Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation (Supplements to Clinical Neurophysiology, Vol. 56)
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Chapter 26

Transcranial direct current stimulation (tDCS)

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1. Transcranial direct current stimulation (tDCS)

Four years ago, at this Göttingen Neurobiology Conference, the idea of using transcranial direct current stimulation (tDCS) arose in the Department of Clinical Neurophysiology during a theoretical talk on neuronal membrane function. Already attempting to modulate neuronal excitability in man by means of repetitive transcranial magnetic stimulation (rTMS), we began to pursue the idea of manipulating membrane potentials directly by passing weak direct currents through the skull. Michael Nitsche agreed to explore tDCS as a possible alternative to rTMS in order to induce excitability changes non-invasively in the human brain. The first ethics committee proposal was written and permission to start was given in 1999. Peter Wenig, our electronics technician, built the first stimulator. At that time Priori et al. (1998) had already used TMS to evaluate tDCS effects during current stimulation. However, this work did not turn out to be very helpful for us, since the results were quite different from what we found (cf. Nitsche et al., this volume). Since the older literature was not well represented in the PubMed system, it took some time to get an overview, which in the end revealed an astonishing number of animal, as well as human, DC stimulation studies (cf. Nitsche et al., this volume). The main finding, which was demonstrated by Bindman et al. (1964), proved to be that in order to get after-effects, a minimum duration of DC stimulation of at least some minutes seemed to be necessary. With this knowledge, M. Nitsche was able quite quickly to show the first after-effects of tDCS by means of single pulse transcranial magnetic stimulation (TMS). Depending on the direction of current flow, excitability increases or decreases could be induced during stimulation which persisted after the end of stimulation (Nitsche and Paulus, 2000).

The tDCS-induced after-effects developed if the stimulation lasted at least 3 min (Nitsche and Paulus, 2000). Prolongation of stimulation duration proportionally increased after-effect duration (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a). Subsequent studies using different methods have added further insight into tDCS-induced excitability changes (cf. Nitsche et al., this volume). An fMRI study with BOLD measurements confirmed that cathodal tDCS lowered cortical activation in interconnected areas significantly, but not in the stimulated motor cortex

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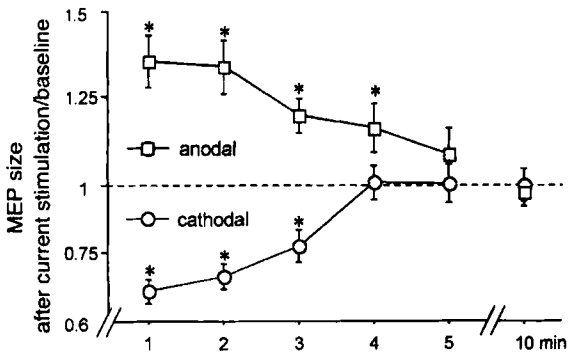

Fig. 1. After-effects of 5 min anodal and cathodal stimulation on the MEP size. (From Nitsche and Paulus, 2000, with permission.)

itself, whereas anodal stimulation tended to raise activation, however insignificantly (Baudewig et al., 2001). Psychophysical measurements (Antal et al., 2001, 2003) in the visual system and behavioural effects (Nitsche et al., 2003b) added confirmatory evidence to the efficacy of tDCS in humans (Lang et al., in preparation).

Does a bridge exist between tDCS and rTMS after-effects? Knowledge about the concept of modulating the neuronal membrane potential may lead to a reconsideration of rTMS-induced after-effects. A first step towards inducing a more direct alteration of the neuronal membrane potential by rTMS could have been made by comparing monophasic and biphasic TMS. It appeared that monophasic TMS pulses produced longer lasting after-effects than biphasic (Antal et al., 2002; Sommer et al., 2002). However, it remains to be proven whether monophasic (or asymmetric) pulses are better suited to induce membrane potential changes than biphasic (or symmetric). Although so far in our lab compared to tDCS rTMS is distinctly less effective in the induction of excitability changes, rTMS still has the advantage that it is restricted to one site and does not bear the possibility of unwanted effects under a second electrode. So far, none have been observed, however stimulation of the cortex at the site of the second electrode with opposite polarity cannot be avoided by tDCS. A possible approach to minimise possible undesired effects could be a relative enlargement of the second electrode.

2. Possible sites of action of transcranial direct current stimulation (tDCS)

In order to gain a better understanding of the underlying mechanisms of tDCS-induced effects, studies should probably focus on neuronal membranes and their behaviour with changing membrane potentials. Since there are no modern membrane studies on DCS effects, much is speculative at the moment. The lipid bi-layer of the plasma membrane of nerve or glial cells is almost impermeable to ions and it serves as an insulator separating cytoplasm and the extracellular fluid. Ions cross the membrane only through specialised pores such as ion channels. Transmembrane crossing of ions is essential for establishing the resting membrane potential as well as for neuronal signaling, which depends on rapid changes in the electrical potential difference across neuronal membranes. Ion channels recognise, select and conduct specific ions, and open and close in response to specific electrical, mechanical or chemical signals. tDCS presumably targets neuronal signaling by manipulating ion channels or by shifting electrical gradients which influence the electrical balance of ions inside and outside of the neuronal membrane, e.g. by changing the membrane potential. It seems unlikely that tDCS distinguishes between those channels responsible for membrane potential changes and those devoted to signal transmission.

Most likely, tDCS affects primarily non-gated or resting channels open in the cell at rest, and voltage-gated channels. Most gated channels are closed when the membrane is at rest, in contrast to resting channels. Gated channels may become involved in tDCS effects after altering the resting membrane potential. Their probability of opening is regulated by changes in membrane potential, ligand binding or membrane stretch. Ligand-gated channels could be affected by tDCS only secondarily, e.g. by modulation of neurotransmission through affecting other cells in a network. Mechanically gated channels will probably not be affected at all. The rate of

transmission between the open and closed states of a voltage-gated channel depends strongly on the membrane potential, with time scales varying from several microseconds to a minute. Also, many but not all voltage-gated channels can enter a refractory state after activation. The response of a single neuron to tDCS after having shifted the resting membrane potential is determined by the proportions of different types of voltage-gated channels in the cell's integrative and trigger zones (for an overview: Kundel et al., 2000).

Even if the reaction of a single neuronal membrane to tDCS became clear, within a complex array of nerve cells tDCS responses would be even more difficult to predict. They depend on neuronal geometry, on direction of current flow and on the type of cells stimulated predominantly: some cells respond to a constant excitatory input with only a single action potential, others with a constant-frequency train of action potentials or with accelerating or decelerating trains of action potentials. In order to target other cells, alternating cathodal with anodal stimulation might be sensible, as they are neurons in which a preceding steady hyperpolarizing input makes the cell less responsive to a succeeding excitatory input and vice versa.

Finally, tDCS may also affect signal transmission to adjacent nerve cells at electrical synapses via gap-junction channels. Gap junctions are found between glial cells as well as between neurons. Electrical transmission is particularly rapid and useful for connecting larger groups of neurons or glial cells. In the latter, the gap junctions seem to mediate both intercellular and intracellular communication. However, the role of glial cells in tDCS effects still has to be determined.

3. Role of neuropharmacology in evaluating tDCS effects in man

The hypothesis that membrane potential changes are involved in the effects of tDCS has been tested in a first human experiment by blocking voltage-dependent Na-channels with the antiepileptic drug carbamazepine (Liebetanz et al., 2002). Here we were able to block anodal excitatory after-effects, whereas inhibitory cathode-induced after-effects were left unchanged. Apart from membrane potential changes, chemical neurotransmission, either pre- or postsynaptically, may also play a role in tDCS effects (Liebetanz et al., 2002) (Fig. 3).

We think that pharmacological studies of tDCS should be separated into three groups. Effects *during*: (i) tDCS may behave differently from short-; (ii) and long-lasting; (iii) tDCS after-effects. Longer lasting, but not short-lasting, effects may include the build-up of new synapses (Engert and Bonhoeffer, 1999), and should therefore be looked at separately. Two of the most relevant neuronal functions in the latter context are long-term potentiation (LTP) and long-term depression (LTD), for years well investigated in neuronal slice preparations. LTP and LTD share at least common characteristics with tDCS regarding the duration of after-effects (Nitsche and Paulus, 2000, 2001).[1] LTP requires the activation of NMDA receptors by glutamate. Therefore, the proof that NMDA antagonists cancelled tDCS after-effects would allow to assume an involvement of an LTP-like mechanism. According to this hypothesis, the afore-mentioned pharmacological study by our group also revealed, that the NMDA antagonist Dextromethor-phan, an anti-coughing drug, which has been widely used in the past as an NMDA antagonist in human studies (e.g. Ziemann et al., 1998), abolished tDCS-induced after-effects (Liebetanz et al., 2002). So far, the glutamatergic system, in particular NMDA receptors, seems to be necessary for induction and maintenance of neuroplastic after-effects, excitability enhancement as well as diminution (Liebetanz et al., 2002). Nevertheless, during almost every reviewing process we were cautioned by the reviewers concerning possible links to LTP and LDP, simply due to the fact that both have been defined on the cellular level and not in complex neuronal systems as the intact human.

1 If tDCS effects turn out to be basically interconnected with LTP and LTD effects, the statement by Andersen (2003) "Responses lasting for more than 1 h were not reported until 1973" might turn out not to be true.

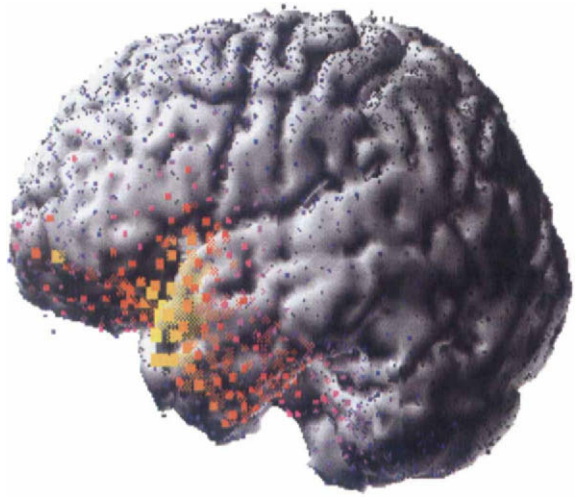

Fig. 2. Recalculated distribution of epileptic activity in a realistic head model by aid of 64 channel recordings. Note that epileptic activity may extend across a somewhat larger region and that in particular opposing walls of a gyrus may be affected. Thus, direct current passing through a gyrus may induce opposite effects on opposing walls.

4. Neuropharmacology and its possible role in overcoming problems due to cortex folding

Apart from the possibility of unraveling receptor and channel effects of tDCS by simultaneous application of specific neuropharmacological drugs, another pharmacological aspect may be of similar importance. This aspect concerns the geometry of the cortex, which will play a distinctive role with regard to the use of tDCS, e.g. in epilepsy (Weiss et al., 1998). Supposing that an epileptic focus extends to both sides of a cortical gyrus, currents passing through this gyrus will elicit a net excitatory effect on one side of the gyrus and an inhibitory one on the opposite wall, or vice versa, depending on the direction of current flow. As has been shown from our very first papers, the direction of current flow plays a critical role with respect to facilitation or inhibition and orientation of neuronal cells.

If an epileptic focus extends to both sides of the wall there will be an unintended effect on at least one site. Thus, a drug which prevents excitatory effects and after-effects in the whole system, might

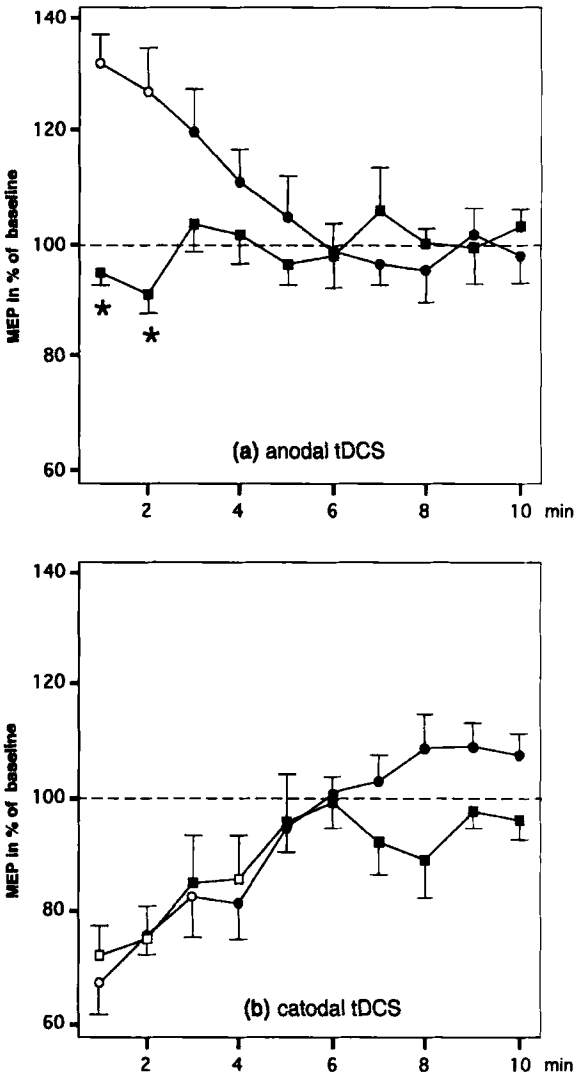

Fig. 3. Carbamazepine eliminates anodal induced tDCS after-effects on the TMS induced MEP, while leaving cathodal effects unchanged. (From Liebetanz et al., 2002, with permission.)

allow epileptic activity to be reduced without the potential of activating it at other sites. As a first approach to this, we showed that all excitatory after-effects were abolished under carbamazepine, probably by blocking voltage-dependent Na^+ channels, whereas the cathodal after-effects remained unchanged (Liebetanz et al., 2002).

This might lead to the (so-far remote) possibility of being able to pass currents in a deliberately chosen

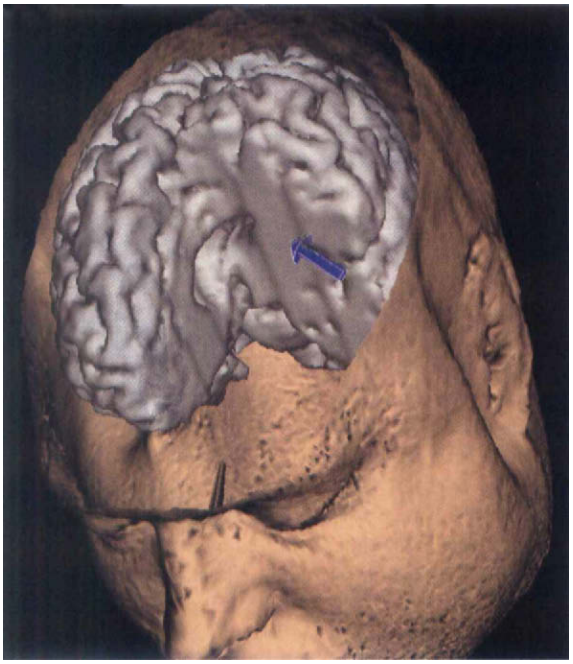

Fig. 4. Dipole orientation (blue arrow) derived from 64 channel surface recordings of epileptic spikes in a realistic head model. Suggested parallel direct current flow (white arrow) for influencing epileptic activity. Passing hyperpolarizing current into an epileptic focus and hereby inhibiting epileptic activity may be a possible future application of tDCS. Nevertheless, although effective in the animal model (Weiss et al., 1998) this idea may turn out to be too simple. Chronic human epilepsies may alter their channel or neurotransmitter characteristics quite dramatically. In carbamazepine-resistant patients the use-dependent block of Na^+ channels by carbamazepine has been shown to be absent (Remy et al., 2003). Also, in human temporal lobe epilepsy GABAergic neurotransmission may be excitatory (Cohen et al., 2002).

direction through the brain in order to induce only inhibitory effects. Nevertheless, it would be most helpful to place the electrodes in such a way that current direction is optimally suited to reduce epileptic activity. A possible approach to this might be to determine the source of epileptic activity, as revealed in Fig. 4 in a realistic, and in Fig. 5 in a spherical, head model. Current flow calculations work in both directions; computer programmes such as BESA® allow optimal electrode positions to be calculated (M. Scherg, personal communication). Back

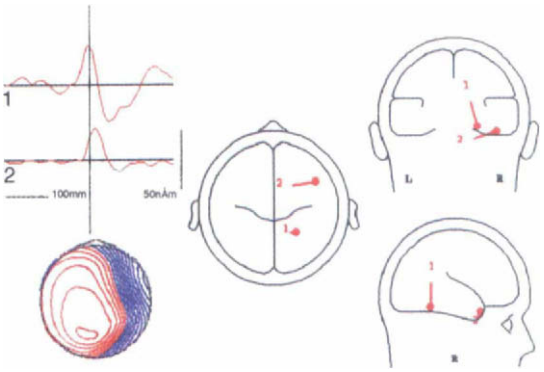

Fig. 5. Dipole modelling of a propagated epileptic spike in a non-realistic head model. Upper right: orientation of two different spike components. Upper left: time course of electric activity in source 1 and 2. Lower left: Projection of electric source activity to the skull surface. The latter method may be used for optimal positioning of electrodes for tDCS.

projection of the equivalent dipole to the surface (Fig. 5, lower left) delineates suggested electrode positions on the skull.

5. tDCS and its possible role in learning

For several reasons motor learning is particularly well suited as a model for studying learning mechanisms in humans: (i) Manipulation of plasticity is possible by a diversity of methods, in many combinations: activity-dependent learning, input manipulation by electrical peripheral nerve stimulation or deafferentation, TMS, neuropharmacological intervention and DC stimulation. In addition, lesions associated with stroke as well as patients with diseases like dystonia, may serve as plasticity models with the motor cortex involved. (ii) Alterations in cortical organisation may be monitored not only by functional imaging, but in addition by movement analysis and by TMS. (iii) The motor cortex provides an easy way to effect evaluation by all available TMS methods.

Here tDCS adds a further tool for manipulating motor cortex function in learning studies. The stable excitability increase or decrease which can so far be achieved for about 1 h allows us to study learning processes during increased or decreased motor cortex excitability (see Lang et al., this volume; Nitsche

et al., 2003b). Interesting aspects being pursued at the moment concern the possibility of altering the signal-to-noise ratio in a circumscribed cortical region. In particular, cathodal stimulation might reduce overall activity. By a larger reduction of background activity when compared with signal activity, the signal-to-noise ratio may be improved. This might be one mechanism for improving skill in overlearned tasks by cathodal stimulation (Antal et al, unpublished results), whereas anodal stimulation may be better in initial learning tasks. Nevertheless, a lot of work remains to be done in order to categorise tDCS effects in such areas as homosynaptic or heterosynaptic mechanisms (Bailey et al., 2000) or others.

6. Summary and conclusions

tDCS appears to be a promising tool in neuroplasticity research with some tentative perspectives in clinical neurophysiology. The next steps to be carried out encompass better histological safety data. In order to preclude the possibility of neuronal damage, extending tDCS duration should be limited until more direct safety criteria are available than those derived from Agnew and McCreery (1987) (cf. Nitsche et al, this volume). Safe stimulation protocols have to be developed which allow an extension of the duration of after-effects towards a somewhat permanent state, supposing a beneficial effect can be found in neurological diseases or in neurorehabilitation.

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