Transcranial direct current stimulation and visual perception

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Abstract. Membrane potentials and spike sequences represent the basic modes of cerebral information processing. Both can be externally modulated in humans by quite specific techniques: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). These methods induce reversible circumscribed cortical excitability changes, either excitatory or inhibitory, outlasting stimulation in time. Experimental pharmacological interventions may selectively enhance the duration of the aftereffects. Whereas rTMS induces externally triggered changes in the neuronal spiking pattern and interrupts or excites neuronal firing in a spatially and temporally restricted fashion, tDCS modulates the spontaneous firing rates of neurons by changing resting-membrane potential. The easiest and most common way of evaluating the cortical excitability changes is by applying TMS to the motor cortex, since it allows reproducible quantification through the motor-evoked potential. Threshold determinations at the visual cortex or psychophysical methods usually require repeated and longer measurements and thus more time for each data set. Here, results derived from the use of tDCS in visual perception, including contrast as well as motion detection and visuo–motor coordination and learning, are summarised. It is demonstrated that visual functions can be transiently altered by tDCS, as has been shown for the motor cortex previously. Up- and down-regulation of different cortical areas by tDCS is likely to open a new branch in the field of visual psychophysics.

1 Introduction
Modulation of cortical excitability and activity is a central mechanism of neuroplasticity (Bennett 2000). Long-term potentiation (LTP) and long-term depression (LTD) have been shown to be involved in learning processes in animal and human studies. As revealed by early animal studies, stimulation with weak electrical direct currents (DCs) can induce stimulation-polarity-dependent prolonged diminishments or elevations of cortical excitability, most probably elicited by hyperpolarisation or depolarisation of resting-membrane potentials. Most of these studies were performed in the 50s and 60s of the last century (Bindman et al 1964; Creutzfeldt et al 1962; Gartside 1968; Purpura and McMurtry 1964; Terzuolo and Bullock 1956). In the cat, anodal stimulation depolarised the soma of pyramidal tract cells, whilst cathodal stimulation hyperpolarised them (Creutzfeldt et al 1962; Purpura and McMurtry 1964). The induced potential shifts were not totally homogeneous, but depended on stimulation strength, cortical layer, and spatial orientation of the neurons. With sufficient duration of stimulation, the effect of stimulation can outlast the duration of the stimulation by several hours (Bindman et al 1964).

Early human studies were largely confined to the treatment of psychiatric diseases, mainly depression and mania. It was found that weak DC stimulation, with the anode placed supraorbitally, diminished depressive symptomatology (Constain et al 1964), while cathodal stimulation reduced manic symptoms (Carney 1969). In healthy subjects, anodal stimulation resulted in increased activity and elevated mood, while cathodal stimulation was followed by quietness and apathy (Lippold and Redfearn 1964). However, these effects could not be replicated by all follow-up studies, possibly because of different patient subgroups or other technical differences. Concerning healthy subjects, several electrophysiological and psychophysical studies were performed in the 80s.
In the visual cortex it was shown that anodal stimulation could modulate perception, the amplitude of the visual evoked potentials, and slow cortical activity during and after the end of DC stimulation (Korsakov and Matveeva 1982). However, despite these interesting combined electrophysiological and psychophysiological effects, the knowledge about the basic physiological properties of DC stimulation in humans remained incomplete.

The recent technique of transcranial magnetic stimulation (TMS) makes it possible to quantify the effects of tDCS on the excitability of the human cortex. TMS is ideally suited for the measurement of the effects of tDCS over the motor cortex, since it elicits motor-evoked potentials (MEPs). 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 in a polarity-dependent way, noninvasively and painlessly (Nitsche and Paulus 2000, 2001; Nitsche et al 2003b). Anodal stimulation increased the amplitude of MEPs while cathodal stimulation decreased them provided the stimulation duration and intensity were sufficient. The relevant stimulation parameters encompass not only the polarity but also the combination of current strength, size of the stimulated area, and duration of the stimulation (Agnew and McCreery 1987), and are considered to be safe (for reviews see Iyer et al 2005 and Nitsche et al 2003a; Poreisz et al 2007). In most studies on humans tDCS is delivered by a battery-driven constant-current stimulator through a pair of conductive rubber electrodes in a 5 cm x 7 cm isotonic-saline-solution-soaked synthetic sponge placed on the scalp. The current is applied for 3–20 min with an intensity of 1 to 2 mA.

2 Applying transcranial direct current stimulation (tDCS) in visual studies

As regards visual modality, the perceptual effects of tDCS were found to be in accordance with its physiological effects and mirrored those produced in the motor cortex: tDCS modulated the amplitude of visual evoked potentials (VEPs) (Antal et al 2004a), evoked by black-and-white sinusoidally modulated gratings in the on–off mode, modified the perception of phosphenes (Antal et al 2003a, 2003b), affected contrast sensitivity (Antal et al 2001) as well as motion detection thresholds (Antal et al 2004c), and reduced the duration of the motion aftereffect (Antal et al 2004d). It was also found that tDCS can modulate visuo-motor performance, and its effect depends on the type of the task and the time of the stimulation related to the phase of the task (learning versus overlearned). Table 1 summarises the stimulation parameters of all the tDCS studies related to the visual cortex.

(1) Cathodal tDCS over the primary visual cortex decreased, whilst anodal tDCS increased, the amplitude of the N70 component of the VEP which is a representative potential with respect to visual-cortex excitability. Significant effects were only observed when low-contrast visual stimuli were applied. High-contrast stimuli may activate the respective visual cortical areas maximally; therefore subthreshold excitability modulation induced by tDCS may produce fewer smaller changes in the VEP in this case. Both anodal and cathodal stimulations were effective, but their effect on the duration of the aftereffect was different: cathodal stimulation was more effective than anodal stimulation. The data are in agreement with other results of using tDCS in animal studies (Bindman et al 1964; Creutzfeldt et al 1962) showing that the effect of cathodal stimulation is stronger than the effect of anodal stimulation when identical stimulation parameters are used. However, as regards the stimulation polarity, an opposite effect was found in a recent study: anodal stimulation resulted in reduced P100 amplitude while cathodal stimulation increased it (Accornero et al 2007). These apparently discrepant results are probably due to different VEP modalities used: sinusoidal pattern onset in the first study and checkerboard pattern reversal stimulation in the second one. Furthermore, the position of the reference electrode (Cz vs neck) could have a strong influence on the tDCS effect.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Electrode position</th>
<th>Electrode size/cm²</th>
<th>Stimulation duration/min</th>
<th>Current strength/A</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accornero et al 2007</td>
<td>Oz vs posterior neck-base</td>
<td>40</td>
<td>3–10</td>
<td>0.001</td>
<td>anodal stimulation reduced P100, cathodal stimulation increased</td>
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<tr>
<td>Antal et al 2001</td>
<td>Oz vs Cz</td>
<td>35</td>
<td>7</td>
<td>0.001</td>
<td>elevated visual perception threshold by cathodal tDCS</td>
</tr>
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<td>Antal et al 2003b</td>
<td>Oz vs Cz</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
<td>phosphene threshold reduced by anodal and increased by cathodal tDCS</td>
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<tr>
<td>Antal et al 2003a</td>
<td>Oz vs Cz</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
<td>moving phosphene threshold reduced by anodal and increased by cathodal tDCS</td>
</tr>
<tr>
<td>Antal et al 2004c</td>
<td>left V5 vs Cz</td>
<td>35</td>
<td>7</td>
<td>0.001</td>
<td>modified motion perception threshold by anodal and cathodal tDCS</td>
</tr>
<tr>
<td>Antal et al 2004a</td>
<td>Oz vs Cz</td>
<td>35</td>
<td>5–15</td>
<td>0.001</td>
<td>elevated N70 amplitude by anodal and reduced N70 amplitude by cathodal tDCS</td>
</tr>
<tr>
<td>Antal et al 2004b</td>
<td>left V5 vs Cz</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
<td>improved visuo–motor learning by anodal tDCS</td>
</tr>
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<td>Antal et al 2004e</td>
<td>Oz vs Cz</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
<td>elevated gamma and beta oscillatory activities by anodal and reduced by cathodal tDCS</td>
</tr>
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<td>Creutzfeldt et al 1962</td>
<td>intracortical, visual, and motor cortex</td>
<td>0.001 seconds</td>
<td>up to 0.001</td>
<td>most neurons activated by anodal and deactivated by cathodal stimulation; reversed effect in deep layers and in sulci</td>
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</tr>
<tr>
<td>Korsakov and Matveeva 1982</td>
<td>occipital vs mastoid</td>
<td>0.79</td>
<td>130–200</td>
<td>0.0002</td>
<td>VEP-modulations by anodal stimulation; slow cortical activity changes; decreased perception sensitivity</td>
</tr>
<tr>
<td>Kupfermann 1965</td>
<td>visual cortex, implanted epidural electrodes</td>
<td>400 (proposed)</td>
<td>0.2 s</td>
<td>0.0002</td>
<td>cathodal stimulation impairs learning, anodal stimulation not effective</td>
</tr>
<tr>
<td>Landau et al 1964</td>
<td>motor, visual, somatosensory cortex surface</td>
<td>10–30 (proposed)</td>
<td>0.25 s</td>
<td>0.0001 – 0.0025</td>
<td>anodal stimulation increases amplitude of negative and decreases that of positive EP-waves, cathodal effect opposite; in surface and deep layers opposite effect; dependent on neuronal orientation</td>
</tr>
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<td>Morrell and Naitoh 1962</td>
<td>epidural electrodes, visual cortex</td>
<td>600 and more</td>
<td>0.05 s</td>
<td>0.00005</td>
<td>cathodal stimulation impairs performance, anodal improves it the next day</td>
</tr>
<tr>
<td>Szeligo 1976</td>
<td>epidural electrodes, visual cortex</td>
<td>45</td>
<td></td>
<td></td>
<td>increased negative VEP-waves by anodal stimulation; more effective with repetitive stimulation, less time needed to learn a visual avoidance task</td>
</tr>
<tr>
<td>Varga et al 2007</td>
<td>P6–P8 vs CZ</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
<td>cathodal stimulation reduced the duration of gender-specific aftereffect</td>
</tr>
<tr>
<td>Ward and Weiskrantz 1969</td>
<td>epidural electrodes, visual cortex</td>
<td>1800</td>
<td></td>
<td></td>
<td>visual discrimination decreased by anodal stimulation; effects depends on stimulation duration and intensity</td>
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Similarly to the effect of tDCS on VEP, cathodal tDCS resulted in decreased static
and dynamic contrast sensitivities of healthy human subjects after stimulation, probably
by decreasing cortical excitability (Antal et al 2001). However, the excitability enhance-
ment effect of anodal stimulation was not apparent, probably owing to a ceiling effect:
the stimulus used in 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. For quantification
of tDCS-induced excitability changes, phosphene thresholds (PTs), that is the lowest
intensity at which the phosphenes are detectable, were measured with short trains of
TMS pulses in healthy subjects before and after the end of anodal or cathodal stim-
ulation. Reduced PT was detected immediately and 10 min after the end of anodal
stimulation while cathodal stimulation resulted in an opposite effect (Antal et al 2003b).
However, we have to consider that phosphene perception is very subjective and phos-
phenes are relatively variable in position and form. Furthermore, the PTs are highly
dependent on the technical implementation of the experiment, for example the shape
and size of the stimulating coil and the induced current directions (Kammer et al 2001;

Our recent results provide evidence that external modulation of neural excitability
in human MT\(^+\)/V5 affects the strength of perceived MAE and support the involve-
ment of MT\(^+\)/V5 in motion adaptation processes (Antal et al 2004d). Both cathodal and
anodal stimulation over MT\(^+\)/V5 resulted in a significant reduction of the perceived
MAE duration, but had no effect on performance in a luminance-change-detection
task used to determine attentional load during adaptation. Similarly, a recent study
demonstrated that cathodal stimulation of the right temporo-parietal cortex reduces the
magnitude of facial adaptation, while stimulation over the V1 produces no significant
effects (Varga et al 2007). These data imply that mainly lateral temporo-parietal corti-
cal areas play role in facial adaptation and in facial gender discrimination, supporting
the idea that the observed aftereffects are the result of high-level, configural adaptation
mechanisms. In agreement with previous studies, we found that the inhibitory effect
of cathodal tDCS on adaptation is possibly related to the focal diminution of cortical
excitability due to membrane hyperpolarisation.

With respect to the functional effects of tDCS, it was surprisingly found that the
percentage of correct tracking movements increased significantly during and imme-
diately after cathodal tDCS of V5, whilst anodal stimulation had no effect when an
already learned manual visuo–motor tracking task was applied (Antal et al 2004c).
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 percep-
tual information processing needed for the task. The complexity of the task probably
produces a kind of noisy activation state of the encoding neuronal pattern in response
to different movement directions. Apart from this activation, not only the correct,
but also some incorrect, directions are activated simultaneously to a certain degree.
In this 'noisy' activation state cathodal stimulation may focus correct perception of
these parameters by decreasing the global excitation level and thus diminishing the
amount of activation of concurrent patterns below threshold. Therefore it improves
the signal-to-noise ratio and improves performance. This hypothesis was supported by
other studies with random-dot kinetograms (Antal et al 2004c). However, when tDCS
was applied during the learning phase of the same visuo–motor coordination task in
a different subject group, the performance increased significantly during a 2–5 min time
interval after the beginning of anodal stimulation of V5 or M1, whereas cathodal
stimulation had no significant effect (Antal et al 2004b). The positive effect of anodal
tDCS was indeed restricted to the learning phase, thus suggesting a highly specific
effect of the stimulation.
These studies imply that the effect of tDCS depends not only on the electrode position and the polarity of stimulation but also the type of the task and the duration of the stimulation with respect to the phase of the task. Previous studies on the motor cortex indicate that the direction of rTMS-induced plasticity critically depends on the pre-existing level of excitability (Lang et al 2004), suggesting the existence of a homeostatic mechanism in the human cortex that stabilises cortical excitability within a physiologically useful range. A similar mechanism in the visual cortex probably exists, and therefore the application of the tDCS before and during the task may result in a different functional state.

2.1 Molecular mechanism of tDCS
Whereas the effects during stimulation are most probably due to the DC-induced shifts of resting-membrane potential, this mechanism does not explain the induction of long-lasting aftereffects. As shown by previous studies (Gartside 1968; Islam et al 1997), the excitability-enhancing effects of anodal stimulation depend on protein synthesis. Additionally, they seem to involve cAMP modulations, changes in intracellular calcium level (Hattori et al 1990; Islam et al 1995a), and early gene expression (Islam et al 1995b). Additionally, it was also suggested that the aftereffects of cathodal tDCS include non-synaptic mechanisms based on changes in neuronal membrane function (Ardolino et al 2005).

Many recent pharmacological studies proved that the aftereffects are NMDA-receptor dependent (Liebetanz et al 2002; Nitsche et al 2004). It is known that long-lasting NMDA-receptor dependent cortical excitability and activity shifts are involved in neuroplastic modification. NMDA-receptor and intracellular sigma 1 receptor blocker dextromethorphan (DMO) intake prevented both anodal and cathodal tDCS-induced aftereffects, demonstrating that DMO critically interferes with the functionality of tDCS, irrespective of the polarity of DC stimulation (Liebetanz et al 2002). It was also demonstrated that D-cycloserine, a partial NMDA-agonist, selectively potentiated the duration of motor cortical excitability enhancements induced by anodal tDCS (Nitsche et al 2004). Dopaminergic mechanisms can stabilise these processes. In a recent study, the dopaminergic influence on NMDA receptor-dependent neuroplasticity was investigated using tDCS. The enhancement of D2 and—to a lesser degree—of D1 receptors by pergolide consolidated tDCS-generated excitability diminution up until the morning after stimulation (Nitsche et al 2006).

2.2 Duration of the aftereffects of tDCS
Previous studies on the motor cortex determined that by varying the duration of tDCS one could change the duration of the aftereffects (Nitsche and Paulus 2000, 2001). Motor cortical tDCS lasting 2–5 min was already effective in eliciting aftereffects, however, in a VEP study (Antal et al 2004a) this was the case only for cathodal stimulation. Stimulation lasting 10 min resulted in a 10 min aftereffect; 15 min of stimulation produced longer (20 min) aftereffects from cathodal stimulation. However, this duration is relatively short compared to the 30–60 min aftereffects elicited by motor cortical tDCS produced by the same stimulation durations. A possible explanation for this difference is provided by anatomical and physiological characteristics of the motor and visual cortices: there are partly different types of neurons and neurotransmitters/neuromodulators in the two cortices, and the motor cortex is more an indirect ‘output’ area while the visual cortex is mainly responsible for filtering and transferring the information towards other cortical areas; therefore it is more like an ‘input’ area. However, it could also be argued that the primary visual cortex is less ‘plastic’ compared to the primary motor cortex under tDCS.
3 Conclusions and perspectives
Weak DC stimulation can induce acute as well as prolonged cortical excitability and activity changes over the motor and visual areas. It influences the activity of the brain electrically and changes organised cortical activity transiently and reversibly in a non-invasive, painless way, like repetitive TMS (rTMS). With respect to the mode of action, however, tDCS and rTMS are somewhat different. Whereas rTMS induces externally triggered changes in the neuronal spiking pattern and interrupts or excites cortical activity in a spatially and temporally restricted fashion, tDCS most likely modulates the spontaneous firing rates of neurons by changing resting-membrane potential and thus modifies ongoing neuronal activity and related functional performance. rTMS is loud and often induces muscle contraction during the stimulation. Furthermore, when stimulus duration is longer than 2 min, a coil-holder is needed. tDCS induces only light itching of the skin under the electrode at the beginning of the stimulation. Therefore it is more suited for studies where sham stimulation is also necessary.

Both methods are safe and their applications over the motor and visual areas are well-documented. However, compared to TMS, tDCS is less focal. Spatially, relatively large electrode size (35 cm$^2$) is used and, temporally, resolution of the stimulation is not so optimal. Nevertheless, in the case of both methods, we also have to consider that modulation of the excitability of a given brain area is unlikely to affect neuronal function only in that targeted brain region. When activity of a given brain area is modified, the behavioural impact is the consequence of how the rest of the brain copes with the modulation of the activity. Our studies show that excitability modulation in a neuronal network of V1, M1, and V5 leads to changes in brain activity which can influence behaviour in different ways.

The early effects of DC stimulation in humans are attributed to changes in membrane polarisation by analogy with the animal studies. However, the current densities applied in the human studies are much lower than those in animal studies (see table 1). Probably the position of the electrodes is more critical in the case of human studies. Future studies will, no doubt, be devoted to the calculation of the effective current, depending on the electrode positions and distances, required to change a perceptual function. The other critical point related to membrane polarisation is the difference in timing between the animal and human studies. However, technically it is not yet possible to determine the lag at the beginning of the DC effects in humans.

To make tDCS relevant not only for basic research purposes, but also for clinical applications, additional studies are necessary, especially studies on extending the duration of the effects and accompanying safety studies. In principle, the use of tDCS could be beneficial in conditions and diseases accompanied by pathological changes of the cortical excitability of the visual areas, eg in amblyopia, migraine, photosensitive epilepsy, and neglect. Our results also raise the possibility of using tDCS in the rehabilitation from brain injuries in which visuo–motor coordination is impaired because of deficient visual processing.

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