Transcranial direct current stimulation and human neuroplasticity

Edina Tímea Varga, M.D.

University of Szeged
Albert Szent-Györgyi Clinical Center
Faculty of Medicine
Department of Neurology

Supervisor: Andrea Antal, Ph.D.

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Summary

Neuroplastic changes are the essence of learning, memory, higher-order cognitive functions and recovery after central nervous system (CNS) injuries (Siebner et al., 2004; Hallett 2001). 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) (Wagner et al., 2007). TDCS is a non-invasive stimulation technique which offers the possibility to induce prolonged excitability alterations in different cortical areas (Priori, 1998; Nitsche and Paulus, 2000; Antal et al., 2001; Antal et al., 2008a, Monti et al., 2008). 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 (Creutzfeldt et al., 1962; Bindman et al., 1964; Purpura et al., 1965). TDCS became a widely used, safe method for non-invasively examining cortical excitability in humans (Poreisz et al., 2007; Antal and Paulus, 2008).

It has been demonstrated, that oscillatory brain activity perpetuates in the formation and transmission of perceptual and behavioral functions (Engel and Singer, 2001). Hence in the first experiment, as it is described in this dissertation, we aimed to modulate the high-frequency oscillatory activity of the visual cortex and register the stimulation-induced alterations with electrophysiological methods. We demonstrated that cathodal tDCS significantly diminished, while anodal stimulation slightly elevated the normalized high-frequency beta and gamma oscillations in the primary visual cortex (V1).

In the second experiment we aimed to test whether middle temporal area (V5) is a part of the neural network involved in visual adaptation-induced motion after-effects (MAE) in healthy human volunteers. After-effects are manifested as visual illusions after prolonged viewing of visual displays (pattern adaptation). The best known after-effect is the MAE, when the stationary stimulus appears to move to the opposite direction from the original image. This phenomenon is belived to be the result of adaptation (Wolgemuth, 1911; Barlow and Hill, 1963). We measured the duration of the MAE evoked by the same adapting motion before, during and after tDCS, when applied over V1 and a part of the extrastriate visual pathway: the middle temporal area V5. We found that external modulation of neural excitability by weak tDCS in human V5 influences the strength of percieved MAE, suggesting that V5 is a part of the neural network underlying motion adaptation.

We also showed in the third experiment that higher-order visuo-cognitive functions, like figural after-effect using faces can be modified by weak tDCS. We found that facial adaptation is linked to the right

temporo-parietal cortex.

In the fourth experiment we compared motion perception in migraineurs with and without aura compared to healthy controls. We used moving dot kinetograms with and without distractor and measured performance and reaction times. We found that the motion perception threshold is higher among migraine patients than healthy controls in the task when the direction of coherent motion needed to be identified in an incoherent environment. Migraineurs showed a better performance in the task when only coherent motion was presented without distractors. These results give evidence for cortical hyperexcitability in migraineurs with and without aura.

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.

List of abbreviations

ACh – acetylcholine

ADA – with adaptation

ADM - abductor digiti minimi muscle

AE - after-effect

CBZ – carbamazepine

CNS - central nervous system

cpd – cycles per degree

DA - dopamine

D1-receptor - dopamine-receptor type 1

D2-receptor - dopamine-receptor type 2

DC - direct current

dCS - dynamic contrast sensitivity

EBA - extrastriate body area

ECBs - endogenous cannabinoids

EEG - electroencephalography

FFA - fusiform face area

fMRI - funtional magnetic resonance imaging

GABA – gamma-aminobutyric acid

LTD - long-term depression

LTP - long-term potentiation

M1 - primary motor cortex

MA - migraine with aura

MAP - motor action potential

MAE - motion after-effect

MEP - motor evoked potential

MoA - migraine without aura

MRI - magnetic resonance imaging

NMDA - N-methyl-D-aspartate

PT - phosphene threshold

rCBF - regional cerebral blood flow

RT - reaction time

rTMS - repetitive transcranial magnetic stimulation

sCS - static contrast sensitivity

SEP - somatosensory evoked potential

tDCS - transcranial direct current stimulation

TMS - transcranial magnetic stimulation

V1 - primary visual cortex

V5 - middle temporal area

VEP - visual evoked potential

Introduction

Plastic changes in the human nervous system can be modulated by tDCS and partly examined by TMS (Wagner et al., 2007). TDCS allows diagnostic and interventional applications (Nitsche and Paulus, 2000; Liebetanz et al., 2002; Webster et al., 2006; Fregni and Pascual-Leone, 2007). They also offer a potential therapeutic use in neurorehabilitation, chronic pain, focal epilepsy and neuropsychiatric disorders (Webster et al., 2006; Fregni et al., 2006a; Liebetanz et al., 2006; Antal et al; 2008).

Neuroplasticity in the central nervous system

Neuroplasticity is the ability of the nervous system to alter its functional organisation as a result of experience (Nudo, 2006). It can be a part of either normal learning procedures or recovery after injuries. Such injuries can occur following stroke, hypoxic events, or trauma (Hallett, 2001; Siebner et al., 2004; Karmarker and Dan, 2006). Cortical plasticity is based on both cellular modifications and changes in neuronal networks (Karmarker and Dan, 2006).

Several types of so-called 'injury-induced plasticity', or rearrangement of the nervous system in response to injury, have been known for decades to generate functional recovery. Among these mechanisms are 'unmasking' of synapses or pathways that may ordinarily be inactive; 'denervation hypersensitivity', in which the target of a partially lesioned projection produces a great number of receptors to bind to a reduced number of available neurotransmitter molecules; and 'compensatory collateral sprounting', wherein the injured distal components of axons that are spared by a lesion sprout to occupy adjacent synapses vacated by lesioned neighbouring axon (Hallett, 2001; Hámori et al., 1990).

The cellular mechanisms of short-term neuroplastic changes are based on different mechanisms (Hallett, 2001), for example by unmasking. The unmasking form of plasticity can occur very rapidly - within minutes of an injury- and it is the change in the balance between excitation and inhibition. A change in neuronal membrane excitability may occur via voltage-gated channels, and most likely via sodium channels. Long-term potentiation (LTP) and long-term depression (LTD) are the fast enhancement and diminution of already existing synapses. However, several studies have shown morphologic evidence for neuroplasticity, which requires a longer period of time (formation of new synapses and sprouting of new axon terminals). Hámori et al. (1990) demonstrated synaptic regeneration in the adult central nervous system following deafferentation: axonisation of dendrites leads to formation of new dendro-dendritic synapses and the reduction in the size of the denervated

nerve cells, leading to the relative increase in density of the surviving axon terminals. Detection of calcium accumulation in the dendritic spines is a well-described method to demonstrate synaptogenesis under electron microscopy (Toni et al., 1999). Peripheral denervation can also lead to the rearrangement of the cortical homunculus in different sensory modalities via axonal sprouting (Elliott et al., 1996).

The role of neurotransmitters is also an essential one with regard to neuroplastic changes (Kuo et al., 2007). For example, the significance of cholinergic neuromodulation in arousal, attention, learning and memory can be modelled in neurodegenerative disorders with cognitive impairments, like Alzheimer´s disease. Acetylcholinesterase inhibitors (rivastigmine, donepezil) are used as a treatment for cognitive impairments like Alzheimer´s disease and vascular dementia (Waldemar et al., 2000). Besides this, Kuo et al. (2007) demonstrated that acetylcholine (ACh) is able to modify both the anodal and cathodal tDCS-induced neuroplastic after-effects in healthy humans. ACh and dopamine (DA) have neuromodulatory effects on cortical excitability and synaptic plasticity leading to LTP, whereas glutamatergic processes participate in LTD. However, dopamine plays a role in LTD processes by activating D2-receptors it leads to the release of endogenous cannabinoids (ECBs), inducing LTD in the striatum (Calabresi et al., 2007). ECBs participate in LTP also, as demonstrated in memory and learning procedures (Zhu, 2006).

Neuroplastic mechanisms participate in diversity of sensory processes involving several brain areas. The stimulus-specific activity is possibly transmitted via high-frequency neuronal oscillations, participating in perceptual and learning processes (Engel and Singer, 2001; Bibbig et al., 2002). These high-frequency oscillations can be registered with scalp electroencephalography (EEG): beta frequency ranges from 15 to 30 Hz, while gamma frequency ranges 30-60 Hz.

Transcranial stimulation techniques in humans

Transcranial magnetic stimulation

One aim of developing external stimulation methods in humans was to modify cerebral excitability in a non-invasive, painless, reversible, and selective way. The first well-known and commonly used non-invasive stimulation method was rTMS, which 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 (Wagner et al., 2007; Antal et al., 2008). The magnetic field is able to pass through tissues with high resistance (bone, fatty acid) without being changed. The selective and transient effect of rTMS over the motor cortex can be quantified by measuring the amplitude of elicited

single pulse motor evoked potentials (MEP) (Barker, 1985; Priori et al., 1998; Nitsche and Paulus 2000; Nitsche et al., 2002). TMS can also modify visual perception when it is applied over the visual cortex (Amassian et al., 1998). TMS has good temporal resolution; however it produces only a short after-effect (AE).

Single pulse TMS is widely used in the routine diagnosis of pathological changes of the corticospinal tract (e.g. amyotrophic lateral sclerosis, multiple sclerosis, compressive myelopathies) and to estimate its integrity (Wagner et al., 2007).

Transcranial direct current stimulation

In contrast to TMS, tDCS has a longer after-effect, which depends on stimulus duration and stimulus intensity (Bindman et al., 1964; Nitsche and Paulus 2000; Nitsche and Paulus, 2001; Antal et al., 2001; Nitsche et al., 2003b; Antal et al., 2004a; Liebetanz et al., 2006). Bindman was the first who has demonstrated that direct current induced AEs can last for five hours in animals (Bindman et al., 1964). Nitsche and co-workers have shown that the AEs of tDCS in the human motor cortex can be detected for up to 90 minutes post-stimulation in a polarity-specific way (Nitsche and Paulus, 2001). AEs on the visual cortex were measured by recording visual evoked potentials (VEP) and oscillatory brain activity (Antal et al., 2004a). The AE observed in the somatosensory cortex were studied by comparing the change in the somatosensory evoked potential (SEP) amplitudes before and after tDCS (Matsunaga et al., 2004). They observed that anodal tDCS over the somatosensory cortex can induce long-lasting (60 minutes) increments in the size of ipsilateral cortical SEP amplitudes. 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 (Lang et al., 2005). 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 mechanisms of transcranial direct current stimulation

The basic neuronal mechanisms of tDCS were first described in the late 1950's and 1960's (Terzuolo and Bullock, 1956; Bindman et al., 1962; Purpura and McMurtry, 1965; Creutzfeldt et al., 1962). Neuronal activity can be described as the frequency of spike firing, which is determined by the neuronal membrane potential (Creutzfeldt et al., 1962; Bindman et al., 1962). 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 (Creutzfeldt et al., 1962). Furthermore, the effect of DC depends on current density, stimulus duration and intensity (Nitsche and Paulus, 2000). TDCS effects may also depend on either the macroscopic arrangement or anatomical ultrastructure of the neurons under the electrode, as it was reported in previous animal (Creutzfeldt et al., 1962) and human motor studies (Nitsche et al; 2003c). The special spatial neuronal structure can lead to altered current flow in the neighbouring areas (e.g. cathodal tDCS of the supplementary motor cortex results in an additional slight anodal stimulation in the primary motor cortex) (Liebetanz et al., 2002; Nitsche et al., 2003a; Antal et al., 2003).

Human tDCS studies regarding the motor cortex

The first experiment detailing non-invasive human brain polarisation with weak direct current was published one decade ago (Priori et al., 1998). They measured the effect of tDCS on TMS-evoked motor evoked potentials (MEP). MEPs of the right first dorsal interosseous muscle were elicited from the left primary motor cortex (M1). They performed four different experiments investigating the effect of DC on the peak-to-peak amplitude, duration and latency of MEPs and the H-reflex. They have found that cathodal DC conditioning (0.3 mA, 7 sec) did not alter the mean amplitude of TMS elicited MEPs. Conversely, anodal stimulation lead to significant increase in MEP amplitudes. The increment of anodal current strength (from 0.075 to 0.5 mA) increased the MEP amplitude. TDCS did not alter either the latency or duration of the MEP or the H-reflex. The fact that scalp DC did not influence H-reflex sustains the hypothesis that DC acts presynaptically on pyramidal cells (on cortical excitatory interneurones) and not on pyramidal cells themselves.

Nitsche and Paulus (2000) published the stimulus dependent effect of tDCS on the human M1 in their study on healthy volunteers. The excitability of the motor cortex was measured by the amplitude changes in the recorded MEPs, elicited by single pulse TMS. The cortical representational field of the right abductor digiti minimi muscle (ADM) in the homunculus (left M1) was identified using single pulse TMS. In the first setting, the baseline MEP amplitude of the right ADM was determined by finding the best coil position that elicited the largest MEP amplitude. They published that a stimulus duration of at least 3 min at 1 mA or an intensity of 0.6 mA for 5 min was required to induce after-effects. They found the optimal electrode arrangement: the active electrode over the motor cortex and the reference over the contralateral orbit. Anodal tDCS enhances the TMS elicited MEP, whereas

cathodal stimulation diminished it. The effect of tDCS was probably induced via the modulation of the resting membrane potential.

For sham (placebo) stimulation the current was delivered for 5-10 sec at the beginning of the measurement with the same electrode positions as for verum stimulation. So subjects can experience the same sensations (mild local tingling) as during the beginning of real anodal or cathodal stimulation (Antal et al., 2004a).

Human tDCS studies of the visual cortex

Antal et al. (2001) have published a pilot study giving evidence for the modulation of visual perception in human V1 in healthy volunteers. The study was based on the measurement of contrast threshold, which is one of the standard paradigms in visual psychophysics (Kelly et al., 1976; Meyer et al., 1991). They applied tDCS (anodal and cathodal stimulation) to the occipital cortex. Visual stimuli were Gabor patches (vertical Gaussian filtered black and white sinusoidal gratings). Binocular static (sCS) and dynamic contrast sensitivity (dCS) were measured. The active electrode was placed over Oz, which is the scalp representation of V1, while the reference electrode was positioned over Cz, according to the International 10/20 System (Deuschl et al., 1999). For anodal stimulation the direction of electric flux was reversed. In this study the current was applied for 7 min with an intensity of 1 mA. Cathodal tDCS significantly diminished both the sCS and dCS during and immediately after stimulation. A 10 min long AE was observed. Anodal stimulation did not influence contrast sensitivity. This was the first human study, revealing that the elementary visual functions can be transiently modified by tDCS, probably by modulating neural excitability.

The first electrophysiological evidence of DC effect on the healthy human V1 was published in 2004 (Antal et al., 2004a). The amplitude and latency of the N70 and P100 VEP peaks were measured. Stimuli were high- and low-contrast sinusoidal luminance gratings. VEPs were recorded at Oz, O1, O2 electrode positions (according to the International 10-20 System). The reference was Fz, while the ground was placed on the forehead. Weak DC stimulation (1 mA) was delivered using a pair of 5x7 cm rubber electrodes enchased in saline-soaked synthetic sponges. The stimulus durations were 5, 10 and 15 min. VEPs were measured immediately after and 10, 20, 30, 40 minutes after the end of the different stimulus durations.

Significant DC after-effects were observed only on the VEP amplitudes using low-contrast stimuli. No significant effects were detected for the latency of the VEP components. The presentation of high-

contrast stimuli did not modify VEP amplitudes. Furthermore, it was found that the optimal stimulation position was over Oz. Anodal tDCS significantly enhanced, while cathodal stimulation diminished the amplitude of the N70 component. Cathodal tDCS could slightly (but not significantly) increase the amplitude of P100. They concluded that cathodal stimulation was more effective than anodal stimulation in this paradigm. This is in agreement with the findings from previous animal and human studies (Bindman et al., 1964; Creutzfeldt et al., 1962; Antal et al., 2001). The authors suggested that the cathodal stimulation of V1 may cause an additional anodal stimulation in the neighbouring V2 and V3 areas (causing an increment in the P100 amplitude).

TMS pulses delivered to V1 can elicit visual sensations called phopshenes (Meyer et al., 1991). The mean TMS intensity required to elicit phosphenes, is defined as the phosphene threshold (PT). PT is stable within subjects across time and is a fundamental representation of visual cortex excitability (Boroojerdi et al., 2000).

Antal and coworkers used TMS elicited phosphenes to determine whether anodal or cathodal DC can modulate PTs (Antal et al., 2003). They elicited phosphenes by applying short trains of 5 Hz rTMS delivered over V1. PTs were measured before, immediately, 10 min and 20 min after 10 min anodal, cathodal or sham DC stimulation (current intensity was 1 mA, stimulating electrode was placed over Oz, reference over Cz). They found that cathodal stimulation significantly increased PT, probably due to diminished cortical excitability. Anodal stimulation resulted in the opposite effect, probably via cortical hyperexcitability. In contrast to effects seen in the motor cortex, the AEs in the visual cortex are of a shorter duration (Bindman et al., 1964; Nitsche and Paulus, 2001). These results suggest that V1 is less plastic than M1, at least with regard to tDCS. Furthermore, the shorter duration of the AEs may be due to the differences in anatomical structure of visual and motor cortices, leading to different effects in the stimulated cortical layers.

Safety aspects of tDCS

To determine the safety limits of tDCS, current density, total charge, charge per phase, charge density and stimulus duration have to be considered (Agnew and McCreery, 1987; Nitsche and Paulus, 2000). **Current density** [stimulus intensity (A)/electrode size (cm^2)], **total charge** [stimulus intensity (A)/electrode size (cm^2) x total stimulus duration (ms)] and **stimulus duration** regulate the application of tDCS. We used 1 mA stimulus intensity in all of our studies, but there are some other groups who have applied 2 mA, e.g. Fregni's pain experiments (Fregni et al. 2006a, Fregni et al., 2006b). All the

safety studies considered this current density safe (Nitsche and Paulus, 2000; Poreisz et al., 2007). Due to safety concerns in humans, the tDCS stimulators (Schneider, Eldith) have a maximum of 10 mA output. This limit is below the human pain threshold. Constant current flow between the electrodes can be controlled by a voltmeter.

We used 5x7 cm (35 cm^2) electrodes in all of the experiments. The calculated current density we used (0.02857 mA/cm^2) is lower than the recommended safety limit (25 mA/cm^2) determined by McCreery et al. (1990). The electrodes are non-metallic, and made of conductive rubber covered completely by saline-soaked synthetic sponges to avoid skin damage (chemical interaction, metal allergy, overheating). Current density is about 0.03 mA/cm^2 under a 35 cm^2 electrode in the case of a 1 mA current intensity application, which is the same intensity used to alter levels of neural excitability in early studies (Bindman et al., 1962; Bindman et al., 1964; Nitsche et al., 2004a; Poreisz et al., 2007). The electrodes were positioned over the scalp according to the International 10-20 System (Deuschl et al., 1999). It is also intriguing to note, that the position of the reference electrode (e.g. Cz vs neck) strongly influences the AE of tDCS, irrespective of the examined cortical area (Nitsche and Paulus, 2000; Antal and Paulus, 2008).

Neither cathodal nor anodal stimulation changed skin temperature under the electrodes (Nitsche and Paulus, 2000). Sham stimulation can be used by switching on the current for a few seconds at the beginning of the 'sham session'. In this way the subject can feel the same itching sensation at the beginning of the stimulation as in case of real tDCS, but there is no brain stimulation.

102 subjects (who performed altogether 567 tDCS sessions over different cortical areas) participated in a retrospective post-DC questionnaire study (Poreisz et al., 2007). Most of the participants were healthy volunteers (75.5%). 8.8% of the subjects were migraineurs, 5.9% post-stroke patients and 9.8% suffered from tinnitus. Subjects described the following, mainly non-specific adverse events during stimulation: 70.6% tingling sensation, 11.8% fatigue, 2.9% nausea, 0.98% insomnia. Interestingly, the intensity of the percieved tingling sensation was significantly higher in healthy subjects than in patients.

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 (Liebetanz et al., 2006). This group also described the histologic analysis of rat brain tissue after tDCS. The samples underwent either light microscopic (haematoxylin and eosin) or immunhistological (expression of activated microglial marker) investigation. No cortical oedema, necrosis, nor any sign of cell death (karyopyknosis, karyolysis and karyohexis) was observed. There is only one publication discussing the increment of intracellular

calcium level following repetitive anodal polarization of the rat brain. This phenomenon is thought to be a part of the procecces underlying the observed neuroplastic changes (Islam et al., 1995).

The measurement of the level of serum neurone-specific enolase (a known marker of neuronal death) did not change during and after tDCS (Nitsche et al., 2003c). This, combined with the results of magnetic resonance imaging (MRI) studies also indicate that tDCS at current parameters, is relatively safe to use within the human population (Nitsche et al., 2004c).

The role of neurotransmitters in the DC-induced neuroplastic changes

As tDCS modulates cortical excitability it may also modify neuroplastic changes. Human pharmacological studies were implemented in order to clarify the molecular and receptor mechanisms of tDCS. Nitsche's group demonstrated the importance of catecholamines in tDCS induced neuroplasticity in the human M1 (Nitsche et al., 2004b, Nitsche et al., 2006). Amphetamine significantly prolonged the anodal DC-induced excitability increase. Nitsche et al. (2003a) observed that both anodal and cathodal tDCS after-effects are N-methyl-D-aspartate (NMDA) receptor dependent, which also play an intrinsic role in neuroplastic changes (Nitsche et al., 2004a). The application of NMDA-receptor antagonist dextromethorphane eliminates the anodal DC-induced, prolonged excitability enhancement as well as the cathodal DC-induced excitability diminution (Liebetanz, 2002; Nitsche et al., 2003a). The use of a partial NMDA-receptor agonist, D-cycloserine in a motor cortex study selectively prolonged, but did not increase the anodal tDCS induced excitability increment causing short- and long-term AEs. The administration of D-cycloserine, did not influence the cathodal tDCS-induced excitability decrement (Nitsche et al., 2004b).

Dopaminergic mechanisms play role in NMDA-receptor dependent neuroplasticity, learning and memory processes as well as in the pathophysiology of neurologic and psychiatric disorders (e.g. Parkinson's disease, cognitive impairments). TDCS induced cortical excitability changes can be modified by blocking D1 and D2-receptors (Nitsche et al., 2006). Selective D2 receptor-antagonist sulpiride significantly reduced the tDCS-induced AE over 24 hours. The combined administration of cathodal tDCS and pergolide (D1-receptor agonist) enhanced and prolonged the tDCS-induced excitability diminution, but did not influence the anodal DC-induced neuroplastic changes (Nitsche et al., 2006). The examination of the combined administration of D1-receptor agonist pergolide and D2-receptor antagonist sulpiride denote that D2-receptor mediated neuroplastic changes play a major role in the human motor cortex, compared that of D1-receptor mediated mechanisms (Nitsche et al., 2006).

Terney et al. (2008) showed that pergolide prolonged the effect of cathodal tDCS (over M1) for up to 24 hours, and significantly lowered the amplitude of the laser-evoked potentials.

The effect of lorazepam, a gamma-aminobutyric acid (GABA)-A-receptor agonist and a widely used benzodiazepine with sedative and anticonvulsant effects, on tDCS-induced neuroplastic changes was examined (Nitsche et al., 2004a): lorazepam significantly enhanced the anodal tDCS-induced motor cortical excitability increment for up to 60 minutes post-stimulation. Lorazepam had no effect on the cathodal tDCS-induced excitability decrement.

The role of the combined effect of glutamatergic and membrane mechanisms on the documented DC after-effect was detected in human M1 (Liebetanz et al., 2002); by application of another antiepileptic drug carbamazepine (CBZ), a voltage-dependent sodium channel blocker. CBZ as well as the calcium channel blocker flunarazine, eliminated or reduced anodal DC-induced excitability enhancement, but did not influence the cathodal DC-induced excitability diminishment. CBZ may act via stabilisation of the membrane potential (Liebetanz et al., 2002).

Table 1. gives a brief overview of the pharmacological approaches to DC stimulation.

Drug	Effect	Short-term anod	Short-term cathod	Long-term anod	Long-term cathod
Carbamazepine	voltage-dependent Na^+-channel-blocker	↓	∅	↓	∅
Flunarazine	Ca^{++}-channel blocker	↓	∅	↓	∅
Dextrometorphane	NMDA-receptor antagonist	∅	∅	↓	↓
D-cycloserine	NMDA agonist	↑	∅	↑	∅
Lorazepam	GABA-A agonist	↑	∅	∅	∅
Sulpiride	D2-receptor antagonist	∅	∅	↓	↓
Pergolide	D1-receptor agonist	∅	↑	∅	↑
Rivastigmine	ACh-estherase inhibitor	↓	↑	↓	↑
Amphetamin	increases catecholamine availability	-	-	↑	∅

Table 1. This table represents the pharmacological approach as concerning DC stimulation in long- and short-term anodal and cathodal stimulation.

-: not examined, ↑: the drug has increased the tDCS-induced effect, ↓: the drug has decreased the tDCS-induced effect, ∅: no effect.

Motion after-effect and detection of motion direction

A uniform lesion to the primary visual cortex results in 'cortical blindness' affecting the contralateral visual hemifield. The residual visual capacity can be observed under experimental conditions. This includes direction of motion, among other features like detection of stationary targets and localization of flashing light patterns, detection and discrimination of velocity (Benson et al., 1998). These

experiments suggest the existence and importance of extrastriate visual areas, participating in motion detection. Further studies have revealed that the human cuneus may represent the link between the striate and extrastriate visual pathways (Vanni et al., 2001). Martinez-Trujillo and colleagues (2007) performed a study to elucidate the corresponding area to unidirectional motion detection with the combination of magnetoencephalography and functional MRI (fMRI). They also found a slight activation in the cuneus, but the most roboust activation during motion direction detection was over the V5 and right infero-parietal cortex. Conversely, speed discrimination is mainly linked to the right cuneus and right lingual gyrus instead of V5 (Orban et al., 1998).

The motion after-effect is one of the fundamental and widely used perceptual manifestations of the neuronal adaptation process, and plays an important role in visual neuroplasticity (Anstis et al., 1998; Niedeggen et al., 1998). It was previously described that motion detection and MAEs are linked to the extrastriate area V5 (Zeki et al., 1991; Niedeggen et al., 1998; Huk et al., 2002).

Bex and colleagues (1999) measured the magnitude of the MAE elicited by gratings viewed through four spatial apertures symmetrically positioned around a fixation point. They observed that MAEs for radiation and rotation were greater than those for translation.

With regard to clinical studies, e.g. Shepherd's group showed that both local and global MAEs are enhanced in migraineurs irrespective of the presence or absence of visual aura, referring to extended suppression of intra-cortical excitation in migraine in both V1 and V5 (Shepherd, 2006).

Face perception and face after-effect

A special type of "higher-level" 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 (Webster and McLin, 1999; Leopold et al., 2005). Webster and colleagues (2004) have published that the above described "figural or face after-effect" plays a crucial role in gender discrimination: after adapting to a male face, the previously ambiguous image appeared distinctly female, and thus, the image that appeared neutral was shifted towards the male image. Conversely, adaptation to the female face induced the opposite changes. This special AE depends on the duration of adaptator face and it is also shape-, orientation- and category-specific (Webster et al., 2004; Rhodes et al., 2003).

Prior neuropsychological and neuroimaging studies tried to find the cortical area(s) responsible for

recognizing the human body (Downing et al., 2001; Coslett et al., 2002; Urgesi et al., 2004; Haxby et al., 2006; Kovács et al., 2006). They implicated the role of superior temporal sulcus, fusiform face area (FFA), ventral occipitotemporal cortex, cingulate gyrus and extrastriate body area (EBA) predominantly in the right hemisphere in face recognition.

Recent fMRI experiments suggest that these anatomical domains are intermingled cortical areas, called cortical spots (Haxby, 2006; Grill-Spector et al., 2006). These spots respond selectively to different object categories other than faces. On the other hand, a TMS study showed that the EBA regions are activated only by body parts and not by faces (Urgesi et al., 2004).

According to these data, we aimed to determine, using tDCS, how the retinotopically organised V1 and higher-level, non-retinotopic right lateral temporo-parietal cortex is involved in facial adaptation (Experiment III.).

Cortical excitability and migraine

Migraine is one of the most common neurological disorders, affecting 12-14% of the female and 6-8% of the male adult population (EFNS guideline, Evers et al., 2006). 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 (Alemdar et al., 2006; Aurora et al., 2007).

Numerous electrophysiological studies have revealed dishabituation (or lack of habituation) in migraineurs. Habituation is a decline in the response to repetitive stimuli. The outcome of this dysfunction can be either due to hyperexcitability or impaired inhibitory processes in cortical circuitry (Welch, 2003). The reason for this central hyperexcitability is multicausal, e.g. calcium channel abnormalities, deficiency in magnesium metabolism, mutant voltage-gated P/Q type calcium channel genes, other ion pump disorders, and/or diminished glutamate uptake in the brain

Indeed, several electrophysiological experiments underlined the notion of hyperexcitability in migraine patients: increased SEP amplitudes during attacks in patients with sensory aura (Chayasirisobbhon, 1995), and similar findings in the interictal period (de Tommaso et al., 1997). Others demonstrated increased VEP amplitudes (Shibata et al., 1997). Gunaydin and coworkers (2006) found that phosphene generation in response to TMS is more common among migraineurs than in healthies, and phosphene threshold (PT) is lower in migraine patients than in healthy volunteers. They did not find any difference in motor action potential (MAP) amplitude, MAP duration and central conduction time measurements

between patients and healthy controls. However, another TMS study found that both motor and visual cortices are hyperexcitable in migraineurs, either in migraine patients with aura (MA) or patients without aura (MoA) (Khedr et al., 2006).

Antal et al. (2005) showed that migraineurs have altered motion detection ability, giving evidence for interictal cortical hyperexcitability (see Experiment IV). According to this phenomenon Chadaide and colleagues (2007) tried to reveal the interictal cortical excitability in migraineurs using TMS and tDCS. They found that migraineurs tended to show lower baseline PT levels (but not significantly lower). They found that anodal tDCS decreased PT in migraineurs similarly to healthies, having a larger effect in MA patients. Cathodal tDCS had no significant effect int he patient groups. Their observations suggest insufficient inhibitory processes in the cortex of migraineus, which is selectively revealed by activity-modulating cortical input.

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.

Our research group had previously reported that contrast perception threshold can be modified by tDCS (Antal et al., 2001) and TMS induced moving phosphene thresholds can be also altered by tDCS (Antal et al., 2003). TMS over V1 elicits static phosphenes, stimulation over V5 leads to moving phosphenes (Stewart et al., 1999). 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 (Chaudhuri, 1990).

Facial adaptation is a special case with respect to after-effects, as it is influenced by higher-order congitive 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 (Áfra et al., 1998; Battelli et al., 2002; Fierro et al., 2003).

Materials and methods

Subjects: All of the participating subjects gave written informed consent according to the Declaration of Helsinki (BMJ 1991; 302:1194). 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.

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. **Table 2.** shows the duration and electrode position data for the different tasks. The electrode position and nomenclature is described and standardized by the American Electroencephalographic Society and approved by the Federation of Clinical Neurophysiology (Deuschl et al., 1999). 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 (as written above) in the other studies. All of the sessions were separated by at least one week to avoid interference effects between anodal and cathodal stimulation.

	Active electrode	Reference electrode	Duration of anodal tDCS (min)	Duration of cathodal tDCS (min)
V1 in experiment I.	Oz	Cz	10	10
V1 in experiment II.	Oz	Cz	15	15
V5 in experiment II.	left V5	Cz	15	15
Temporo-parietal cortex in experiment III.	P6-P8	Cz	10	10
V1 in experiment III.	Oz	Cz	10	10

Table 2. Electrode positions and stimulus durations in the different experiments. The table shows the electrode position and stimulus duration parameters in our different tasks. Current intensity was 1.0 mA in all of our experiments.

Materials and methods in the first experiment (oscillatory brain activity):

Subjects: Thirteen healthy volunteers (7 male) were involved in this study (age range 22-40 years).

Visual stimuli: Stimuli were 4 cycles/degree (cpd) sinusoidal luminance gratings presented in an on-off mode on a display size of 18x15°. The duration of the on-phase was 333 ms, followed by a 1000 ms off-phase. During the off-phase the screen was blank at the mean luminance level (60 cd/m^2). The contrast of the pattern was 50%, calculated by the Michelson contrast formula (Michelson, 1927). In each trial the patterns were presented 50 times. Stimuli were generated with a standard Vision Work system (Vision Works, Durham, USA).

VEP recording: Electrodes were positioned according to the International 10-20 System (Deuschl et al., 1999) with a Neuroscan, SynAmp system (NeuroScan, Sterling, VA, USA). VEPs were recorded at Oz. The reference electrode was placed over Fz and the ground electrode was positioned over the forehead. The resistance of the electrodes was continually kept below 5 kOhm. The sampling rate was 1000 Hz. A 50 Hz notch filter, a 0.05 Hz high-pass and 70 Hz low-pass filter was used to eliminate 50 Hz, low and high frequency interferences. Data were recorded continuously for 700 ms time period after the stimulus onset. The raw data were baseline-corrected based on the 50 ms pre-stimulus interval. Trials containing artifacts 30 μV, were automatically rejected.

TDCS: The current was applied for 10 min with an intensity of 1.0 mA. For cathodal stimulation the active electrode was placed over Oz, while the reference over Cz. For anodal stimulation the direction

of the current was reversed. All subjects received anodal and cathodal tDCS in randomized order in different sessions, separated by at least one week. For control stimulation we used displaced electrodes 6 cm lateral to Oz.

Experimental procedure, the task: Subjects were seated in a comfortable armchair opposite to the stimulator monitor (Sony). The background luminance in the experiment room was approximately 8 cd/m^2. The viewing distance between the display and the subject´s eye was 0.75 m. Subjects were asked to fixate a small cross in the middle of the screen during the presentation of the stimuli. Baseline VEPs were recorded before the DC stimulation. The VEP recording was repeated immediately after and 10, 20 and 30 minutes after the end of the stimulation.

Measurement and analysis of the data: VEPs were analyzed off-line. Spectral power was determined for the onset VEP responses in a 50-120 ms time-window for the following frequency bands: beta (15.625-31.25 Hz) and gamma (31.25-62.2 Hz) using fast Fourier transformation for each measurement for each subject. The spectral power values were averaged for each time point. The power values of the given frequency bands were entered in a 2 x 5 (stimulation x measurement time points) repeated measures ANOVA. For post-hoc analysis, a Fisher´s LSD test was used.

Materials and methods in the second experiment (motion after-effects):

Subjects: Thirteen healthy subjects participated in the study (age range: 19-40 years; six female).

Stimuli:

A.Visual stimuli: Each trial consisted of two parts: adaptation phase and motion after-effect test. The adapting and test stimuli were displayed in a rectangular aperture (6°) in the right visual field, 3° from the fixation point (centered in the middle of the monitor). The adapting stimulus consisted of 100 coherently moving dots (with limited lifetime: 200 ms), each substanding 3.6 min of arc, drifting at $0{,}8^\circ$/s against a black background.

B. Attentional task: During adaptation, which lasted 80 s, 60% of the dots increased in luminance for 200 ms. 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. These luminance-change events occurred 6 times per trial. The motion after-effect test consisted of a static field of 100 randomly placed dots.

TDCS: For cathodal stimulation the active electrode was placed over the left V5 or V1 and the reference over Cz (Kohn and Movshon, 2003). For anodal stimulation the direction of the current was

changed. The current was applied for 15 min with an intensity of 1.0 mA. All subjects received anodal and cathodal tDCS in randomized order in different sessions, separated by at least one week. For sham stimulation, the electrodes were placed over the same sites as in the real stimulation sessions, but the current was applied for only 5 s.

Experimental procedure, the task: Subjects were seated in a comfortable armchair opposite to the stimulator display (Sony). The background luminance in the experiment room was about 3 cd/m^2. The viewing distance between the monitor and the subject´s eye was 0.75 m. Subjects were asked to fixate on a small cross in the middle of the screen during the adaptation and MAE test. During adaptation phase subjects were instructed to press a key as soon as they detected a luminance-increase event. Responses within 1 sec from the beginning of the onset time of an event were recorded as hits. Responses outside of this time frame were considered as false alarms. A miss was scored if the subject failed to respond within this interval (Sohn et al., 2004). A 600 ms blank, black screen preceeded the MAE test field. The test field of static dots was visible until observers pressed a key when the MAE had decayed, thereby indicating their perception of its duration. The next trial began 1 sec after the observer´s response. MAE values were collected before, during, immediately after, 15 and 60 min after the end of stimulation (20 trials each).

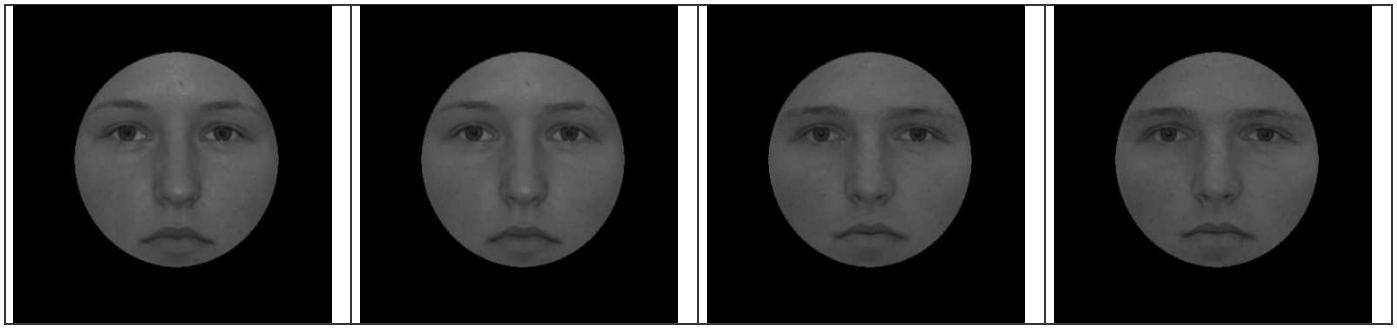
Measurement and analysis of the data: Duration of MAE was averaged and normalized to baseline values for each subject for each time point and were entered in a 3 x 5 (stimulation types x measurement time point) repeated measures ANOVA separately. Separate ANOVAs were applied for V1 and V5 data. For post-hoc test unequal Tukey´s HSD test was used.

Materials and methods in the third experiment (face perception):

Subjects: Seventeen healthy volunteers participated in the study (age range: 18-30 years; 9 males). Seven subjects (4 males) participated in the occipital and ten (5 males) in the parietal stimulation task.

Visual stimuli: Stimuli were presented centrally on a black backgrund (luminance 0.009 cd/m^2). Full-front face images were used as adaptor and test stimuli. The face images did not exhibit any obvious gender-specific features, like facial hair, jewelery, glasses or make-up (Kovács et al., 2006). Pairs of female and male faces were entered into a morphing algorithm (WinMorph 3.01), using landmark based morphing and 100 faces were created along each female-male axes. Altogether five facelines were used in this experiment. (**Picture 1.** shows the adaptor stimulus – 'Eva face' and **picture 2.** represents four faces of a faceline.) From each morphed facelines nine images were chosen (0%, 88%/12%, 25%/75%, 33%/67%, 50%/50%, 67%/33%, 75%/25%, 88%/12%, 100% male).

Picture 1. "Eva face"



Picture 2. Four different faces of a faceline

Two different adaptation conditions were presented in separate blocks:

1.Control condition, in which the adaptor stimulus was a grey circle (luminance 1,3 cd/m^2) with a white fixation cross in the center of the circle.

2. Adaptation condition (prototypical, 100% female face (so called 'Eva-face') as adaptor stimulus. Within a block we presented each test stimulus 6 times, so a block consisted of 270 trials. All softwares were written in MATLAB 6.5 (MathWorks Inc.) using PsychoToolbox 2.45 for Windows.

TDCS: For the stimulation of V1 the active electrode was placed over Oz, the reference over Cz. During the temporo-parietal tDCS for cathodal stimulation the active electrode was placed over P6-P8 and the reference over Cz. For anodal stimulation the direction of the current was reversed. The current was applied for 10 min with an intensity of 1.0 mA. All subjects received anodal, cathodal and sham tDCS in randomized order in different sessions, separated by at least one week. For sham stimulation, the electrodes were placed over the same sites as in the real stimulation sessions, but the current was applied for only 5 s.

Experimental procedure, the task: Subjects were seated in a comfortable armchair opposite to the stimulator display (Sony). The viewing distance was 0.70 m. The background luminance in the room was 3 cd/m^2. Subjects were instructed to fixate on a cross in the center of the monitor. In each trial, after a randomized period between 500 and 700 ms the adaptor was presented for 5000 ms followed by the stimulus, presented for 200 ms. Subjects were instructed to perform a two-alternative forced choice gender discrimination task: they were instructed to press the left mouse button if a female face was presented, and the right mouse button in case of a male face. The reaction times (period till pressing the mouse button) were measured and the ratio of female/male responses were counted during the experiments.

Measurement and analysis of the data: The magnitude of the adaptation was calculated as the difference in performance between the NOADA (without adaptation) and ADA (with adaptation) conditions for all of the 9 morph levels for the parietal and occipital tDCS stimulation separately. The performance and latency differences were entered into a 3 x 9 (type of stimulation: cathodal, anodal or sham x difference at each morph level) ANOVA. For post-hoc test Tukey's HSD test was used.

Materials and methods in the fourth experiment (motion perception in migraineurs):

Subjects: Twenty migraine subjects and 20 healthy volunteers participated in the experiment [age range: 20-56 years; 9 migraine patients without (MoA) and 11 with aura (MA)]. Migraine was diagnosed by consultant neurologists at the Department of Neurology, University of Göttingen, according to the International Headache Criteria (Cephalalgia 2nd Edition 24; 2004). None of the patients received prophylactic medication. General frequency of migraine attack was 20.7/year between the patients. All of the experiments were conducted between migraine attacks (1-90 days after the last attack). None of the subjects had a migraine attack within the following 3 days after the studies. The experimenter was blinded as to the diagnosis of the subject at the time of the testing.

Experimental procedure, the task: Subjects were seated in a comfortable armchair opposite to the stimulator display in a semidarkened room. The viewing distance was 0.75 m. Random dot kinetograms are widely accepted psychophysical methods for investigating motion perception threshold (Newsome and Pare, 1988; Watamaniuk, 1993). Random dot kinetograms were generated using a standard VisionWork system (VisionWorks; Vision Research Graphics, Durham, NC, USA) and presented on a colour high-resolution monitor (Sony). The steady-state luminance of a stationary dot was 10 cd/m^2, while the background luminance was 2 cd/m^2. In the first task, a single-interval, forced-choice, motion-direction discrimination task was used. Subjects had to report direction (up or down) of coherent motion in a 10° x 10° random dot stimulus by pushing the suitable button on a computer mouse. The middle of the stimulus was placed 10° away from the fixation point on the left side of the screen, to stimulate the left hemifield more. Motion perception threshold was the lowest percentage of coherently moving dots needed to identify a direction.

1. Coherently moving dots with distractors: In this experiment the presentation time was 72 ms and the stimuli contained 300 white square dots, the dot speed was 5°/s. The diameter of a dot was 3 pixels. The direction of the coherent motion was randomly varied between up and down. At the beginning of this trial, 40% of the dots were moving coherently, while the remaining 60% moved randomly in different spatial directions (no noise dots were moving in exactly the same direction as the signal dots). If the dots moved outside of the 10° x 10° window, they were randomly re-plotted within the window of the next frame. After two consecutive correct or incorrect responses the percentage of coherently moving dots was decreased or increased by 4%, respectively. After two staircase reversals, the step size increased 1%. The trial was terminated after six staircase reversals. The use of six staircase reversals conforms to standard practice in psychophysical experimentation. In this way, the lowest percentage of coherently moving dots needed to identify a direction (i.e. motion perception threshold) was determined. The trial was repeated three times, and the average duration of the experiment was about 3 times 5 minutes.

2. Coherently moving dots without distractors: In this experiment, the method of constant stimuli was used. The presentation time was 48 ms, a paradigm which was used in a previous experiment belonging to our group, which included healthy subjects (Antal et al., 2004b). The stimuli contained 200 dots, all moving coherently. In each block, 70 stimuli were presented and the dot speed was 5°/s. The subject´s task was to identify the direction (up or down) by pushing the appropriate mouse button. In this task the number of correctly identified directions was counted. The average

reaction time (RT) was also measured (period till pressing the mouse button). The trial was repeated three times, and the average duration of the experiment was about 3 times 4 minutes.

Measurement and analysis of the data: the percentages of coherently moving dots at threshold or the number of correctly identified directions were entered into a between-subject factor ANOVA [patients without aura and migraineurs with aura, controls]. For post-hoc analysis Tukey´s unequal HSD test was applied.

Results

I. Results of the first experiment (oscillatory brain activity)

I/1. Beta frequency range (15.625-31.25 Hz): The two-way ANOVA revealed no significant main effect with regard to the type of the stimulation [$F(1,25)=1.406$, $p>0.05$] and measurement time [$F(4,100)=0.633$, $p>0.05$]. The interaction between type of stimulation and time was significant [$F(4,100)=3.933$, $p<0.005$]. Post-hoc tests revealed a significant decrement immediately and 10 min after the end of cathodal stimulation. Anodal stimulation did not result in a significant effect, however a trend for beta power increment was observed **(Figure I/1).** Asterics indicate significant effects.

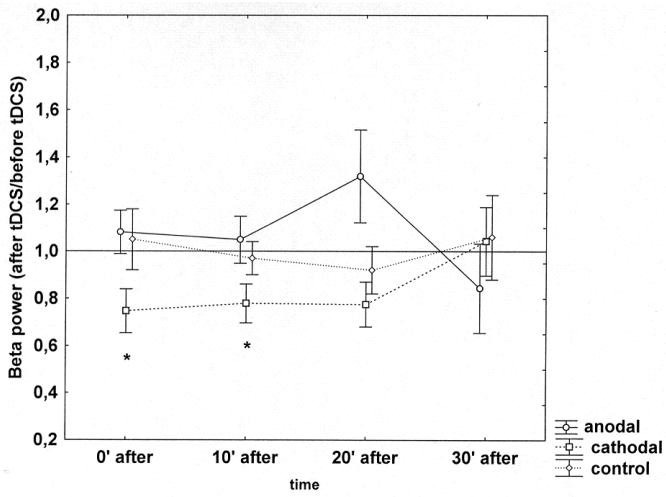


Figure I/1. The effect of tDCS on beta power

I/2. Gamma frequency range (31.25-62.2 Hz): The two-way ANOVA revealed a significant main effect on the type of stimulation [$F(1,25)=5.213$, $p<0.05$]. The interaction between type of stimulation and time was also significant [$F(4,100)=4.32$, $p<0.005$]. Post-hoc test revealed a significant diminution of gamma power immediately, 10 and 20 min after the end of cathodal stimulation. Anodal stimulation did not result in significant changes, however a

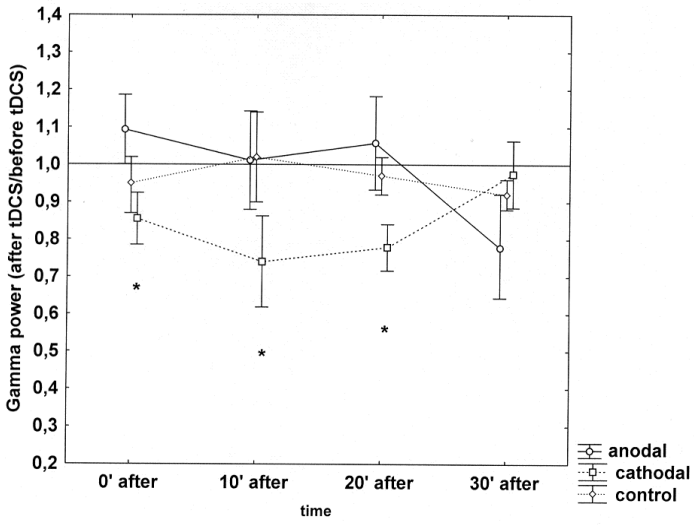


Figure I/2. The effect of tDCS on gamma power

trend for gamma power increase was seen after anodal stimulation **(Figure I/2)**. Asterics indicate significant effects.

I/3. Control experiment: The stimulation resulted in no significant main effect of stimulation or time course, non of the interactions were significant ($F<1,5$, $p>0.3$), regardless of whether beta or gamma power was analyzed.

II. Results of the second experiment (motion after-effects):

II/1. V5 stimulation:

a. Both cathodal and anodal stimulation decreased motion after-effect duration **(Figure II/1A).** The two-way ANOVA revealed no significant main effect of stimulation: $F(2,21)=1.649$, $p>0.05$.

b. The effect of measurement time points [$F(3,36)=3.049$, $p<0.05$] and the interaction between the type of stimulation and time points were significant [$F(6,63)=3.069$, $p<0.05$].

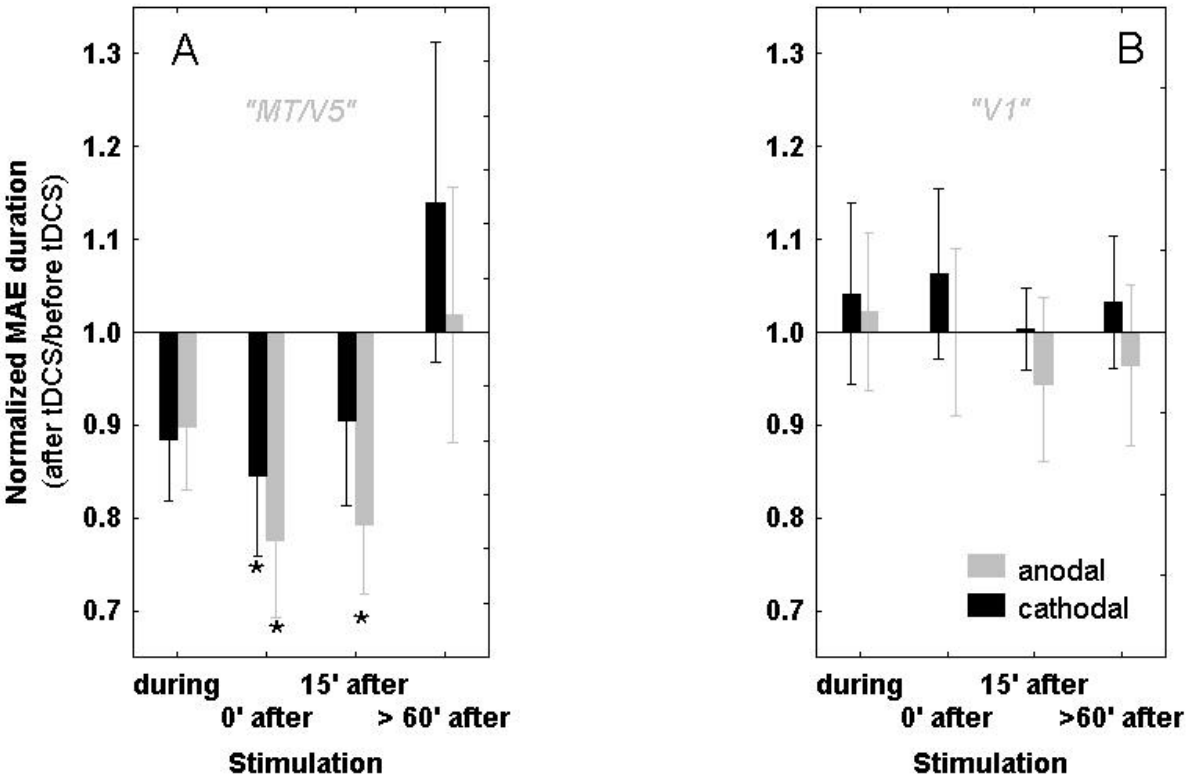


Figure II/1. Effect of tDCS on motion after-effect duration. **A**: V5 stimulation, **B**: V1 stimulation.
The results are normalized, duration corresponds to the reported motion after-effect duration before DC stimulation.

c. The post hoc unequal Tukey´s HSD test revealed significant diminishment of motion after-effect duration immediately after the end of cathodal and anodal stimulation and 15 min after the end of

anodal tDCS compared to baseline values. In contrast, the sham stimulation had no significant effect on the motion after-effect duration (p>0.48).

d. We also analyzed the effect of tDCS on the attentional task that was performed during adaptation. The performance of the subjects in the luminance-change-detection task was not influenced by either anodal or by cathodal tDCS **(Figure II/2)**.

e. There was no main effect of stimulation or time points and their interaction was also not significant [F(0,6), p>0.5].

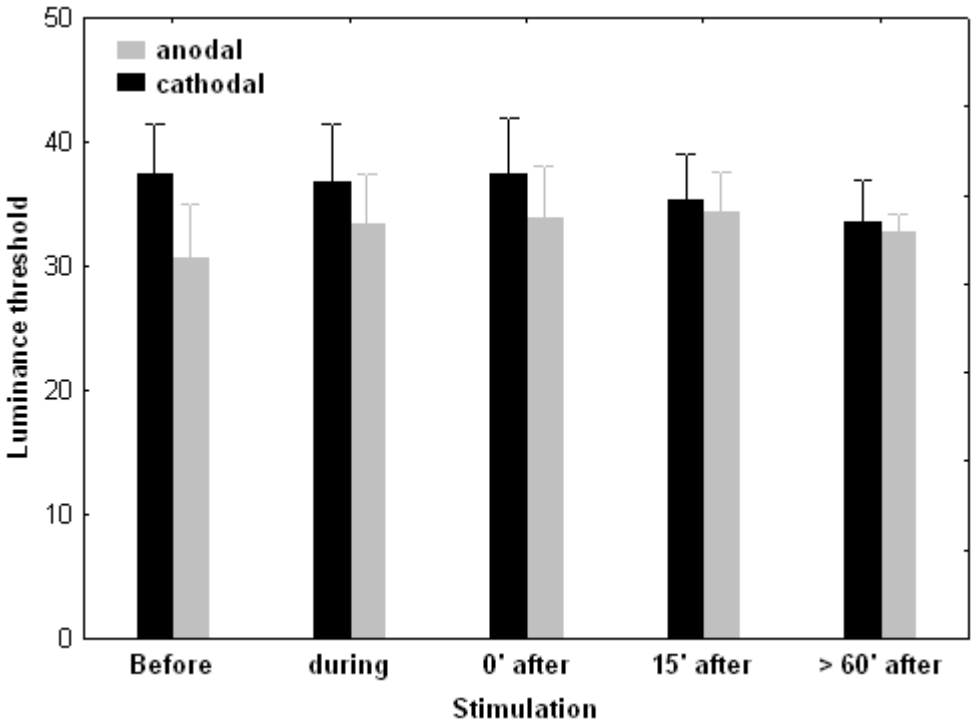


Figure II/2. Effect of tDCS on the luminance increase detection threashold.

II/2. V1 stimulation

a. Cathodal, anodal and sham stimulations had no significant main effect on motion after-effect durations [F(2,13)=0.129, p>0.8] **(Figure II/1B)**.

b. The effect on measurement time points [F(3,39)=0.863, p>0.46] and the interaction between type of stimulation and time points were also not significant [F(6,39)=0.17, p>0.1].

c. The performance of the subjects in the attentional (luminance-change-detection) task was not affected by either anodal, cathodal or by sham tDCS. There was no main effect on stimulation [F(2,13)=0.217, p>0.8] or time points [F(3,39)=1.062, p>0.35] and their interaction was also not

significant [F(6,39)=1.52, p>0.15].

III. Results of the third experiment (face perception):

III/1. We have observed in the right temporo-parietal cortex, that:

a. Adaptation to a 100% female face ("Eva-face") stimulus causes strong perceptual (facial) after-effect: the test faces were perceived as more masculine when compared to the control condition (grey circle as adaptator). The main effect of adaptation: F(8,72)=2,53, p=0.017. **Figure III/1** demonstrates the effect of adaptation on facial gender discrimination under the sham stimulation condition. Bars show standard errors.

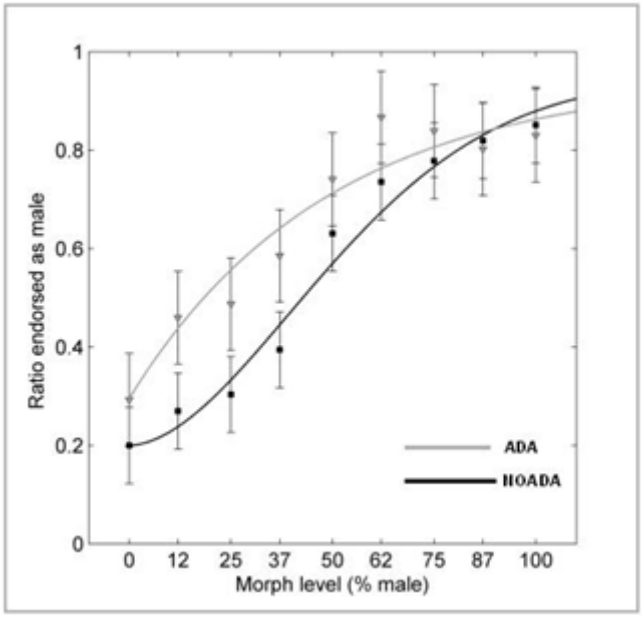


Figure III/1. The graph illustrates the control condition (NOADA), in which the adaptor stimulus was a grey circle, and an adaptation condition (ADA), in which we used a prototypical 100% female face adaptor. It is substantial that adaptation to a 100% female picutre modifies gender discrimination.

b. The ANOVA revealed significant interaction between the type of stimulation and the differences between the NOADA and ADA conditions at the 9 morph levels: F(2,36)=6.31, p=0.0004.

c. According to the post-hoc test cathodal stimulation decreased the magnitude of adaptation (p<0.05) **(Figure III/2)**, while neither the anodal tDCS nor the control stimulation modified facial adaptation significantly (p<0.005). Bars show SE.

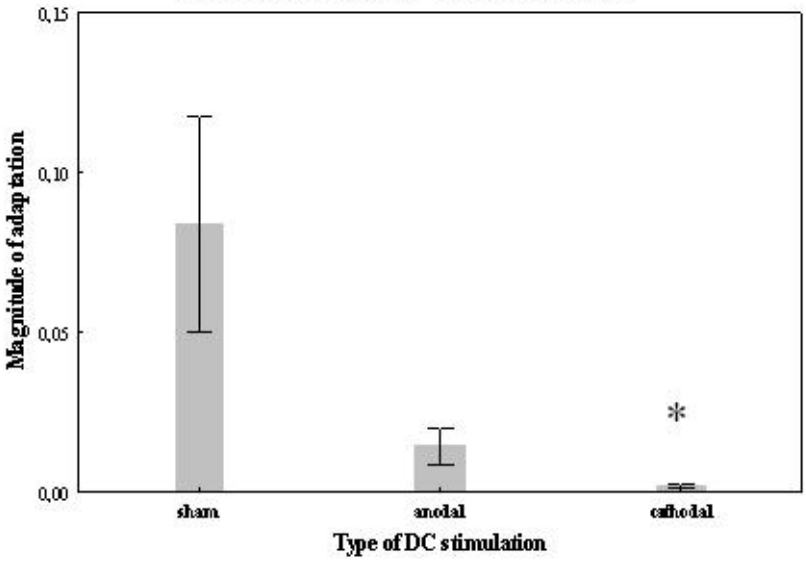


Figure III/2. The effect of parietal tDCS on adaptation. The third column represents the significant diminution of the strenght of facial adaptation after cathodal stimulation (p<0.005). Asteriks idicate significant changes.

d. The effect of the reaction time differences between the ADA and NOADA condition was also analyzed. We found

significant interaction between the type of stimulation and reaction time differences [F(2,52)=7.78, p=0.0001].

e. The post hoc test showed that cathodal stimulation could significantly decrease the reaction time difference between the NOADA and ADA conditions (p=0.0009).

III/2. Statistical analysis of the primary visual cortex revealed that the stimulation had no significant effect on adaptation over the primary visual area [F(2.38)=0.20, p>0.05]. **Figure III/3**. This illustrates the NOADA-ADA differences in performance after cathodal, anodal and sham stimulation. Bars show standard errors.

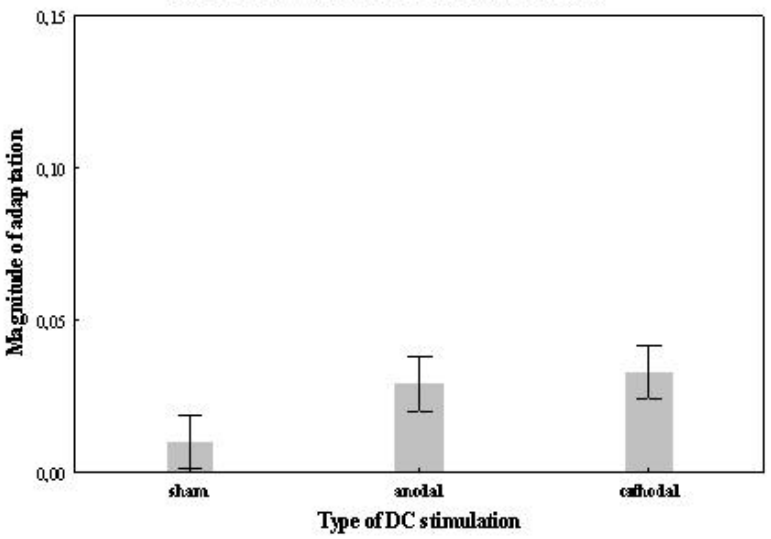


Figure III/3. The effect of occipital DC stimulation on adaptation. There was not any significant effect of facial adaptation over V1 of either stimulation conditions.

IV. Results of the fourth experiment (motion perception in migraineurs):

IV/1. Coherently moving dots with distractors:

The mean motion perception threshold was 37,0% (SD 9,86) in controls, 63,25% (SD 11,82) in MA and 59,0% (SD 7,2) in MoA. The ANOVA revealed significant differences between controls and patients (F(2.29)=23.25, p<0.0001) **(Figure IV/1)**. The post-hoc test revealed significant differences between controls and MA subjects (p<0.05).

IV/2. Coherently moving dots without distractors:

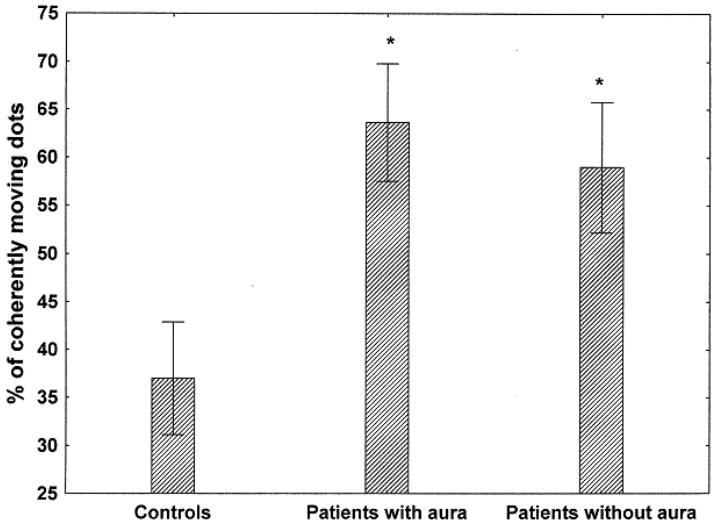


Figure IV/1. The graph illustrates motion perception thresholds of control subjects among migraineurs when subjects were asked to detect the direction of coherent movement among randomly moving dots. Error bars represent SD, asteriks indicate significant effects.

The mean percentage of correct responses was 81.1% (SD 12.2) in controls, 93.65 (SD 6.6) in MA and 89.76 (SD 7.0) in MoA from the total of 3 x 70 trials. The ANOVA revealed significant differences between controls and patients [$F(2,29)=3.67$, $p<0.05$]. The post-hoc test revealed significant differences between control and MA subjects ($p<0.05$) **(Figure IV/2).**

IV/3. Reaction times:

The mean RT in the distractor-free task was 550 ms (SD 114.7) in controls, 563.5 ms (SD 159) in MA and 534.9 ms (SD 108.6) in MoA. The ANOVA revealed no significant differences between these three groups **(Figure IV/3)**.

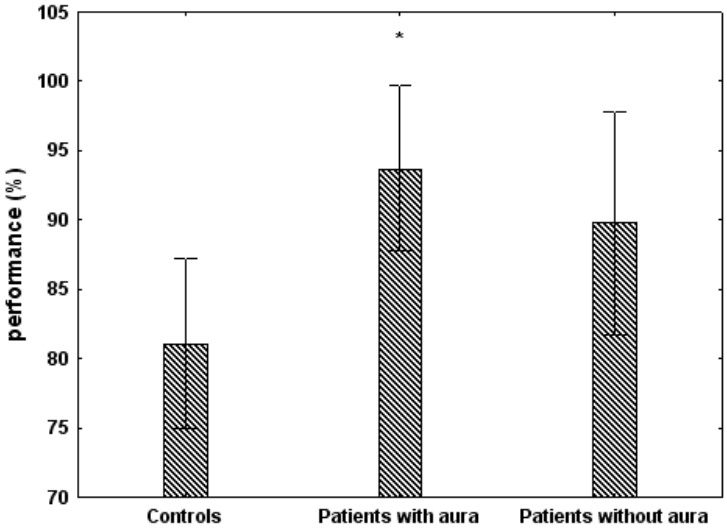


Figure IV/2. Columns represent the percentage of correct responses of the subjects when only coherent motion was presented. Error bars show SE.

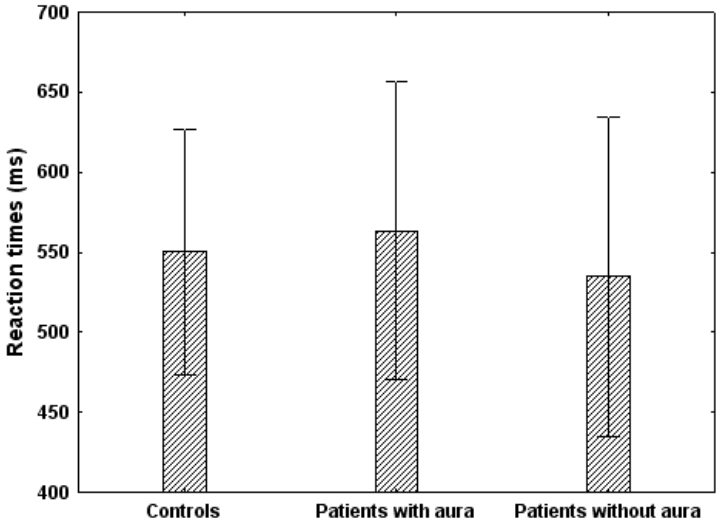


Figure IV/3. The figure shows reaction times of the subjects. Error bars represent SE.

IV/4. Relationships between performance and clinical parameters:

Non of the statistical analyses could reveal correlations between the performance of the subjects and the duration of the migraine attacks (task with distractors: r=-0.03; task without distractors: r=0.11) or the frequency of migraine attacks (task with distractors: r=0.13; task without distractors: r=-0.02) or the time between the last migraine attack and the date of the experiment (task with distractors: r=0.11; task without distractors: r=-0.54).

Discussion

I. First experiment (oscillatory brain activity)

TDCS applied over V1 altered beta and gamma power to elementary visual stimuli in a polarity specific way: while cathodal tDCS significantly decreased, anodal stimulation slightly increased both beta and gamma oscillatory activity. Cathodal stimulation was more effective than anodal tDCS, as seen in a prior tDCS study (Antal et al., 2001). The observed cathodal effect exceeded the stimulation itself and endured over the next 20 minutes, and returned to baseline values 30 min after the end of stimulation, suggesting that tDCS is able to induce after-effects on the oscillatory activity of the visual cortex. This is in concordance with previous experiments on the motor (Nitsche and Paulus, 2000) and visual cortices (Antal et al., 2001), may be due to a ceiling effect. This is in line with the observation that in the CNS the inducibility of neuroplastic effects is asymmetrical: it is easier to elicit excitatory diminutions than excitatory elevations, as demonstrated in a study exploring neuroplastic functions in rats (Froc et al., 2000). To exclude the possibility that stimulation of the parietal cortex via Cz electrode modified the oscillatory activity of the visual cortex by top-down projections, we conducted a control experiment with one electrode over Cz and the other at 6 cm left to Cz. This electrode position did not result in any changes in the recorded oscillatory activity, so the involvement of parietal areas in these alterations is improbable.

However, the duration of the induced AEs in the primary visual cortex was definitely shorter than those observed in the motor cortex. This could be caused by

-a different level of tDCS-induced plasticity in the primary visual and motor cortices,

-the different types of neurotransmitters/neuromodulators in these cortical areas,

-the different functional properties of these regions.

Previous studies suggest that the glutamatergic system, in particular NMDA-receptors, seem to be

necessary to induce and maintain tDCS induced excitability enhancements as well as diminutions, at least when the motor cortex is stimulated (Liebetanz et al., 2002). However, the catecholaminergic and cholinergic systems also participate in the generation of VEPs.

Synchronisation of the neuronal activity and the involvement of high-frequency neuronal oscillations are an important part of inducing neuroplastic changes; participating in perceptual and learning processes, perceptual analysis and object recognition (Engel and Singer 2001; Bibbig et al., 2002). Oscillatory components in the beta and gamma ranges are also involved in field potential responses evoked by elementary sensory stimuli, used in this experment (Bodis-Wollner et al., 2001). These oscillations could be generated by local neurons due to their membrane properties or by local intracortical connections, being a part of shorter-term neuroplastic changes (Hallett 2001; Karmarker and Dan 2006).

Previously the combined application of TMS and EEG was used to detect changes in the oscillatory neuronal activity, but it had several technical disadventages: TMS induces widespread EEG artifacts and TMS itself, can evoke transient synchronisation of neuronal activity in motor cortical neurons in the beta frequency range (Paus et al., 2001). TDCS offers an easier way to induce acute and persistent neuronal excitability changes without disrupting the ongoing neuronal activity. The temporal resolution of tDCS is worse compared to rTMS, whereas duration of the induced AE is longer. Therefore the combination of tDCS and EEG might offer a useful additional method with which to modify and trace cortical excitability.

II. Second experiment (motion after-effects):

The results of this study provide evidence that external stimulation of neuronal populations, in the human V5 modulates the strength of MAE. Both cathodal and anodal stimulation significantly reduced MAE durations during and after the stimulation within a 20 min time window. More importantly, since the subjects´ attentional load was controlled with a luminance change-detection task during adaptation, the effect of tDCS on MAE duration cannot be attributed to changes in general arousal or to the possible effects of the stimulation on the attentional functions.

The fact that tDCS did not alter the performance in the attentional task suggests that the detection of luminance changes in moving objects and surfaces is not based on neural processes in V5. This is in agreement with prior neuropsychological results (Sclar et al., 1990), showing that neuronal responses to contrast saturate very rapidly in V5. Accordingly, the high-contrast moving dot pattern used in this

experiment probably evoked a saturated response of V5 neurons, which could not be changed due to a ceiling effect.

In order to interpret our V5 results as evidence for the involvement of this cortical area in the neural network underlying MAE, it is important to exclude the possibility that the stimulation effects are due to a diffused modulation by the V5 stimulation of the neural processes in the earlier cortical areas, including the primary visual cortex. To exclude this possibility we performed a control study where the effect of stimulation of the posterior occipital pole on MAE strenght was measured using the same stimulus configuration and testing protocol. We reasoned that if our V5 stimulation effects are due to the diffused stimulation of the more posterior early cortical regions, including V1, direct stimulation of these areas should lead to similar or even augmented modulation of the MAE strength. The results of this control experiment have shown that neither cathodal nor anodal tDCS over V1 had a significant effect on MAE duration. These findings make it highly unlikely that our V5 stimulation effects on MAE duration in the main experiment are due to a diffused activation of the more posterior visual areas, suggesting the focal effect of tDCS. Thus, we conclude that the tDCS effects on MAE strength found in this study are specific for the stimulation of the V5 region.

It is important to note, however, that our negative results with tDCS over area V1 do not imply that area V1 is not involved in the adaptation processes underlying the motion after-effect. Since our adaptation stimulus was placed outside the fovea, according to the known retinotopic organisation of the human V1 (Tootell et al., 1998), the neural presentation of the stimulus is expected to be not in the occipital pole itself but more anterior along the calcarine sulcus in the ventral surface of the occipital lobe. Therefore, the lack of tDCS effects on the MAE strength as a result of occipital pole stimulation might be due to the fact that tDCS is unable to reach the neural representations of the adapting and test stimuli in our experimental conditions.

Based on these results, it is tempting to speculate that tDCS induced changes in the stimulated regions might interfere with the cellular mechanisms underlying the processes of neural adaptation and plasticity.

Another possible explanation, however, is that tDCS affects the interaction between the neural presentations of different motion directions in V5. It has been demonstrated that there is mutual inhibition between different motion directions, which is strongest between the opposite directions, and it is suggested that adaptation results in an imbalance in these interactions (Vidnyánszki et al., 2002), which in turn will lead to an illusory MAE. These two hypotheses are possible explanations as to the

mechanistic effects of tDCS on MAE strength, but are not mutually exclusive.

III. Third experiment (face perception):

In this study we have observed that cathodal stimulation of the right temporo-parietal cortex (P6-P8) decreased the strength of facial adaptation while tDCS over the V1 resulted in no effect. The data implies that higher-level, non-retinotopic cortical areas play role in the creation of facial after-effects and probably also in gender discrimination.

Several previous studies attempted to reveal cortical regions participating in face recognition and gender discrimination. Urgesi et al. (2004) could interrupt the visual processing of nonfacial objects by rTMS of the extrastriate body area. Pourtois et al. (2004), using TMS found that the somatosensory cortex and superior temporal regions play a role in the perception of facial expressions and gaze direction, in accordance with fMRI data (Downing et al., 2001; Haxby et al., 2002). Electrophysiological studies determined the role and specificity of right temporo-parietal regions in face recognition. Recent results of event related potential studies suggest that these areas play a role in facial gender discrimination as well (Kovács et al., 2006).

We have found, using the combined technique of adaptation and tDCS, that cathodal stimulation could modify higher-level facial adaptation over the right temporo-parietal areas. In agreement with previous studies, the inhibitory effect of cathodal tDCS on adaptation is possibly related to the focal reduction in cortical excitability due to membrane hyperpolarisation (Nitsche and Paulus, 2000; Antal et al., 2001).

In summary, the fact that tDCS had no effect on facial after-effect over the V1, but had a strong effect over temporo-parietal ares suggests the importance of higher-level, non-retinotopic regions in facial adaptation and the involvement of these areas in neuroplastic changes during fundamental social interactions like gender discrimination and face recognition. These findings are in accordance with previous electrophysiological and neuroimaging experiments (Downing et al., 2001; Leopold et al., 2005; Ng et al., 2006; Kovács et al., 2006).

IV. Fourth experiment (motion perception in migraineurs):

We demonstrated that the performance of migraineurs differed significantly from those in the healthy control group with regard to motion perception: first, migraineurs showed better performances in the task where only coherent motion was present. These results are identical to a prior study including healthy subjects in which an externally induced cortical excitability enhancement improved motion

perception in elementary motion direction discrimination tasks when the motion was uniform (Antal et al., 2004c). Here, increased excitability should elevate the activation of the respective motion-encoding cortical representations and thus improve perception. In the case of hypoexcitability in migraineurs, the performance should have gradually worsened due to the impaired primary visual processing caused by decreased activity of the motion-encoding representation. Secondly, with regard to the task in which the direction of the coherent motion needed to be identified in an incoherent environment, the motion perception thresholds in migraineurs were higher compared with healthy subjects, showing that a higher percentage of dots were necessary for migraineurs to see a pattern as coherent. The latter results are probably caused by a 'de-focusing' effect of the enhanced excitability: when more than one neuronal motion-encoding pattern is active and their activities are above threshold, a generally higher cortical excitability could impair the signal-to-noise ratio and therefore diminish motion-discrimination performance in a task in which the target is presented with distractors. In contrast, moderate hypoexciatbility would have resulted in an improvement of performance due to the focusing effect, as shown in the cathodal stimulation condition of a prior experiment (Antal et al., 2004b). Alternatively, if the hypoexcitability was prominent enough to result in a substantial activational deficit of all of the motion encoding patterns, it could also have impaired performance. However, according to the pattern of results with regard to both tasks and previous studies (McKendrik and Badock, 2004), it is highly probable, that migraine patients differ in performance from healthy subjects due to cortical hyperexcitability.

Using a similar but not identical random dot kinetogram, a higher motion perception threshold was observed in migraineurs with aura (McKendrik and Badock 2004). Furthermore, in additon to motion threshold measurements, several studies have investigated low- and high-level visual tasks in subjects with migraine (Wray et al., 1995; Fierro et al., 2003). Migraineurs were better in low-level (e.g. orientation detection, temporal order judgement) but not in higher-level visual processing (e.g. visual priming), suggesting a hypersensitivity of the primary visual cortex but not of the extrastriate visual regions. These partly contradictory results can be explained by the different difficulty levels of the applied tasks. Subjects did not perform the tasks appropriately in these experiments. Therefore, the reaction times were probably not the best indicators of the visuo-cognitive demands of the task. Aside from this, the different results can also be due to the characteristics of different types of tasks used by various studies: it is possible that by using a 'noisy' task in which several neuronal encoding patterns in a given cortical area are activated, results in an impaired performance by migraineurs, while a

distractor-free task improves performance in the same patient group.

In our study we have found a modulation of motion perception, both in MA and MoA patients. MA subjects did not differ significantly from MoA patients concerning motion perception performances. This is in accordance with other experiments, which report no differences among migraine subgroups (Shepherd, 2000; Mulleners et al., 2001; Shepherd, 2006). In contrast, a few studies have found differences between migraine subgroups (Aurora et al., 1998; Àfra et al., 1998; Mulleners et al., 2001). It was suggested that in subjects with aura the cumulative physiological effects of many aura episodes and the occurrence of spreading depression may cause stronger ultrastructural changes in the visual system. And therefore the visual changes observed in MA patientsare more pronounced than in MoA subjects. The group studied here consisted of younger subjects; it is possible that this is the reason for the absence of group difference. However, it is very difficult to estimate total auras retrospectively, as migraine frequency and aura appearance fluctuate dramatically across years as a result of hormonal changes, life stressors and many other, yet unknown factors. Finally, we did not find any correlation between the psychophysical performances of the subjects and the clinical parameters, including the duration of the disease, or the frequency or the duration of the migraine attacks. Further investigations using larger patient populations would be necessary to examine these possible correlations.

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 (McCreery et al., 1990).

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 (Fregni et al., 2006a; Liebetanz et al., 2006; Webster et al., 2006; Antal et al., 2008; Terney et al., 2008; Wu et al., 2008).

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