (TIS) has been reported in the visual cortex [29–33]. TIS is a process where the second eye at the level of visual cortex suppresses information from one eye. This can manifest itself in the form of a decreased sensitivity [30] of the right eye: decrease of the VEPs [31] and decrease in visual acuity [33]. This mechanism is found in amblyopia – a state resulting from an overly strong suppression of information from one eye by the other one [29, 32]. In our study the left eye had slightly better visual acuity than the right eye what could be due to the advantage of TIS of the left eye over the right one. The tDCS could affect the level of TIS and therefore set a balance between both eyes. As a result, sensitivity of the right eye could increase, facilitating detection of the blurring image on the retina and consequently a stronger AR. This interpretation seems possible, since recent studies have showed that short-time transcranial stimulation influences visual parameters as visual acuity and/or stereo acuity [19, 34]. The beneficial effect of tDCS in amblyopia is explained by a reduction of the GABA mediated inhibition [1, 8, 35], what is treated as a key mechanism underlying suppression of the amblyopic eye [19, 36].

The impact of tDCS on AR may take place in human of all ages, excluding people with developed presbyopia (very rigid lens is capable of changing its front). Even though the current density is the highest between the electrodes, part of the current also flows through other tissues, possibly muscles, and increases or decreases their activity. We cannot exclude that tDCS partly affects the efficiency of ciliary muscles. In this scenario, the stimulation of tDCS could positively influence the AR in the early phase of presbyopia through delay time when a person would have to use reading glasses. This hypothesis needs further studies.

5. Conclusions and clinical application

To sum up, the current study showed that tDCS method is able to influence AR by changing excitability of visual cortex and this effect is most evident with a stimulus of 3.0 D (adequate range for a close work): anodal stimulation resulted in the increase, but cathodal stimulation decreased AR. Additionally, the results suggest that tDCS may increase AR of the eye with lower sensitivity, possibly by changing the level of interocular cortical inhibition.

Poor accommodative functions commonly occur in modern society. Our eyes are kept in a long-term state of accommodative tension during close work (*e.g.*, on a computer, mobile phone). Symptoms of accommodative dysfunction are usually related to blurred vision when looking up from near work, headaches, and problem with concen-

tration of attention. It is possible that tDCS, which is an easy and comfortable procedure, in combination with the standard vision training techniques of accommodation or near lenses, would be an effective and fast way for improving accommodative functions.

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