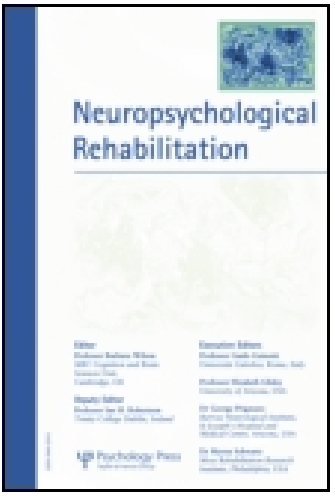

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Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods

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Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods

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Weak transcranial direct current stimulation (tDCS) with a homogenous DC field at intensities of around 1 mA induces long-lasting changes in the brain. tDCS can be used to manipulate brain excitability via membrane polarisation: cathodal stimulation hyperpolarises, while anodal stimulation depolarises the resting membrane potential, whereby the induced after-effects depend on polarity, duration and intensity of the stimulation. A variety of other parameters influence tDCS effects; co-application of neuropharmacologically active drugs may most impressively prolong or even reverse stimulation effects. Transcranial alternating stimulation (tACS) and random noise stimulation (tRNS) are used to interfere with ongoing neuronal oscillations and also finally produce neuroplastic effects if applied with appropriate parameters.

Keywords: Transcranial direct current stimulation (tDCS); Transcranial alternating current stimulation (tACS); Transcranial random noise stimulation (tRNS); Transcranial magnetic stimulation (TMS); Rehabilitation; Plasticity.

INTRODUCTION

Two methods of non-invasive electromagnetic stimulation of the human brain have dominated the last decades: transcranial magnetic stimulation (TMS), which activates axons via short-pulsed stimulation and leads thereby to new action potentials; and transcranial electric stimulation, predominantly

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by tDCS, which can be used to manipulate the membrane potential of neurons and modulate spontaneous firing rates, but is insufficient on its own to discharge resting neurons or axons. Using diametrically opposite stimulation techniques such as high constant magnetic fields does not seem to influence cortical excitability (Schlamann et al., 2010), nor can short-pulsed electric transcranial stimulation be pursued regularly, since it induces significant skin pain (Merton & Morton, 1980). Despite their very different modes of action, however, prolonged application of both rTMS and tDCS can cause after-effects on the excitability of neurons and networks that outlast the stimulus by minutes or even hours. There have been a number of recent advances in both methods: theta burst stimulation (TBS) is a rapid TMS method of achieving long-term effects allowing lower intensities and duration of stimulation, it is only mentioned in the present context because of interesting parallels concerning the total stimulation duration and sign of after-effects; transcranial random noise stimulation (tRNS) is a highly effective method of avoiding directional sensitivity of standard tDCS; sinusoidally varying transcranial stimulation (transcranial alternating current stimulation: tACS) may be able to interact with ongoing rhythms in the cortex. Other, usually older, methods such as Limoge current have been tried in the past, but are more complicated in their stimulation parameters and less well validated (overview in Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010).

tDCS

Technique

Transcranial electrical stimulation methods have a very long tradition. As early as about 1800, when Volta invented his electric pile, researchers began to investigate the application of direct current (DC) in a variety of neurological diseases. In, by modern standards not well-documented, case reports, it was claimed that chronic stroke could benefit from direct current application (Hellwag & Jacobi, 1802). Numerous investigations soon followed in the 19th century. These early efforts were given up mainly because of the lack of sufficiently reliable evaluation methods. When effects of direct current application were measured by transcranial magnetic stimulation at the motor cortex (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998) tDCS became reliable in terms of parameters such as stimulation intensity and duration and validation of its plastic after-effects (Nitsche, Nitsche, et al., 2003; Nitsche & Paulus 2000; 2001) (overview in Nitsche et al., 2008). In order to achieve after-effects, it appears to be necessary to stimulate for at least three minutes with the intensity of at least 0.6 mA (Nitsche & Paulus, 2000). Not surprisingly, the direction of

electrode polarisation is decisive in the direction of the after-effects. If the anode is placed above the motor cortex, transcranial magnetic stimulation will result in a larger motor evoked potential (MEP). If the cathode is placed at the motor cortex, MEP size will be reduced. Both electrodes introduce a uniform steady state extracellular electric field responsible for plastic effects in neural tissue (Bikson et al., 2004). Originally it seemed to be that the longer the stimulation lasted, the longer the after-effects would last. So, for instance, when applying tDCS with a duration of 5–13 minutes anodally, after-effects increase proportionately, with a duration of about 1–2 hours (Nitsche & Paulus, 2001). Cathodal stimulation turned out to be somewhat more efficient than anodal stimulation with an after-effect duration of 1 hour after 9 minutes tDCS (Nitsche, Nitsche, et al., 2003). Most recent data, however, have shown that there is an upper limit for sustaining the excitatory after-effects from anodal tDCS. The application of 26 minutes of continuous anodal tDCS finally resulted in inhibition (Monte-Silva et al., 2011). Following application of cathodal tDCS continuously for 18 minutes, after-effects did not switch into excitation, and turned out not to be as impressively prolonged as with time increments of shorter durations (Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010). We expect a similar pattern with ever longer cathodal tDCS, since we recently obtained other evidence for the reversal of theta burst after-effects with prolonged duration (Gamboa, Antal, Moliadze, & Paulus, 2010). Most likely, this effect is related to calcium homeostasis (Wankerl, Weise, Gentner, Rumpf, & Classen, 2010). In a complex theta burst design targeting the L-type voltage gated calcium channel (L-VGCC) and involving the antagonist nimodipine, the N-Methyl-D-aspartic acid (NMDA) receptor antagonist dextromethorphan and a comparison between rest and activated conditions, the authors argued that calcium dynamics determine the polarity of LTP/LTD-like changes *in vivo*. L-VGCCs were suggested to act as molecular switches mediating metaplasticity induced by endogenous neuronal activation. Of particular relevance to neurorehabilitation is the finding of increased tDCS efficacy with repetitive stimulation over days (Reis et al., 2009). Thus in the near future the most efficient stimulation protocols may turn out to be repetitive daily stimulations, further optimised with repetitive tDCS applications. So far not much attention has been put on the importance of intervals. With 5 Hz rTMS it could be shown that an uninterrupted stimulation turned out to be inhibitory, only the introduction of intervals seems to be responsible for the otherwise generally accepted facilitatory features of 5 Hz rTMS (Rothkegel, Sommer, & Paulus, 2010). Since, as already mentioned, pure prolongation of tDCS duration will lead to a reversal of the sign of stimulation after-effects, one way of optimising the relation between stimulation parameters and induced plasticity is the introduction of intervals. Here it appears that, for example, 13 minute

intervals with a break of 13 to 20 minutes leads to longer plastic after-effects than uninterrupted stimulation or intervals of three hours (Monte-Silva et al., 2011).

tDCS applied with 1 mA needs larger electrodes than those used for electroencephalography in order to avoid skin burns. Even when using electrode sizes of 35 cm^2, current application starts to become painful (Furubayashi et al., 2008) at 3 mA. This can also be seen as a natural safety protection against higher intensities, although the method itself is regarded as safe as demonstrated by animal experiments (Liebetanz et al., 2009). In order to provide a more physiological comparability and better safety criteria, other parameters have been used (see overview in Liebetanz et al., 2009; Nitsche, Liebetanz, et al., 2003):

Current density

The current density is defined as the electric current per unit of cross-sectional area, and if this current density is flowing homogeneously through an area A, then the current density J can be written as:

$$J = \frac{I}{A}, \tag{1}$$

where I is the electric current (Heald & Marion, 1995).

In the case of an electrode, the cross-sectional area A is given by the active area of the electrode (McCreery, Agnew, Yuen, & Bullara, 1990).

Total charge

Given the fact that the electric current I is the amount of charge that is flowing through a cross-sectional area A per unit of time (Heald and Marion, 1995), it is possible to calculate the charge Q that flowed in terms of the electric current as:

$$Q = \int_{t_1}^{t_2} I(t)dt, \tag{2}$$

where t_1 and t_2 are the limits of the interval in which the flow of charge is studied (Figure 1).

Having n electric impulses (Figure 2), of intensity and duration I_p and τ, respectively, it can be demonstrated that the total charge is given by the product among the intensity, the duration and the amount of pulses.

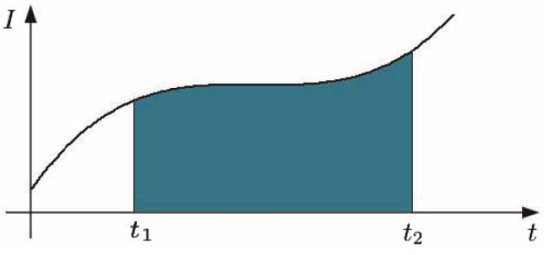

Figure 1. Example of a curve *Current vs Time*. The shaded area represents the charge that flowed during the interval [t_1, t_2].

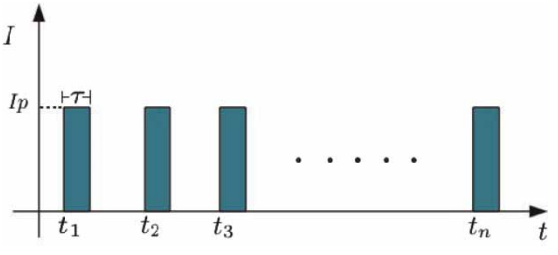

Figure 2. Scheme of a sequence of electric pulses.

Proof:

The charge, Equation (2), takes the form:

$$Q_t = I_p\left[\int_{t_1}^{t_1+\tau} dt + \int_{t_2}^{t_2+\tau} dt + \cdots + \int_{t_n}^{t_n+\tau} dt\right], \tag{3}$$

$$Q_t = I_p[t_1 + \tau - t_1 + t_2 + \tau - t_2 + \cdots + t_n + \tau - t_n]. \tag{4}$$

Perfoming the algebraic sum among all the terms, is easy to see that the term τ appears n-times in the Equation (4). Thus, the total charge corresponding to the n pulses is:

$$Q_t = n\tau I_p. \tag{5}$$

In the present context, as shown by (Nitsche, Liebetanz, et al., 2003), the total charge refers to the stimulated area. Hence, the total charge is given then by:

$$\sigma_t = \frac{n\tau I_p}{A}, \tag{6}$$

where A, is the active area of the electrode (McCreery et al., 1990).

Charge density

Similarly, as with the total charge, it can be demonstrated that for pulses, the charge density for each pulse is given by:

$$\sigma = \frac{\tau I_p}{A}, \tag{7}$$

Electrode size itself can be varied. Larger electrodes may be used as reference electrodes, for instance on the forehead, whereas smaller electrodes may allow a selective stimulation of thenar and hypothenar muscles (Nitsche, Doemkes, Karakose, Antal, & Liebetanz, 2007). Since tDCS induces a polarisation of brain tissue the position of the reference electrode is critical (Miranda, Lomarev, & Hallett, 2006). Originally we only found a stimulation effect with the reference electrode on the forehead and not at other localisations on the skull (Nitsche & Paulus, 2000). Most studies at the motor cortex have been performed so far with a contralateral reference electrode, although application of extra-cephalic return electrodes, e.g., at the deltoid muscle, is possible (Priori et al., 2008). However, this set up needs higher stimulation intensities proportional to increasing inter-electrode distance (Moliadze, Antal, & Paulus, 2010b). Complex calculation models are under way (Wagner et al., 2007) to determine the optimal electrode position for targeting a certain area, taking into account different current flow routes in the cerebrospinal fluid of normal subjects and stroke patients (Datta et al., 2009). Also, diffusion tensor-imaged MRI weighting is integrated in these models in order to take into account the 10 times better conductivity of fibre tracts along the tract as compared to a perpendicular current flow.

Pharmacological effects

tDCS effects can be modified, abolished, prolonged or even reversed by co-application of drugs acting on the central nervous system. Thus drug co-application allows to control for final tDCS outcome in a most important way. It may be even more important in the context of drugs being applied for stroke treatment, such as those reducing spasticity or treating depression. First it was shown that neuroplastic after-effects are NMDA-receptor dependent (Liebetanz, Nitsche, Tergau, & Paulus, 2002), whereas acute effects are not (Nitsche et al., 2003a). Anodal after-effects can be selectively suppressed by both the sodium channel blocker carbamazepine and the calcium channel blocker flunarizine (Nitsche, Fricke, et al., 2003). Most important to neurorehabilitation seems to be the possibility of selectively prolonging anodal but not cathodal after-effects by a factor of about 20 into the next day by co-application of either d-cycloserine (Nitsche, Jaussi, et al., 2004) or

amphetamine (Nitsche, Grundey, et al., 2004). In contrast, a low dose of a dopamine D2 receptor antagonist selectively prolongs cathodal inhibition effects by a similar amount into the 24-hours range (Nitsche et al., 2006). The application of 100 mg l-dopa which roughly doubles the dopamine concentration in the brain (overview in Paulus & Trenkwalder, 2006) has a most interesting effect. Anodal after-effects are converted into inhibition, whereas cathodal inhibition remains. Whereas under tDCS and a placebo drug after-effects vanish after 30–90 minutes, under tDCS and l-dopa inhibitory after-effects are now prolonged by a factor of 30 lasting until the following evening. As a control we added a paired associative stimulation protocol (PAS 25) (Kuo, Paulus, & Nitsche, 2008). In this case excitation was maintained and not converted into inhibition, it showed however a similarly impressive prolongation by about a factor of 30. Here we argued that synapse-specific plasticity, as induced by PAS, is boosted by this dose of l-dopa whereas synapse-unspecific plasticity, as induced by tDCS, is suppressed. This effect however only holds true for the 100 mg dose; with low (25 mg) or high (200 mg) doses of l-dopa facilitatory as well as inhibitory plastic after-effects were abolished. This clear non-linear, dosage-dependent effect of dopamine on both facilitatory and inhibitory plasticity supports the assumption of the importance of a specific dosage of dopamine optimally suited to improve plasticity (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010). This might be important for the therapeutic application, especially for rehabilitative purposes.

Other drugs of relevance for boosting tDCS after-effects are rivastigmine, which increases the acetylcholine content of the CNS and provides results similar to 100 mg of l-dopa (Kuo, Grosch Fregni, Paulus, & Nitsche, 2007), and the serotonin re-uptake inhibitor citalopram, which converts cathodal inhibitory after-effects into excitation and prolongs standard tDCS after-effects into the 24-hours range (Nitsche et al., 2009).

tDCS under-activation

The effects described so far used mainly MEP measurements. Intracortical excitability parameters such as short latency intracortical inhibition (SICI) or facilitation (SCF) (overview in context with pharmacological alterations in Paulus et al., 2008) were also influenced both during and after tDCS (Nitsche et al., 2005). tDCS after-effects however only provide this clear-cut picture if tDCS is applied during muscle relaxation. In cases of mental challenge, after-effects show a tendency to be reversed; in cases of active movement during tDCS, application excitation switches into inhibition and cathodal inhibition tends to increase further (Antal, Terney, Poreisz, & Paulus, 2007). Also, homeostatic priming is able to reverse both tDCS and rTMS effects (Lang et al., 2004; Siebner et al., 2004). Understanding of these complex relations is far

from complete. It is however of particular importance for neurorehabilitation since, in general, preconditioning by activation may reverse or significantly alter rTMS (Ziemann, Ilic, Pauli, Meintzschel, & Ruge, 2004), theta burst (Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008) or tDCS after-effects (Nitsche, Roth, et al., 2007) as measured in terms of MEP size. However, the effect on learning is obviously dissociated from the MEP after-effects since all positive learning effects, either with tDCS (Nitsche, Schauenburg, et al., 2003), tRNS (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008) or tACS (Antal et al., 2008; Moliadze, Antal, & Paulus, 2010a), were obtained during stimulation. A further frequency-specific dissociation occurred between MEP size increase and effect on implicit learning with tACS at high frequencies (see below) (Moliadze et al., 2010a).

Recently it could be shown by the aid of multichannel EEG recordings through functional connectivity and graph theoretical analysis that tDCS induces changes in brain synchronisation and topological functional organisation. In this study functional connectivity patterns significantly increased within premotor, motor, and sensorimotor areas of the stimulated hemisphere during motor activity in the 60–90 Hz frequency range. Additionally, tDCS induced significant intrahemispheric and interhemispheric connectivity changes in all the studied frequency bands (Polania, Nitsche, & Paulus, 2011).

On the basis of fMRI data it was shown that nodal minimum path lengths significantly increased in the left somatomotor (SM1) cortex after anodal tDCS whereas functional coupling significantly increased between premotor and superior parietal areas with the left SM1. Also, the nodal connectivity degree in the left posterior cingulate cortex (PCC) area as well as in the right dorsolateral prefrontal cortex (right DLPFC) significantly increased (Polania, Paulus, Antal, & Nitsche, 2011).

Apart from TMS evaluation methods, tDCS effects were also localised by quantifying cerebral blood flow during an H_2O PET investigation (Lang et al., 2005). Other methods which have been used for evaluating tDCS after-effects are evoked potentials (Accornero, Li Voli, La Riccia, & Gregori, 2007; Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004), EEG (Ardolino, Bossi, Barbieri, & Priori, 2005), psychophysics (Antal, Nitsche, & Paulus, 2001; Antal & Paulus, 2008), phosphenes (Antal, Kincses, et al., 2004; Lang et al., 2007), visuomotor learning paradigms (Antal, Nitsche, et al., 2004), fMRI (Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011), a variety of clinical studies (cf. other chapters in this issue), cognitive performance in normal subjects, such as naming facilitation (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010), and cognitive neurorehabilitation (Miniussi et al., 2008).

In particular, tDCS was shown to improve neurorehabilitation in stroke patients (Hummel et al., 2005) and is now the subject of a large European trial in stroke (Christian Gerloff, personal communication). Many more ongoing trials are registered, e.g., on the National Institutes of Health

homepage under clinical trials. Other applications on a behavioural level have been published, e.g., for Alzheimer's disease (Ferrucci et al., 2008).

tDCS induces behavioural effects as shown by an implicit motor learning paradigm (Nitsche, Schauenburg, et al., 2003) and a probabilistic classification learning task (Kincses, Antal, Nitsche, Bartfai, & Paulus, 2004). Although tDCS is much easier to blind in clinical studies as compared to rTMS, awareness of a prickling skin sensation starts at an intensity of about 500 μA (Ambrus, Paulus, & Antal, 2010). Blinding options can be achieved in the placebo group with a short stimulation and the electric current being switched off after some 20 seconds. An alternative can be the use of short electric pulses without a DC offset. tDCS is usually faded in for seconds in order to avoid retinal phosphenes when a forehead reference point close to the eyes is used. Apart from easier blinding, another advantage of tDCS compared to rTMS studies seems to be the robustness against brain-derived neurotrophic factor (BDNF) polymorphisms (Antal et al., 2010), which, in theta burst stimulation, impedes plasticity in the Met allele carriers (Cheeran et al., 2008). In the mouse model, the BDNF dependency however seems to be higher (Fritsch et al., 2010). The role polymorphisms will play in the context of neurorehabilitation needs to be investigated.

tRNS

Alternating current is no longer sensitive to the direction of current flow. In order to screen for most efficient frequencies in a physiological range, we used a random noise frequency pattern (tRNS: transcranial random noise stimulation) (Terney et al., 2008) with a potential to desynchronise (pathological) rhythms. A frequency spectrum between 0.1 Hz and 640 Hz was chosen to screen for whether or not any plastic after-effects could be seen. This tRNS paradigm includes a normally distributed random level of current generated for every sample at a sampling rate of 1280 samples per second with no overall DC offset. In the frequency spectrum all coefficients had a similar size with a "white noise" characteristic. All other parameters were taken over from the established tDCS studies. A consistent excitability increase lasting at least 60 minutes, through both physiological measures and behavioural tasks, was induced by 10 minutes of tRNS stimulation (Terney et al., 2008). Unexpectedly higher frequencies (100–640 Hz) and not frequencies in the EEG range were responsible for generating this excitability increase. This effect may either be attributed to the repeated opening of Na channels or to a higher sensitivity of neuronal networks to field modulation than the average single neuron threshold (Francis, Gluckman, & Schiff, 2003) (see tACS at 140 Hz below). During tRNS and finger tapping, a reduction of the blood-oxygen-level dependence (BOLD) response in the motor cortex can be seen

on the fMRI (Chaieb et al., 2009). While tRNS appears to possess at least the same therapeutic potential as anodal tDCS, it is easier to blind than tDCS (Ambrus et al., 2010) with the 50% perception threshold for tDCS at 400 μA while this threshold was at 1200 μA in the case of tRNS.

tACS

Sinusoidally applied transcranial alternating current stimulation (tACS) allows manipulation of intrinsic cortical oscillations with externally applied electrical frequencies. Of course, any combination of any frequency is possible, the more frequencies are involved the closer the results may approach tRNS effects. A combination with tDCS has been shown to be effective for boosting memory (Marshall, Helghadottir, Molle, & Born, 2006), although without control experiments it cannot be decided if the tDCS or the tACS effect is responsible for the memory improvement. A later study on the motor cortex argues in favour of a tDCS effect for motor cortex plasticity (Groppa et al., 2010). More complex stimulation protocols, such as Limoge's current, have been reviewed recently (Zaghi et al., 2010). TACS after-effects induced with a single frequency and close to efficacy intensity threshold (Antal et al., 2008b) were confined to an improvement of motor learning which was only seen with 10 Hz, a frequency imminent in the motor cortex (Castro-Alamancos, Rigas, & Tawara-Hirata, 2007). Since other tACS frequencies between 5 Hz and 40 Hz failed to induce any measurable efficacy, this finding appeared disappointing at first glance. However, because the intensity was limited to 400 μA in order to avoid retinal phosphenes with higher amplitudes (Antal et al., 2008b), the results are not directly comparable with the tDCS effects which were obtained at 1 mA (Nitsche, Liebetanz, et al., 2003). This higher sensitivity of the retina to electric stimulation is also the reason why tDCS intensity is ramped up over seconds to avoid phosphene sensations. Other evidence for the influence of tACS on the motor cortex with 20 Hz is slowed voluntary movement (Pogosyan, Gaynor, Eusebio, & Brown, 2009). Also it was possible to increase alpha power by stimulating with a tACS frequency in the individual EEG range (Zaehle, Rach, & Herrmann, 2010).

A second paper using tACS at Oz reports trying to circumvent the induction of retinal phosphenes by a different reference electrode remote from the eye (Kanai, Chaieb Antal, Walsh, & Paulus, 2008). The closer one or both tACS electrodes are to the retina the more likely retinal stimulation occurs. Stimulation of the visual cortex at Oz with a reference at Cz seemed to be able to elicit directly cortical phosphenes in a frequency-dependent way, with a peak slightly lower in darkness than in brightness. Phosphene threshold was at 250 μA; stimulation effects were explored up to 1 mA. This finding

was however challenged by arguing that even remote electrodes may be able to stimulate the retina by far field potentials (Schutter & Hortensius 2009; Schwiedrzik 2009). Separation of retinal and cortical phosphenes is not easy (Paulus 2010). However, while it is clear that tACS at the visual cortex influences TMS-induced phosphenes (Kanai, Pulus, & Walsh, 2010), more studies are necessary for a clearer separation. tACS seems likely to open a new era of directly interfering with cortical rhythms and is expected to synchronise actively cortical rhythms, although at present interference with phosphenes in the frequency range of about 10 to 40 Hz is a problem.

This problem does not occur if tACS is used in the so-called ripple frequency range (Moliadze et al., 2010a). Ripples are short hippocampal oscillations in the frequency range between 100 and 250 Hz associated with memory encoding. If in the resting condition tACS is applied for 10 minutes at 140 Hz with 1 mA at the motor cortex, an hour-long MEP increase by TMS has been documented. Stimulation at 80 Hz remained without an effect, while 250 Hz clearly had a smaller efficacy. With activation, tACS after-effects are abolished or even reversed as those seen with tDCS (Antal et al., 2007). However, this reduction of MEP size with activation was least with 140 Hz or, in other words, this frequency turned out to be most resistant against the decrease of MEP size under activation. Motor learning under an implicit motor learning paradigm (Nitsche, Schauenburg, et al., 2003) was however better with 250 than with 140 Hz, a finding that demands further investigation.

CONCLUSION

In summary, an almost infinite spectrum of stimulation possibilities arises with the use of transcranial electrical stimulation techniques. For future applications it will be a most challenging task to unveil their individual physiological mechanisms, one such investigation is already under way, e.g., in the Bikson group (Bikson, Radman, & Datta, 2006; Radman, Su, An, Parra, & Bikson, 2007). Most importantly, it can be demonstrated that also in symmetrical dendritic arborisations, superimposed electrical direct current fields can alter membrane potential (Radman, Ramos, Brumberg, & Bikson, 2009). Nevertheless, it will ultimately be of importance to pursue the simplest solutions in order to best facilitate the finding of targeted cortical excitability manipulations in the context of neurorehabilitation. Possible applications focus on facilitating the impaired functions of lesioned areas as well as suppressing maladaptive plasticity. Further areas concern the ability of electrical fields to foster neuronal growth. It has been shown that nerve growth can be enhanced and directed by an electric field (McCaig, Rajnicek, Song, & Shao, 2005).

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