Transcranial direct current stimulation and the visual cortex

Andrea Antal *, Michael A. Nitsche, Walter Paulus
Department of Clinical Neurophysiology, Georg-August University of Göttingen, 37075 Göttingen, Germany
Received 29 June 2005; received in revised form 30 August 2005; accepted 7 October 2005
Available online 2 November 2005

Abstract
Neuroplastic changes are defined as enduring changes in the organization of the central nervous system, such as the strength of connections, representational patterns, or neuronal properties, either morphological or functional. In recent years, new tools have emerged to induce and manipulate ongoing neuroplastic changes by external stimulation, either by modification of synchronized neuronal activity or modulation of the spontaneous firing rate. The first is performed by transcranial magnetic stimulation (TMS), the latter by direct current stimulation (tDCS). tDCS as a tool aims to induce prolonged neuronal excitability and activity alterations in the human brain via alterations of the neuronal membrane potential and results in prolonged synaptic efficacy changes. Apart from its impressive persistent excitability effects, it is a non-invasive method and can be applied painlessly. Most likely that up- or downregulation of different cortical areas by tDCS will open a new branch in the area of visual psychophysics.

© 2005 Elsevier Inc. All rights reserved.
Keywords: Visual cortex; tDCS; TMS; VEP; Motion perception; Neuroplasticity

1. Introduction
In the last centuries, lots of neuroscientists used electric stimulation of the cortex to make fundamental discoveries on brain organization and function. The first systematic studies regarding electrical stimulation of the cortex were carried out by intracranial electrical stimulation of the brains of neurological patients during neurosurgery by Penfield and Boldrey[37]. Occipital stimulation produced light sensations, called phosphenes, whose position, color and shape varied according to the position of the electrodes. Later Brindley and Lewin[16] stimulated the occipital cortex of a blind subject with implanted electrodes and described in detail the properties of elicited phosphenes. Since these elementary visual perceptions did not prove of functional relevance to the patients, visual neuroprothetics remained in its infancy.

These early invasive approaches were followed by non-invasive stimulation methods. The first of these stimulation techniques, transcranial electrical stimulation (TES), which aimed to induce alterations of brain functions through the intact skull, was developed by Merton and Morton in 1980[27]. Compared to the invasive methods, they had to increase voltage and shorten discharge duration for effective stimulation. They showed that stimulation of the scalp over the occipital cortex could produce phosphenes. The disadvantage of this method, which diminished its application as a routine research tool, was that the high voltage electrical current needed caused pain and contraction of the scalp muscles. In contrast, transcranial magnetic stimulation (TMS), which also induces a current flow in the brain but by painless transcranial stimulation, developed as the gold-standard for a powerful, non-invasive, non-painful method for changing the activity of cortical neurons. In the classic report on TMS in humans, Barker et al.[12] not only described its excitatory effect on the motor cortex but also mentioned that light sensations were evoked by magnetic stimulation of the occipital cortex. Since that time, several studies have verified that TMS of the visual cortex and related areas is able to modify visual perception, imagination, motion processing and cognition (for reviews see: 2,42–44)).

In the last few years, another non-invasive method has extended stimulation possibilities in the study of human brain function. Transcranial direct current stimulation (tDCS) applied through the skull was shown to directly modulate the excitability of the motor[13,29–35,40], somatosensory[26,39] and visual...
2. Applications in humans

2.1. Animal studies

First knowledge about the origin and mechanisms of cortical DC stimulation has been gained from animal experiments. In cats and rats it was shown that applying an anodal DC stimulus to the surface of both the motor and the visual cortex increased cortical excitability and activity by depolarizing neuronal membranes at subthreshold level, whilst a cathodal current resulted in the reverse effect, due to hyperpolarizing neurons [15,17,38,45]. In cats, the effect on the visual cortex was less pronounced than on the motor cortex, possibly due to the different structures of the cortices and different spatial orientations of the neurons [17]. The elicited effects were not restricted to the duration of the stimulation itself but could outlast it for several hours if stimulation intensity and duration were sufficiently high [15].

Cathodal polarization of the striate cortex in the rabbit led to a large decrement in the performance of a conditioned response when light flashes were used as the conditioning stimuli [28]. The same effect was found in pattern or brightness discrimination tasks in rats [23]. However, Ward and Weiskrantz [45] found that anodal polarization applied to the surface of the striate cortex of monkeys resulted also in impaired visual discrimination. The task-dependency of tDCS on information processing was later explained and underlined by studies in humans [7].

2.2. Applications in humans

In the last few years, it has been shown that transcranially applied DC can modulate excitability and activity of the motor cortex in healthy subjects, both during and after stimulation, as now measured by TMS and functional magnetic resonance imaging (fMRI) [13,29–35,40]. The after-effects can last from 3 to 15 min with an intensity of 1.0 mA [3–5,8].

Contrast sensitivity [8], as well as motion detection thresholds [7] in a polarity specific way. VEPs characterize occipital activation in response to visual stimulation. Using several stimulating electrode combinations, only the occipital—vertex (Oz-Cz) electrode position was effective, showing that the stimulation efficacy of tDCS depends on current flow direction [3]. This mirrors the situation regarding the effect of tDCS observed in the motor cortex [33]. Cathodal tDCS over the primary visual cortex decreased whilst anodal tDCS increased the amplitude of the N70 component of the VEP. However, significant effects were only observed when low contrast visual stimuli were applied. High contrast stimuli may activate the respective visual cortical areas maximally, therefore, cathodal excitability modulation induced by tDCS might produce less clearer changes in the VEP in this case. The duration of the induced after-effects depended on stimulation polarity and also on stimulation duration, where longer stimulation durations resulted in longer lasting after-effects. Both stimulation polarities were effective, but the duration of the induced after-effect was different. The explanation of this asymmetry is still on the hypothetical level: first, in some experimental paradigms the visual system is probably already optimally tuned in healthy subjects and, thus, an excitatory enhancement induced by anodal tDCS cannot improve the perception of visual stimuli further. Second, it is also probable that there is a significant involvement of GABAergic neurons selectively activated by cathodal stimulation. The data are in agreement with other results using tDCS in animal studies [15,17] 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, i.e. it is easier to elicit excitatory diminutions than excitatory elevations, as shown in animals in vivo [18].

There is growing evidence that changes in oscillatory activity of the brain play important roles in the formation of perceptions and memory and, therefore, they are essential for perceptual and behavioural functions. This oscillatory activity can be grouped into different frequency bands. An increment of the beta (15.625–31.25 Hz) and gamma (31.25–65.2 Hz) frequency ranges of the cortical electrical activity in humans is closely related in time to the N70 peak of the VEP elicited by elementary visual stimuli. These VEP-related oscillatory activities were studied to determine whether they could be modulated externally by tDCS [9]. Cathodal stimulation decreased, whilst anodal stimulation slightly increased the normalized beta and gamma frequency power. Since gamma activity is also related to higher-level information processing, e.g. different stages of perception and learning processes, tDCS might be a suitable method to induce alterations in higher order cognitive processes. Similar to the effect of TMS on contrast threshold [21], cathodal tDCS resulted in decreased static and dynamic contrast sensitivities (CSs) of healthy human subjects after stimulation, probably by decreasing cortical excitability [8]. However, the excitability enhancement effect of anodal stimulation was not apparent, probably due to a ceiling effect: the stimulus used...
by this study had ‘optimal’ spatial frequency and its perception could not be improved further by anodal stimulation.

Magnetic stimulation over V1 results in stationary phosphenes whilst stimulation over V5 produces moving light sensations [36,42]. For quantification of tDCS induced excitability changes phosphene thresholds (PTs) were measured using short trains of 5 Hz TMS pulses in healthy subjects before and after the end of anodal or cathodal stimulation [4]. Reduced PT was detected immediately and 10 min after the end of anodal stimulation while cathodal stimulation resulted in an opposite effect.

There is a long running debate regarding the visual awareness centers, on whether V1 is necessary or whether the functionally specialized area V5 is sufficient for the perception of moving phosphenes [36]. By a study, anodal and cathodal tDCS was applied to V1 and moving phosphenes were elicited by V5 TMS [5]. Reduced moving PTs were detected after anodal tDCS, whilst cathodal stimulation resulted in the opposite effect. This, further, supports the ‘V1 hypothesis’ of moving phosphene perception and suggests that not only a functional interruption of V1, but also a shift in excitability of V1 influences the perceptual process of moving phosphenes.

With respect to the functional effects of tDCS, it was surprisingly found that the percentage of correct tracking movements increased significantly during and immediately after cathodal tDCS of V5, whilst anodal stimulation had no effect when an already learned manual visuo-motor tracking task was applied [7]. Upon first inspection, these results are surprising. Since weak cathodal stimulation decreases cortical excitability by membrane hyperpolarization, it should impair performance. The highly specific effect of reducing excitability in V5 but enhancing performance of this visually guided tracking task is most likely explained by the complexity of perceptual information processing needed for the task. The subject had to choose the correct direction, to compare and optimize motion velocity and direction of the target and the feedback-cursor. The complexity of the task probably produces a kind of noisy activation state of the encoding neuronal pattern in response to different velocity and movement directions, where not only the optimum, but also some sub-optimum patterns are activated simultaneously, to a certain degree. In this case, cathodal stimulation may focus the correct perception of these parameters by decreasing the global excitation level and, thus, diminishing the amount of activation of concurrent patterns below threshold. This hypothesis was underlined by other studies using random dot kinetograms [7]. Cathodal stimulation significantly improved motion perception in a paradigm in which the task was to identify the direction of coherent motion in a random noise background and again, anodal stimulation had no effect. However, when the task was to identify the direction of coherently moving dots presented without distractors, the number of correctly identified directions was decreased significantly by cathodal stimulation, whilst it was enhanced by anodal tDCS. This strongly implies that cathodal stimulation—which is known to diminish cortical activation—enhances performance by noise reduction in a ‘noisy’ condition (coherent motion with distractors), whilst worsening performance in a noise-free condition (coherent motion only) by decreasing global network activation.

3. Learning and tDCS

Since learning processes are accompanied by cortical excitability shifts and by changes of synaptic efficacy and considering that the after-effect of tDCS is NMDA-receptor dependent [25], there is a possibility that cortical excitability changes induced by weak dc stimulation could improve learning-related NMDA-receptor strengthening. In a recently conducted study, the excitability of MT+V5 and MI was increased or decreased by anodal or cathodal tDCS in healthy human subjects whilst they were learning a visually guided manual tracking task [6]. The percentage of correct tracking movements increased significantly during a 2–5 min time interval after the beginning of anodal stimulation, whereas cathodal stimulation had no significant effect. For the MI stimulation, a similar result was demonstrated for implicit motor learning in healthy human subjects [35]. Additionally, it was recently shown that anodal stimulation could improve visual probabilistic classification learning when the left prefrontal cortex is stimulated [22]. Interestingly, for the tracking task, the positive effect of anodal tDCS was restricted to the learning phase, thus, suggesting a highly specific effect of the stimulation.

4. The possible mechanisms of action of tDCS

Recently, several studies have aimed to clarify the cellular mechanisms of tDCS over the motor cortex [25,29,30]. The impact of the sodium channel blocker carbamazepine, the calcium channel blocker flunitrazepine and the NMDA-receptor antagonist dextromethorphan on tDCS-elicited motor cortex excitability changes in healthy human subjects was tested. Carbamazepine selectively eliminated the excitability enhancement induced by anodal stimulation during and after tDCS. Flunarizine resulted in similar changes. Antagonizing NMDA-receptors did not alter current-generated excitability changes during a short stimulation, which elicits no after-effects, but prevented the formation of after-effects independent of their direction. These results suggest that cortical excitability shifts induced during tDCS in humans depend on membrane polarization, thus, modulating the conductance of sodium and calcium channels. Moreover, they suggest that the after-effects may be NMDA-receptor dependent. In a recent study, it was demonstrated that n-cycloserine, a partial NMDA-agonist, selectively potentiated the duration of motor cortical excitability enhancements induced by anodal tDCS [30]. Additionally, it was also suggested that the after-effects of cathodal tDCS include non-synaptic mechanisms based on changes in neuronal membrane function [11].

There are no currently available data about the underlying cellular-molecular mechanisms of tDCS-induced effects over the visual areas. Although it is very likely that tDCS acts similarly in the visual cortex and in the motor cortex because the functional effects are comparable, the findings of the motor studies cannot simply be translated to the visual areas due to anatom-
5. Conclusions

tDCS allows the manipulation of cortical network activity in humans and, in parallel, a psychophysical evaluation of correlated perceptual changes. It influences the brain’s activity electrically and changes organized cortical activity transiently and reversibly in a non-invasive, non-painful way, similar to TMS. Both stimulation techniques can produce bidirectional after-effects on the excitability of corticospinal output neurons depending on the frequency (rTMS) or polarity (tDCS) of stimulation. With respect to the mode of action, however, tDCS and TMS are somewhat complementary. Single pulse TMS has a good temporal resolution and produces short-lasting effects. The effect of tDCS is probably intracortical [33] and may be focally good temporal resolution and produces short-lasting effects. The TMS are somewhat complementary. Single pulse TMS has a modulation on the excitability of corticospinal output neurons depending on the frequency (rTMS) or polarity (tDCS) of stimulation. With respect to the mode of action, however, tDCS and TMS are somewhat complementary. Single pulse TMS has a good temporal resolution and produces short-lasting effects. The effect of tDCS is probably intracortical [33] and may be focally restricted [41], however, its temporal resolution is low. rTMS lies in between the aforementioned methods, depending on the strength, frequency and duration of stimulation. The spatial resolution of tDCS is somewhat poorer when currents are delivered through two 35 cm² water-soaked sponges, therefore, larger cortical areas are covered, compared to TMS where the diameter of the hot-spot is about 2 cm when a focal coil is used. Research is under way to clarify what extent the electrode sizes can be reduced. In particularly, when considering the interindividual variability of the visual cortex, MRI studies in the individual brain might turn to be also necessary. Thus, single pulse TMS is ideally suited to deliver information about the global involvement of a given cortical area in the performance of a task and its highly resolved time course. Specific gradual changes in performance, however, caused by tDCS-induced cortical excitability modulations, may deliver additional information about the specific functional role of a given area and help gain insight into the details of cortical information processing.

How specific is the technique? A recent PET study reported widespread spatial activation after tDCS [24]. Are these modifications simply due to a widespread change of the neuronal activities or do they represent topographically restricted processes? To our knowledge, there is no available fMRI data related to the effect of tDCS over the visual areas. A previous study investigated fMRI before and after 5 min tDCS of the left M1 to study movement-related changes in BOLD response during a finger opposition task [13]. Cathodal stimulation caused a decrease in the mean number of the activated pixels in the supplementary motor area (SMA) but not in the left M1, maybe due to technical difficulties elicited by the stimulation electrode. Additionally, in a recent study, we have measured motion after-effects after the stimulation of V5 and V1 (as a control) [10]. V5 stimulation resulted in a significant decrease of the duration of motion after-effects while V1 stimulation had no such effect. If the stimulation was simply related to a widespread neuronal activity, V1 stimulation would have also resulted in decreased after-effect, if we consider the huge number of feedback and feed-forward connections between V1 and V5. However, this was not the case. A similar result was obtained after the stimulation of M1 using a serial reaction-time task [35]. According to these studies, it is very likely that the functional effectiveness due to the stimulation is restricted mainly to the area under the electrode.

How safe is the technique? Most of the research groups are using 1 mA applying a 35 cm² surface area, thus, the actual current density is about 28 µA/cm². Nevertheless, higher current densities (up to 80 µA/cm²) are also applied and considered to be safe in human studies [20]. A single report described reversible functional neuronal changes in the brain of rats after repeated sessions of polarization using current densities higher than 300 µA/cm² [19] but there is no human evidence suggesting that similar currents can harm the brain. Indeed, much has to be learned about the safety of higher current densities and repeated applications. The relevant animal studies are being performed currently. Finally, it is important to mention that the first tDCS studies of the visual cortex in humans came from a single research group. These appeared only recently and are in the beginnings. There are independent ongoing studies performed by other groups, which include healthy subjects and patient groups (amblyopia, migraine). Therefore, it is likely that the literature concerning tDCS on the visual areas will increase profoundly in the future.

Since NMDA-receptors are involved in neuroplastic changes [14], the results suggest a possible application of tDCS in the modulation or induction of these processes in a clinical setting. Future work on tDCS as a potential rehabilitive tool in cases of cognitive impairment also represents a challenge.

References

tory brain activity changes following transcranial direct current stimu-

Z. Vighanszky, Direct current stimulation over M1 or V5 modulates

nisms underlie the after-effects of cathodal transcranial direct current stim-

[12] A.T. Butler, R. Jadhao, I.L. Freeston, Non-invasive magnetic stimula-

tion of BOLD-MRI responses to human somatosensory activation by transcranial

[14] M.R. Bennett, The concept of long term potentiation of transmission at

ing currents on the cerebral cortex of the rat (1) during current flow and (2)


changes during polarization of the motor cortex, J. Neurophysiol. 28
(1965) 179–189.

[18] M.A. Nitsche, J. Frahm, Regional modulation of
probabilistic classification learning by transcranial direct current stimu-


motor cortex by weak transcranial direct current stimulation, J. Physiol.

[21] L. Stewart, L. Battelli, V. Walsh, A. Cowey, Motion perception and

[22] A. Antal, M.A. Nitsche, J. Frahm, W. Paulus, Facilitation of implicit motor learning by weak tran-
scranial direct current stimulation of the primary motor cortex in the

[23] N. Islam, A. Moriwaki, Y. Hattori, Y. Hori, Appearance of dark neurons
following anodal polarization in the rat brain, Acta Med. Okayama 48

mann, Safety and cognitive effect of frontal dc brain polarization in

463
459