

Transcranial direct current stimulation and human neuroplasticity

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Summary of Ph. D. thesis
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Summary

Neuroplastic changes are the essence of learning, memory, higher-order cognitive functions and recovery after central nervous system injuries. These can be modulated by transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) and partly examined by single pulse transcranial magnetic stimulation (TMS). TDCS is a non-invasive stimulation technique which offers the possibility to induce prolonged excitability alterations in different cortical areas. Early animal experiments have revealed that depending on the direction of the current in the targeted brain region, cathodal tDCS reduces spontaneous firing rates of cortical cells, most likely by hyperpolarizing the cell body, while anodal stimulation results in the opposite effect. TDCS became a widely used, safe method for non-invasively examining cortical excitability in humans.

Transcranial direct current stimulation

One aim of developing external stimulation methods in humans was to modify cerebral excitability in a non-invasive, painless, reversible, and selective way. RTMS is the most widely used stimulation method in the experimental neurophysiology. It is able to induce externally triggered alterations in the spiking pattern of neuronal populations, and interrupts or excites neuronal firing in a spatially and temporally restricted route.

In contrast to TMS, tDCS has a longer after-effect (AE), which depends on stimulus duration and stimulus intensity. It was demonstrated in animal studies that direct current induced AEs can last for five hours. The AEs of tDCS in the human motor cortex can be detected for up to 90 minutes post-stimulation in a polarity-specific way. AEs on the visual cortex were measured by recording visual evoked potentials (VEP) and oscillatory brain activity. The AE observed in the somatosensory cortex were studied by comparing the change in the somatosensory evoked potential (SEP) amplitudes before and after tDCS. The long-lasting AE of DC stimulation was detected by the alteration in regional cerebral blood flow (rCBF) by $H_2^{15}O$ positron emission tomography. Anodal tDCS induced an increase in rCBF, while cathodal stimulation diminished rCBF in cortical and subcortical areas. This effect remained stable for 50 minutes.

Neuronal activity can be described as the frequency of spike firing, which is determined by the neuronal membrane potential. Single-cell recording studies have shown that direct current (DC) is able to modulate resting membrane potential in a polarity-specific way, but direct current stimulation does not cause spontaneous neuronal firing. While negative currents

(cathodal stimulation) can reduce firing rates, positive currents (anodal stimulation) are able to reverse this effect. Furthermore, the effect of DC depends on current density, stimulus duration and intensity.

According to the literature and our experiments, tDCS is a safe, non-invasive, repeatable stimulation technique. The most commonly mentioned, non-specific side effects can be: local tingling sensation, fatigue, nausea, insomnia. There is no data in the literature reporting epileptic jerks elicited by tDCS. Furthermore, the anticonvulsant effect of cathodal tDCS in a rat model was published.

Several pharmacological studies tried to reveal the role of neurotransmitters in the DC-induced neuroplastic changes. The importance of catecholamines, as well as GABAergic, glutamatergic and dopaminergic mechanisms were described in tDCS induced neuroplasticity in humans.

Neuroplasticity

Neuroplasticity is the ability of the nervous system to alter its functional organisation as a result of experience. It can be a part of either normal learning procedures or recovery after injuries. Such injuries can occur following stroke, hypoxic events, or trauma. Cortical plasticity is based on both cellular modifications and changes in neuronal networks. Plastic changes in the human nervous system can be modulated by tDCS and partly examined by TMS.

After-effects

The motion after-effect (MAE) is one of the fundamental and widely used perceptual manifestations of the neuronal adaptation process, and plays an important role in visual neuroplasticity. It was previously described that motion detection and MAEs are linked to the extrastriate area V5. A special type of AE has been described that involves the perception of face: prior adaptation strongly biases face perception by causing the original face to appear distorted in a direction opposite to that of the adapting distortion, so the prolonged exposure to a face can result in the consistent misperception of subsequently presented faces. It was also published that the above described “figural or face after-effect” plays a crucial role in gender discrimination.

Cortical excitability and migraine

Migraine is one of the most common neurological disorders. There are contradictory data concerning the evidence of cortical hypo- or hyperexcitability between and during migraine attacks. The background of this idiopathic headache is probably linked to interictal central neuronal hyperexcitability.

The aim of the studies

In the first experiment we tried to elucidate whether tDCS is able to influence primary visual information processing, so we recorded VEPs using black and white sinusoidal gratings and analysed VEP-related beta and gamma wave oscillations before and after anodal and cathodal tDCS of the primary visual area (V1).

Our research group had previously reported that contrast perception threshold can be modified by tDCS and TMS induced moving phosphene thresholds can be also altered by tDCS. TMS over V1 elicits static phosphenes, stimulation over V5 leads to moving phosphenes. The aim of our second experiment was to clarify whether V5 is linked to the neural network involved in the adaptation-induced MAE in healthy humans. Simultaneously with this task, the attentional load of the subjects was tested during adaptation, because it has been previously described, that attention can affect the strenght of MAE.

Facial adaptation is a special case with respect to after-effects, as it is influenced by higher-order cognitive functions. In the third study we tried to elucidate the impact of tDCS in healthy volunteers over the temporo-parietal cortex, revealing either fundamental visual and higher-order cognitive functions, like face recognition and gender discrimination, interact with adaptation mechanisms.

In the fourth experiment we tried to clarify the underlying mechanisms of altered motion perception in V5 in migraine patients between attacks using different moving dot kinetograms. We also tried to find relationships between performance and clinical parameters (the duration and frequency of migraine attacks, and the time between the last attack and the task). Our main aim in this study was to find psychophysical evidence for cortical hypo- or hyperexcitability in migraineurs between migraine attacks, as previous results are still conflicting.

Our experiments

Materials and methods

Subjects: All of the participating subjects gave written informed consent according to the Declaration of Helsinki. The experiments were approved by the Ethics Committee of the University of Göttingen, Germany. All of the subjects had a visual acuity better than 0.9 (with or without correction). None of them were pregnant or had any metallic implants (either intra- or extracranially). They had no previous history of drug or alcohol abuse nor psychiatric disorders. None of the subjects were under any medication at the time of the experiments. All of the participants were blinded concerning the type of the stimulation. Healthy volunteers participated in the first, second and third experiment. Healthy subjects were compared with migraine patients in the fourth study.

TDCS studies: TDCS was delivered through a pair of rubber electrodes (placed in 5x7 cm saline-soaked sponges) by a battery-driven constant current stimulator (Schneider Electronic, Gleichen, Germany stimulator was used in the visual cortex experiments and Neuro Conn GmbH stimulator from Ilmenau, Germany in the face perception tasks). Current intensity was 1.0 mA in all of the experiments. Electrodes were positioned according to the International 10-20 System. For control stimulation we used displaced electrodes 6 cm lateral to Oz in the first experiment and sham stimulation in the other studies. All of the sessions were separated by at least one week to avoid interference effects between anodal and cathodal stimulation.

First experiment (oscillatory brain activity):

An increase in the high-frequency oscillatory activity in the beta and gamma frequency ranges are closely related in time to the N70 peak of VEP, which is an early sensory component of visual activation. Therefore, VEPs were recorded in 13 volunteers to observe changes in high-frequency oscillatory activity in V1. VEPs were recorded using sinusoidal luminance gratings in an on/off mode before, during, immediately after and 10, 20, 30 min after the end of 10 min anodal and cathodal tDCS. Cathodal stimulation significantly decreased, while anodal stimulation slightly increased the normalized beta and gamma oscillations.

We have shown that tDCS transiently and reversibly changed the organized cortical activity elicited by visual stimulation. Since gamma activity is also linked to higher level information

processing, tDCS might be a useful method to affect higher-order cognitive functions.

Second experiment (motion after-effects):

TDCS was used to test whether extrastriate area V5 is part of the neural network involved in the long-term adaptation-induced MAE in 13 healthy human volunteers. We measured the duration of MAE before, during, immediately after and 15 and 60 min after the end of 15 min anodal and cathodal tDCS over left V5 and V1.

Each trial consisted of two parts: adaptation phase and motion after-effect test. The adapting and test stimuli were displayed in a rectangular aperture in the right visual field. The adapting stimulus consisted of 100 coherently moving white dots against black background.

Simultaneously with this task, the attentional load of the subjects was tested during adaptation. During adaptation, 60% of the dots increased in luminance. Luminance changes were controlled by a staircase to keep performance at a 70% level of correct responses in the attentional task and thus to ensure a constant attentional level in all testing conditions. The motion after-effect test consisted of a static field of 100 randomly placed dots.

We found that both cathodal and anodal tDCS over V5 has significantly reduced the perceived MAE duration, but did not influence the performance of the subjects in the attentional task. Our control experiment over V1 excluded the possibility that the observed V5 stimulation effects were due to a diffused modulation of the early cortical regions, i.e. by the stimulation applied over V5. These results provide evidence that the external, non-invasive modulation of neural excitability in human V5 affects the strength of perceived MAE and support the involvement of V5 in motion adaptation processes.

Third experiment (face perception):

Figural or face after-effect plays crucial role in social interactions and gender discrimination. The aim of this study was to determine, using tDCS, how the retinotopically organised V1 and higher-level, non-retinotopic right lateral temporo-parietal areas interact with facial adaptation processing. Seventeen healthy subjects received 10 min anodal, cathodal or sham stimulation over these areas during a facial adaptation task.

Cathodal stimulation of the right temporo-parietal cortex reduces the magnitude of facial adaptation while stimulation over the V1 results in no significant effects. These data imply that mainly lateral temporo-parietal cortical areas play role in facial adaptation and in facial gender discrimination, supporting the idea that the observed after-effects are the result of high-level, configurational adaptation mechanisms.

Fourth experiment (motion perception in migraineurs):

We aimed to clarify whether cortical hypo- or hyperactivity is responsible for the interictal abnormal visual processing in migraineurs. Twenty migraine subjects and 20 healthy volunteers participated in the experiment [9 migraine patients without (MoA) and 11 with aura (MA)]. Two types of dot kinetograms were used: in the first part coherently moving dots were presented in an incoherent environment, while in the second part only coherent motion was seen. Migraineurs displayed significantly impaired motion perception compared with healthy volunteers when they had to detect the direction of the coherently moving dots in an incoherent environment, while they were slightly better in a direction discrimination task, where only coherent motion was presented. These results are comparable with those achieved by an external excitability enhancement of V5 induced in healthies in the second experiment. According to this, a cortical excitability enhancement can result in an impaired focusing on a given signal against a noisy background, but improves perception of non-ambiguous stimuli. Thus we conclude that migraine patients display enhanced visual cortical excitability between attacks in V5.

Conclusions

We have demonstrated that tDCS permits a non-invasive, painless method for manipulating cortical network activity in the human and as a result can cause perceptual changes. We have shown that tDCS is able to alter the oscillatory brain activity in V1. It can also modulate the visual cortex excitability of extrastriate visual cortical area V5, suggesting that this region is part of the neural network underlying motion adaptation. Our data also imply that mainly lateral temporo-parietal cortical areas participate in facial adaptation and facial gender discrimination. These support the idea that tDCS can modulate not only basic visual but higher-order cognitive functions as well. The results of our migraine study give evidence for cortical hyperexcitability in migraineurs with and without aura.

In comparison with TMS, the other widely used non-invasive stimulation technique, tDCS offers an easier and cheaper way to induce acute and persistent neuronal excitability changes without disrupting ongoing neuronal activity. The temporal resolution of tDCS is smaller when compared to TMS or even rTMS, whereas the duration of the induced after-effect is longer. We could see in the second experiment that the relatively closely located V1 and V5

areas can be separately stimulated in spite of the large electrodes, suggesting that tDCS has a focal effect, confirming prior data.

From the perspective of the subjects tDCS does not cause any pain, and the overall side-effects (mild tingling sensation under the electrode, fatigue, nausea, insomnia) are tolerable. The results of tDCS studies are easily reproducible; the sham stimulation is also easily executed without muscle and noise artefacts and without causing any inconvenience to the subjects.

We believe that the further application of tDCS will help us to understand higher-order cognitive functions and neuroplastic changes either in the healthy or impaired nervous system. Furthermore, tDCS may offer therapeutic options for patients suffering from focal epilepsy, dystonia, pain, and stroke.

Original papers listed in the thesis

I. Andrea Antal, **Edina T. Varga**, Tamás Z. Kincses, Michael A. Nitsche and Walter Paulus. Oscillatory brain activity and transcranial direct current stimulation in humans. *NeuroReport* 2004; 15(8):1-4.

II. Andrea Antal, **Edina T. Varga**, Michael A. Nitsche, Zoltán Chadaide, Walter Paulus, Gyula Kovács, Zoltán Vidnyánszky. Direct current stimulation over MT+/V5 modulates motion aftereffect in humans. *NeuroReport*, 2004; 15(16):2491-2494.

III. **Edina T. Varga**, Elif Kaya, Andrea Antal, Marta Zimmer, Iren Harza, Walter Paulus, Gyula Kovacs. Cathodal transcranial direct current stimulation over the parietal cortex modifies facial gender adaptation. *Ideggyogy Sz* 2007; 60(11-12):474-479.

IV. Antal A, Temme J, Nitsche MA, **Edina T. Varga**, Lang N, Paulus W. Altered motion perception in migraineurs: evidence for interictal cortical hyperexcitability. *Cephalalgia* 2005; 25(10):788-94.

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