

Homeostatic Metaplasticity of the Motor Cortex is Altered during Headache-Free Intervals in Migraine with Aura

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Preconditioning of the human primary motor cortex (M1) with transcranial direct current stimulation (tDCS) can shape the magnitude and direction of excitability changes induced by a subsequent session of repetitive transcranial magnetic stimulation (rTMS). Here, we examined this form of metaplasticity in migraine patients with visual aura and healthy controls. In both groups, facilitatory preconditioning of left M1 with anodal tDCS increased the mean amplitudes of motor-evoked potentials (MEPs) elicited in the contralateral hand, whereas inhibitory preconditioning with cathodal tDCS produced a decrease in amplitude. Following cathodal tDCS, a short train of low-intensity 5-Hz rTMS antagonized the suppression of the mean MEP amplitude in both groups. In contrast, the homeostatic effects of 5-Hz rTMS differed between groups when rTMS was given after anodal tDCS. In controls 5-Hz rTMS induced a marked decrease in MEP amplitudes, whereas in migraineurs rTMS induced only a modest decrease in MEP amplitudes, which were still facilitated after rTMS when compared with baseline amplitudes. These findings indicate that short-term homeostatic plasticity is altered in patients with visual aura between the attacks.

Keywords: metaplasticity, migraine, motor cortex, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS)

Introduction

In 1982, Bienenstock, Cooper, and Munro introduced an influential model of homeostatic metaplasticity that stabilizes neuronal excitability within a physiological dynamic range. According to the Bienenstock–Cooper–Munro model, a “sliding modification threshold” controls the threshold for inducing synaptic plasticity (Bienenstock et al. 1982): A prolonged reduction in postsynaptic activity will reduce the threshold for inducing long-term potentiation (LTP) and increase the threshold for long-term depression (LTD). In accordance with the Bienenstock–Cooper–Munro rule, several studies have shown that the susceptibility of cortical neurons to change their excitability in response to presynaptic inputs can indeed be adjusted to the level of postsynaptic activity prior to conditioning (Sejnowski 1977; Huang et al. 1992; Kirkwood et al. 1996; Wang and Wagner 1999).

Using transcranial stimulation, we have recently introduced an experimental paradigm, which can be used to investigate short-term homeostatic plasticity in the intact human cortex (Lang et al. 2004; Siebner et al. 2004). In this paradigm, the conditioning effects of repetitive transcranial magnetic stimulation (rTMS) on the excitability of the primary motor cortex (M1) is primed by a preceding session of transcranial direct current stimulation (tDCS): In healthy individuals, a subsequent

rTMS protocol induces a lasting reduction of corticospinal excitability when the excitability level of the corticospinal projection has been increased by a preceding session of anodal tDCS. Conversely, corticospinal excitability is facilitated by the same rTMS protocol when cortical excitability has been decreased by cathodal tDCS prior to rTMS. This paradigm has been successfully used to demonstrate an abnormal pattern of homeostatic plasticity in patients with writer’s cramp, a task-specific dystonia affecting handwriting (Quartarone et al. 2003).

In migraine, it has been hypothesized that abnormal cortical excitability renders patients susceptible to spontaneous cortical spreading depression (CSD) which is thought to represent the pathophysiological basis of the aura experienced during migraine attacks (Welch 2003). Functional magnetic resonance imaging during visual aura showed a blood oxygenation level-dependent signal intensity progression in a speed that very closely resembled that of CSD (Hadjikhani et al. 2001). In humans the inducing event of the aura is unknown, but triggering an aura is possible in some subjects by flickering light, which is a strong activator of the visual system. In migraineurs a decreased level of inhibitory processes during extensive cortical activation might induce a spreading hyperactivity.

However, there is diverging evidence regarding the direction of cortical excitability changes. Many authors found a hyperexcitability of the visual cortex (Aurora et al. 1998, 2003; Antal et al. 2005; Khedr et al. 2006) and the M1 (Aurora et al. 1999; Khedr et al. 2006) or an extended suppression of intracortical excitation (Shepherd 2006). However, other groups reported a hypoexcitability of the visual cortex (Afra et al. 1998; Bohotin et al. 2003) and the M1 (Bettucci et al. 1992; Maertens de Noordhout et al. 1992).

Psychophysical and electrophysiological measurements in migraineurs suggest that the individual changes in cortical excitability that can be induced by rTMS might depend on the basal degree of cortical excitability. Low-frequency rTMS which usually induces a decrease in cortical excitability produced an increase in cortical excitability when given to the visual cortex at a rate of 1 Hz (Brighina et al. 2002). The paradoxical “facilitatory” response to 1-Hz rTMS was attributed to a failure of inhibitory mechanisms. Alternatively, this paradoxical effect may be related to an altered control of homeostatic plasticity biasing the cortical response toward a lasting increase in cortical excitability.

In the present study, we interleaved tDCS with a brief period of 5-Hz rTMS to explore homeostatic control of cortical excitability of the M1. The experimental paradigm to probe homeostatic metaplasticity in the human M1 was similar to our

previous study on healthy human volunteers (Lang et al. 2004). We hypothesized that the homeostatic mechanisms, which counteract a tDCS-induced increase in M1 excitability, would be deficient in migraineurs with visual aura when compared with healthy age-matched controls.

Methods and Materials

Participants

Thirteen migraineurs (10 women; mean age \pm SD: 33 ± 12 years; age range 20–54 years) and 13 age- and sex-matched control subjects (10 women; mean age 31 ± 10 years; age range 21–54 years) participated in the study. All patients had been diagnosed typical aura with migraine headache (ICHS-II code 1.2.1) in accordance with the International Classification of Headache Disorders (2004), by an expert neurologist. Ten patients suffered from migraine with unilateral headache, in the remaining 3 patients migraine presented as bilateral headache. The frequency of migraine attacks was between 0.3 and 4.2 per month (mean \pm SD: 1.3 ± 1.1 attacks per month). Nine patients reported a familiar history of migraine. The patients suffered from migraine for between 3 and 45 years (mean \pm SD: 14 ± 13.3). Control subjects had no personal or family history of migraine, nor any headache syndromes. None were diagnosed with any other neurological, psychiatric or internal diseases. All subjects were medication-free. Patients with migraine were not on any continuous, for example, prophylactic, medication. Patients were only included if they had taken no analgesic medication for at least 1 week before the study.

Experiments were conducted during the headache-free interval. Measurements were only considered if patients were free of pain for at least 3 days prior to and after the experiment. All of the subjects gave their written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the University of Göttingen.

Experimental Procedures

During the experiments, subjects were seated in a comfortable reclining chair with head and arm rests. The subjects were not visually deprived during the experimental sessions and the luminance of the room was the same for each subject and for each experiment. Figure 1 illustrates the experimental design. The study consisted of 2 experiments, which were performed at least 1 week apart. In each experiment, a preconditioning tDCS session was followed by a session of rTMS. The only difference between the experiments was the polarity of tDCS (i.e., anodal vs. cathodal tDCS). The order of anodal and cathodal tDCS was pseudorandomized and balanced in both groups. tDCS and rTMS were always given to the left primary motor hand area. MEPs were recorded from the right contralateral hand before (baseline) and immediately after 10 min of tDCS, as well as immediately after rTMS and 5 and 15 min later.

TMS of the left M1 was performed using a standard Magstim double “figure-of-8” coil (radius of 1 half-coil is 7 cm) with an initial anterior–posterior current flow in the coil, connected to a biphasic Magstim Rapid² (Magstim Company, Whiteland, Wales, UK). The coil was placed tangentially to the scalp over the left M1, with the handle pointing postero-laterally at a 45° angle from the midline. The optimum position was defined as the site where TMS resulted consistently in the largest MEP in the resting 1st dorsal interosseus (FDI) muscle of the right hand (referred to as motor hot spot). This position was marked with a skin pen to ensure that the coil was held in the correct position throughout the experiment. Surface electromyography (EMG) was recorded from the right FDI by use of Ag–AgCl electrodes in a belly-tendon montage. The signals were amplified and filtered (1.59 Hz–1 kHz, sampling rate of 5 kHz), digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK), recorded by a computer using Signal software (Cambridge Electronic Design, version 2.13). Data were analyzed offline on a personal computer. Complete muscle relaxation was controlled through auditory and visual feedback of EMG activity. RMT was defined as the lowest stimulus intensity, which elicited MEPs with peak-to-peak amplitudes of 50 μ V or more in the resting FDI, in the majority of measurements (Rothwell et al. 1999). The test stimulus was set at an intensity that evoked EMG responses of approximately 1 mV peak-to-peak amplitude (SI_{1mV}) and kept constant throughout the experiment.

Interventions

The rTMS protocol consisted of 100 biphasic pulses, which were given at an intensity of 90% of the individual resting motor threshold (RMT) and a constant rate of 5 Hz. Similar protocols did not alter corticospinal excitability when given alone (Lang et al. 2004; Quartarone, Bagnato, et al. 2005). rTMS stimulator, coil, and pulse configuration were identical as described above for single-pulse TMS.

Continuous tDCS was delivered through a pair of electrodes in a 5 \times 7 cm water-soaked synthetic sponge using a battery driven constant current stimulator (NeuroConn, Ilmenau, Germany). For cathodal stimulation of M1, the cathode was placed over the left M1 and the 2nd electrode over the contralateral right orbita. The center of the electrode overlying the M1 corresponded to the motor hot spot of the right FDI muscle as defined with TMS. The current flow was reversed for anodal stimulation. Subjects were blinded to the type of tDCS (anodal, cathodal). The current was applied for 10 min with an intensity of ± 1 mA. Currents were ramped up or down over the 1st and last 8 s of stimulation. All of the subjects felt a mild transient tingling under both electrodes at the beginning and end of tDCS, which only lasted for a few seconds.

Statistical Analyses

Peak-to-peak amplitude of each MEP (mV) was measured offline and a mean MEP amplitude was calculated for each block of measurements and experimental session. The mean MEP amplitudes were then entered into a 3-way repeated-measures analysis of variance (ANOVA)

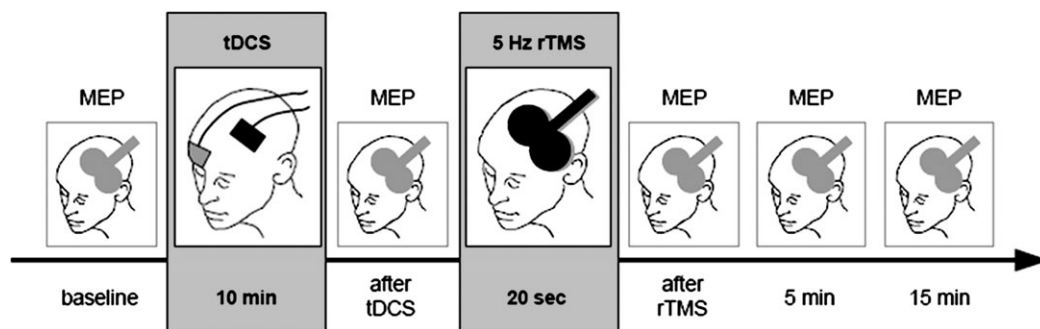


Figure 1. Time course of experiments. Ten minutes of tDCS was followed by a 20-s period of rTMS. MEPs were used to assess cortical excitability at baseline, between interventions and at 3 time points after rTMS. In different session, separated by at least 1 week, participants received either anodal (+1 mA) or cathodal (–1 mA) tDCS of the left motor cortex, whereas the rTMS protocol (5 Hz, 100 pulses, 90% RMT) was kept identical.

with “group” (2 levels: migraineurs, controls) “intervention” (2 levels: anodal tDCS followed by rTMS, cathodal tDCS followed by rTMS) and “time” (5 levels: baseline, after tDCS, after rTMS, 5 and 15 min after rTMS) as within-subject factors. The ANOVA was calculated using the Greenhouse–Geisser correction for nonsphericity. Conditional on a significant F value, paired samples t -tests were used for post hoc comparisons. Post-hoc t -tests were also used to compare baseline SI_{1mV} and RMT values between groups. Because the protocol was tested primarily by an ANOVA, correction for multiple comparisons for post-hoc t -test that aim to characterize significant findings from a previously performed ANOVA were not necessary. A P value of < 0.05 was considered significant. Data are given as mean \pm SEM.

Results

None of the subjects reported any adverse events during and after the experiments. There were no between-group differences in the SI_{1mV} and RMT values at baseline between groups ($P > 0.65$). The mean \pm SEM SI_{1mV} values were 69.2 ± 3.6 (before anodal tDCS) and 68.7 ± 3.2 (before cathodal tDCS) for the patients and 67.8 ± 3.2 (before anodal tDCS) and 67.9 ± 2.9 (before cathodal tDCS) for the controls. The mean \pm SEM RMT values were 56.0 ± 3.0 (before anodal) and 56.0 ± 3.1 for the patients and 54.8 ± 2.5 (before anodal tDCS) and 53.8 ± 2.3 (before cathodal tDCS) for the controls.

Figure 2 illustrates the relative changes in mean MEP amplitude after tDCS and rTMS for both groups. ANOVA revealed a significant interaction between “group,” “intervention,” and “time” ($F_{4,99} = 2.709$; $P = 0.035$; epsilon = 0.99),

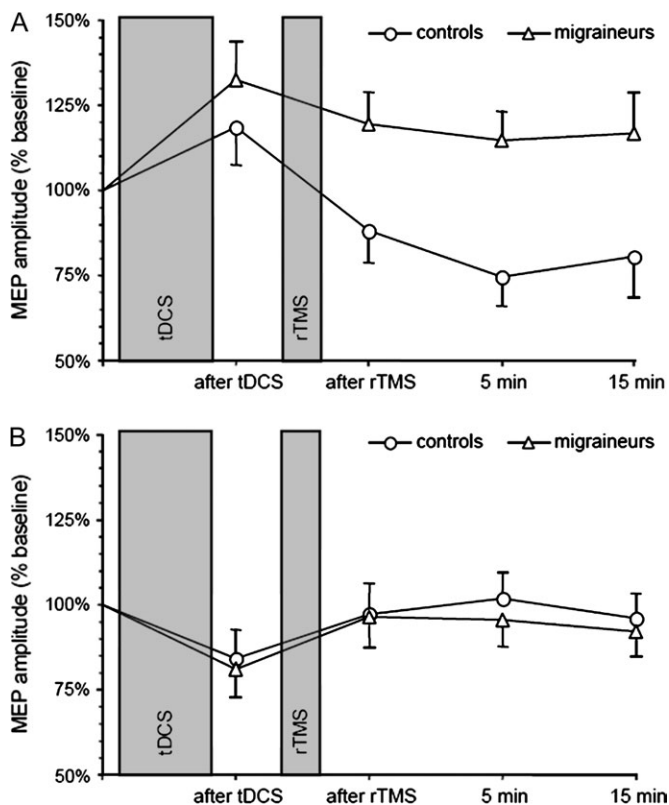


Figure 2. Stimulation-induced changes of motor cortex excitability in migraineurs and controls. The figure plots mean MEP amplitudes \pm SEM (normalized to baseline) after anodal tDCS (A) and cathodal tDCS (B). The direction of effects induced by rTMS depended on the type of preconditioning with tDCS in both groups. However, in migraineurs metaplastic inhibition induced by rTMS after anodal tDCS was significantly impaired compared with healthy controls.

a significant interaction between “intervention” and “time” ($F_{4,96} = 10.447$; $P < 0.001$; epsilon = 0.99) and a trend for an interaction between “group” and “intervention” ($F_{1,24} = 3.680$; $P = 0.067$).

Within groups pairwise post-hoc comparisons demonstrated that anodal stimulation produced a relative increase in mean MEP amplitudes in patients ($P < 0.001$) and controls ($P = 0.01$). Conversely cathodal stimulation decreased mean MEP amplitudes in patients ($P = 0.05$) and controls ($P = 0.02$) relative to baseline values.

When compared with the mean MEP amplitudes after anodal tDCS, the 5-Hz rTMS protocol induced a stable decrease of MEPs in controls (post-hoc t -tests; immediately after rTMS: $P < 0.001$; 5 min after rTMS: $P < 0.001$; 15 min after rTMS: $P = 0.01$). This inhibitory effect was less pronounced in migraineurs (Fig. 2A). In this group, 5-Hz rTMS resulted in a moderate decrease in MEP amplitudes that became marginally significant only 15 min after rTMS ($P = 0.042$). Although 5-Hz rTMS after anodal tDCS suppressed mean MEP amplitudes below baseline levels in healthy controls, mean MEP amplitudes were still significantly enhanced ($P < 0.02$) compared with baseline level in the patients group at all time points after 5-Hz rTMS.

When 5-Hz rTMS was preceded by cathodal tDCS, both groups showed comparable changes in mean MEP amplitudes (Fig. 2B). In both groups, 5-Hz rTMS induced a relative increase in MEP amplitude when compared with the mean MEP amplitudes recorded immediately after cathodal tDCS. This relative increase in MEP amplitude was significant 5 min after the end of rTMS in controls ($P = 0.022$) and immediately after the end of rTMS in the patients group ($P = 0.05$). Although 5-Hz rTMS did counteract the decrease in MEP amplitude that had been produced by the preceding tDCS session, it did not result in an increase of mean MEP amplitudes above baseline levels.

Discussion

In this study, we used the mean MEP amplitude as an index of primary motor cortex excitability to examine the priming effects of tDCS on subsequent rTMS conditioning. In agreement with our previous study (Lang et al. 2004), healthy controls displayed a decrease in corticospinal excitability in response to 5-Hz rTMS when motor cortex excitability had been previously enhanced by anodal tDCS. The same 5-Hz rTMS protocol raised the excitability of the motor cortex back to baseline values after corticospinal excitability had been suppressed by a preceding cathodal tDCS session.

The critical new finding was that migraine patients with visual aura displayed an altered pattern of short-term homeostatic plasticity when studied off medication in the pain-free interval between attacks. Although patients showed a normal facilitation of corticospinal excitability after 5-Hz rTMS when rTMS was primed by cathodal tDCS, the suppression of corticospinal excitability was attenuated when 5-Hz rTMS followed anodal tDCS. This unequally distributed response pattern indicates an asymmetry in homeostatic regulation of motor cortex excitability in migraineurs with visual aura. “Inhibitory” preconditioning with cathodal tDCS turned the rTMS after-effect into facilitation, yet “facilitatory” preconditioning with anodal tDCS failed to flip the direction of the after-effect of rTMS toward inhibition. The attenuation of “inhibitory” homeostatic plasticity suggests that the motor cortex has a reduced ability to prevent excessive increases in cortical

excitability. The BCM rule states that stabilization of neuronal activity is ensured by a dynamic adaptation of the modification threshold (the level of postsynaptic response below which gives LTD and above which gives LTP) to the time-averaged value of the postsynaptic activity. It is regarded as a fundamental, possibly protective mechanism of cortical processing. The present study adds data to the long debated issue of interictal cortical excitability in migraineurs with visual aura using a new approach. With regard to the motor cortex, we could not find that cortical excitability was generally high as reported by previous studies (e.g., Khedr et al. 2006) or the intracortical inhibitory mechanisms were impaired, because cathodal stimulation was well able to decrease MEP amplitudes. Furthermore, the RMT and the TMS intensity needed to elicit 1-mV MEP responses were not significantly different between patients and controls. However, the intrinsic inhibitory counter-mechanisms did not properly function when the preexisting cortical excitability was further increased by anodal stimulation. With regard to the neuronal mechanisms of the migraine with visual aura, this might suggest a hypersensitivity that suggests to an imbalance between excitation and inhibition in the patient group.

Though the significance of this finding to the pathophysiology of migraine with visual aura remains to be shown, it is tempting to speculate that impaired “inhibitory” metaplasticity may contribute to the emergence of migraine attacks. Furthermore, this result confirms previous research showing a generalized alteration of cortical excitability that extends beyond the visual cortex in patients with migraine (Brighina et al. 2005; Curra et al. 2007; Siniatchkin et al. 2007).

With regard to the visual cortex of migraineurs, a recent study investigated the dynamics of visual cortical excitability after external modulation using tDCS and determined that cathodal stimulation did not induce any significant inhibition in patients with aura (Chadaide et al. 2007). These results strengthen the notion of deficient inhibitory processes in the cortex of migraine patients. However, the external stimulation of the motor and visual cortex might reveal different results (Lang et al. 2007). The relative distance and orientation of intracortical and cortico-cortical axons with respect to the stimulation, may result in site-specific preferences to excite different neuronal populations within the cortical target area.

In agreement with previous work (Afra et al. 1998; Werhahn et al. 2000; Brighina et al. 2005), we found no differences in RMTs between migraine patients and controls. Patients also showed a shift in corticospinal excitability after tDCS that was comparable to healthy controls without migraine. Moreover, the stimulation setting during tDCS and rTMS were matched between groups. Therefore, the attenuated priming effect of anodal tDCS cannot be attributed to differences in the conditioning protocols or differences in the initial response to tDCS conditioning, but reflects a genuine difference in the homeostatic regulation of cortical excitability.

Previous TMS studies that examined the excitability of the M1 in migraineurs have revealed inconsistent results. Some studied reported decreased levels of cortical excitability (Bettucci et al. 1992; Maertens de Noordhout et al. 1992; Afra et al. 1998), whereas others found an increase in motor-cortical excitability (Aurora et al. 1999; Khedr et al. 2006) or no significant differences between patients and controls (Werhahn et al. 2000; Ozturk et al. 2002).

The observed impairment of short-term inhibitory metaplasticity in the M1 may at least in part account for the inconsistent results obtained in previous TMS studies. It is possible that cortical excitability may be normal or even decreased after a recent migraine attack. Indeed, Judit et al. (2000) previously showed that the normalization of visual evoked potentials just before and during the attack that might reflect an increase in the cortical preactivation level. An impaired ability to counteract activity-driven increases in cortical excitability would favor a gradual build-up of cortical excitability, which may eventually facilitate the occurrence of the next attack. According to this hypothesis, patients may display a tendency toward reduced levels of excitability when studied shortly after the last attack, but may show increased levels of excitability shortly before the next attack. If this were the case, repeatedly measuring cortical excitability during the pain-free intervals should reveal systematic shifts in cortical excitability during the interval of 2 consecutive attacks. Further studies will be necessary to address this issue.

We have to keep in mind that in our study we investigated migraine patients with visual aura and the results might not be true for a group of patients without visual aura. Indeed, concerning epidemiological studies, that using a population based survey in twins with migraine (e.g., Russel et al. 2002) it was suggested that migraine with and without aura are distinct disorders. However, given the overlap and the interictal presence of other neurological symptoms indicates that these are subtypes of 1 disorder.

Quartarone, Rizzo, et al. (2005) recently used a similar paradigm to explore tDCS-induced metaplasticity in the motor cortex of patients with focal hand dystonia. In analogy to the present study, they observed an absence of any inhibitory effects of 1-Hz rTMS after cortical excitability had been increased with anodal tDCS and argued that short-term homeostatic control of motor cortex excitability is impaired in focal hand dystonia, probably due to deficient inhibitory mechanisms. Taken together, these findings suggest that a dysregulation of inhibitory homeostatic plasticity represents a feature that is shared by various neurological disorders and may play a permissive rather than causal role in the pathophysiology by destabilizing the normal homeostatic control of cortical excitability.

Our experimental approach provides a paradigm to probe in the intact human brain whether and how patients with neuropsychiatric diseases express aberrant forms of homeostatic plasticity in the corticospinal motor system. Because measurements can be repeated over time, it is also possible to explore how therapeutic interventions shape homeostatic plasticity and how it is related to therapeutic efficacy.

Funding

“Kompetenznetz Schmerz” (FKZ: 01EM0117) funded by the German Ministry of Research and Education.

Notes

We would like to thank Leila Chaieb for the English corrections. *Conflict of Interest:* None declared.

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