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CHAPTER 27

Modulation of cortical excitability by weak direct current stimulation – technical, safety and functional aspects

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1. Introduction

Achieving short- or even long-term neuroplastic functional modifications of cortical networks through the modulation of activity and excitability of neuronal ensembles has been the focus of many research activities in the past decades (Bennett, 2000). The application of weak direct currents has been shown to elicit cortical excitability and activity shifts during, and after, the end of stimulation in animals and humans, and thus, could evolve as a promising technique in this field of research. In animals, intracortical or epidural electrodes have been used for DC stimulation. However, even transcranial application of weak direct currents can induce an intracerebral current flow sufficiently large to achieve the intended effects. In monkeys it has been shown that approximately 50% of the transcranially applied currents enter the brain through the skull (Rush and Driscoll, 1968), and these results have been replicated in humans (Dymond et al., 1975). Thus, weak direct currents can be applied to humans non-invasively, transcranially and painlessly to induce focal, prolonged but yet, reversible shifts of cortical excitability, the duration and direction of which depend on stimulation duration and polarity (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). This chapter will first give an overview of the basic and functional effects of weak direct current stimulation in animals and in the humans. Then, technical considerations will be discussed and available safety criteria, which are expected to prevent harmful or unwanted effects of the stimulation will be summarised.

2. Basic effects

2.1. Physical parameters

The combination of current strength, size of stimulated area and stimulation duration are thought to be the relevant parameters that describe stimulation

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strength and thus, control the efficacy of stimulation (Agnew and McCreery, 1987). A formula referring directly to these parameters is total charge ((current strength (A)/area (cm^2)* stimulation duration (s)) (Yuen et al., 1981). This formula was originally developed for suprathreshold electrical stimulation. It seems to be appropriate also for weak subthreshold DC stimulation, because different current intensities per area will result in different amounts of neuronal de- or hyperpolarisation and it has been shown that different stimulation durations result in a different time course of the induced excitability shifts (Bindman et al., 1964; Nitsche and Paulus, 2000). Thus, in the following sections, stimulation strength will be referred to as total charge wherever it is possible to deduce these from the original studies (Tables 1 and 2). Apart from the above-mentioned physiological reasons, this is carried out in order to render stimulation paradigms used in different studies comparable and because for total charge at least preliminary limits for a safe stimulation are available (Yuen et al., 1981). However, it has to be kept in mind that different charges combined with different stimulation durations, which result in an identical total charge, may result in qualitatively quite different effects: a short strong stimulation may induce supra-threshold depolarisation, whereas a weak prolonged stimulation may fail to elicit action potentials of a given neuron, both resulting in identical total charge. Thus, the comparability of different studies in behalf of total charge is limited and should always be qualified by a separate equation of current density and stimulation duration.

Another parameter which seems to be important to achieve the intended stimulation effects – most probably by determing the neuronal population stimulated – is the direction of current flow, which is defined generally by the electrode positions and polarity. As shown for the human motor cortex, only two of six different electrode position-combinations tested so far effectively influenced cortical excitability, and the effective combinations may have modulated different neuronal populations (Priori et al., 1998, see below; Nitsche and Paulus, 2000). This has not been tested in animals directly, but it was shown that differently oriented neuronal populations were influenced differently by a constant current flow direction (Creutzfeldt et al., 1964; Purpura and McMurtry, 1965), which strongly suggests that the relation of current flow direction and neuronal orientation is crucial for the efficacy of stimulation and the direction of the current-induced changes of cortical excitability and activity.

2.2. Cortical excitability and activity changes during DC stimulation

For the human motor cortex, it was shown recently that short transcranial direct current stimulation (tDCS) with a total charge of 0.00014 C/cm^2 can change motor cortical excitability during stimulation: anodal stimulation *diminished* cortico-spinal excitability, as revealed by single pulse TMS, if it was preceded by cathodal stimulation and a motor cortex-chin electrode montage was used (Priori et al., 1998). By using a different electrode montage (motor cortex-contralateral orbit) under otherwise similar stimulation conditions (Table 1), an excitability *enhancement* by anodal and a respective *diminution* by cathodal stimulation was found by studies of another group (Nitsche and Paulus, 2000). These changes were in the range of 30% compared to base-line. Since electrode position was the only variable which differed substantially between these studies, it most probably caused the discrepant effects.

More detailed knowledge about the origin and effects of cortical DC stimulation has been gained from early animal experiments. For the visual and motor cortex of the cat and rat, it was shown that a DC stimulus between 0.00013–0.3 C/cm^2 increased spontaneous neuronal activity if the anode was placed above or within the cortex, whilst cathodal polarity resulted in reduced activity (Creutzfeldt et al., 1962; Bindman et al., 1964; Purpura and McMurtry, 1965). This was due to a subthreshold membrane depolarisation by anodal and a hyperpolarisation by cathodal stimulation (Purpura and McMurtry, 1965; Scholfield, 1990). However, the results were not the same for all neurons studied: Apart from the dominant net shift of cortical activation, some

TABLE 1. Overview of stimulation parameters and functional effects of tDCS in humans.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Antal et al., 2001	Oz vs. Cz	35	420	0.001	0.00002857	0.012	Elevated visual perception threshold by cathodal tDCS
Antal et al., in press	Oz vs. Cz	35	420	0.001	0.00002857	0.012	Phosphene threshold reduced by anodal and increased by cathodal tDCS
Baudewig et al., 2001	C3 vs. contralateral supraorbital	35	300	0.001	0.00002857	0.008571	Reduced BOLD answer after cathodal tDCS (fMRI, finger tapping task)
Bogdanov et al., 1994	Anode frontal right hemisphere, cathode C3 or mastoid left side	6	3,000	0.0002–0.0008	0.000033–0.00013	0.099–0.39	In cerebral palsy clinical severity, muscular hypertonus and reflex answers diminished, enhanced motor learning even after the end of stimulation
Dymond et al., 1975	Frontal vs. mastoid	90 (proposed)	0.001	0.0001–0.0015	0.0000011–0.000016	0.0000000011–0.000000016	Intracerebral voltage linearly correlated to current strength
Elbert et al., 1991	Vertex vs. ear lobe	1.77	5	0.00026	0.00014711	0.00073555	Improved performance in a forced choice reaction time task during anodal stimulation
Jaeger et al., 1987	C3 vs. C4	0.50	2	0.0003	0.00059675	0.0011935	Improved performance in a forced choice reaction time task during anodal stimulation
Korsakov and Matveeva, 1982	Occipital vs. mastoid	0.79	8,000–12,000	0.0002	0.00025461	2.03688–3.05532	Anodal stimulation. VEP-modulations, slow cortical activity changes, less perception sensitivity
Lippold and Redfearn, 1964	Frontal vs. knee	0.5 (proposed)	Up to 14,400	0.0005	0.001	14.4	Anodal stimulation induces elated mood, cathodal withdrawal and silence, but not tiredness

TABLE 1. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Nitsche and Paulus, 2000	Primary motor cortex vs. contralateral supraorbital	35	4–300	0.0002–0.001	0.000006–0.00003	0.00012–0.009	Excitability enhancement by anodal and reduction by cathodal stimulation
Nitsche and Paulus, 2001	Primary motor cortex vs. contralateral supraorbital	35	300–780	0.001	0.00003	0.009–0.0234	Long lasting excitability enhancement by anodal stimulation
Nitsche et al., 2003a	Primary motor cortex vs. contralateral supraorbital	35	300–540	0.001	0.00003	0.009–0.0162	Long lasting excitability reduction by cathodal stimulation
Nitsche et al., 2003b	Primary motor cortex vs. contralateral supraorbital	35	540/780	0.001	0.00003	up to 0.0187	Improved implicit motor learning by anodal tDCS
Priori et al., 1998	Primary motor cortex vs. chin	25	7	0.0005	0.00002	0.00014	After cathodal stimulation, anodal tDCS diminishes motor cortical excitability
Pfurtscheller, 1970	Eyes vs. neck or extremities	5.25	4	0.00005–0.0005	0.00001–0.0001	0.00004–0.0004	In regard to evoked potentials diminished 5a/P2 during cathodal, and enhanced during anodal stimulation; EEG: anodal stimulation enhances ß- and reduces alpha/theta activity, theta/alpha is enhanced by cathodal stimulation
Shelyakin et al., 1998	Anode frontal right hemisphere, cathode C3 or mastoid left side	1–6	1,200–2,400	0.0003	0.00005–0.0003	0.06–0.72	In cerebral palsy clinical severity diminished. Muscular hypertonus, and reflex answers diminished, enhanced motor learning

TABLE 1. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Wieser, 1998	Implanted electrodes amygdala, hippocampus, reference scalp	0.01	120	0.000001–0.00006	0.0001–0.006	0.012–0.72	Anodal stimulation diminished epileptic activity in EEG, one time psychosis because of forced normalisation; cathodal stimulation resulted in seizure

TABLE 2. Overview of stimulation parameters and functional effects DC-stimulation in animals.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Basics							
Andreasen and Nedergaard, 1996	Electrodes near slices	0.2	0.12	0.00005–0.0045	0.000417–0.0375	0.0000834–0.0075	According to direction of electrical field hyper- or depolarisation; in distal apical dendrites by supra-threshold stimulation (0.05–0.3 mA) Na- and Ca-channel-triggered spiking
Bindman et al., 1964	Epidural sensori-motor cortex	up to 1,200	0.12	0.000003	0.000025	0.03	Anodal stimulation reduces positive evoked potential (EP) wave and increases negative wave, increases spontaneous activity, cathodal stimulationinduces reverse changes, effects maximum after minutes, remaining up to hours if stimulation lasts sufficiently long
	Intracortical. sensori-motor cortex	up to 1,200	0.0000000707	0.00000025	3536.0	4342.2	Same effects
Bishop and O'Leary, 1950	Corpus geniculatum laterale	No information available					Anodal stimulation increases threshold and action potential-amplitude, diminishes positive EP-wave, and increases negative wave. Cathodal stimulation results in opposite effects. Dendritic amplitudes increased by anodal and diminished by cathodal stimulation
Chan and Nicholson, 1986	Cerebellum in chamber, electrodes at bottom and ceiling of chambers	1–20	2	0.0002–0.005	0.0001–0.0025	0.0001–0.05	Field strength correlates with discharge rate. Purkinje-cell somata, primary as well as distal dendrites and most of the stellate cells showing enhanced activity during cathodal stimulation, but other during anodal stimulation; effectivity of stimulation depends on dendritic/neuronal geometry

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Chan et al., 1988	Cerebellum in chamber, electrodes at bottom and ceiling of chambers	10	2	0.002–0.01	0.001–0.005	0.01–0.05	Same polarisation results in different effects in different layers (hyper-, or depolarisation); stronger polarisation elicits spiking
Creutzfeldt et al., 1962	Intracortical, visual and motor cortex	0.001	0.0078525	bis 0.001	0.12735	0.00012735	Most neurons activated by anodal and deactivated by cathodal stimulation; reversed effect in deep layers and in sulci. Linear correlation between current strength and effects from 200 µA on.
Gartside, 1968a	Surface sensorimotor cortex	600	0.12	0.0001–0.0005	0.00083–0.0041	0.498–2.46	Increased spontaneous activity by anodal stimulatiom even after electric decoupling and cooling
Gartside, 1968b	Surface sensorimotor cortex						After-effect following anodal polarisation can be prevented by application of cytostatics
Landau et al., 1964	Motor, visual, somatosensory cortex surface	10–30 (proposed)	0.25	0.0001–0.0025	0.0004–0.01	0.004–0.3	Anodal stimulation increases amplitude of negative and decreases amplitude of positive EP-waves, cathodal effect opposite, in surface and deep layers opposite effect; dependent on neuronal orientation; stronger stimulation results in stronger effects
Lukhanina and Litvinova, 1986	Implanted electrodes caudate, thalamus vs. fronto-nasal bone	bis 180	0.000201	0.0003–0.0005	1.4925–2.4875	268.65–447.75	Inhibition at 300µA by anodal stimulation, after-effects for up to 20 min

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Morrell, 1961	Implanted electrodes motor cortex	more than 60					In case of anodal stimulation light flash results in motor reaction, even 20 min after cessation of stimulation; increased motor neuron discharges following an acoustic trigger stimulus
Purpura and McMurtry, 1964	Epidural electrodes motor cortex	5–40	0.04–0.2	0.0006–0.0012	0.003–0.008; 0.01–0.04	0.015–0.32; 0.03–1.92	Positive EP-waves diminished and negative increased by anodal stimulation; reversed effect by cathodal stimulation; below 80μA no effect on PT-neurons; above this values depolarisation of PT-cell soma by anodal and hyperpolarisation by cathodal stimulation; in non PT-cells different effects; long lasting stimulation (40 s and longer) results in long lastig aftereffects
Richter et al., 1994	Epidural electrodes	30	0.08	0.000005–0.00002	0.0000625–0.00025	0.001875–0.0075	Spreading depression suppressed by DC-stimulation, reoccurs 45–60 min following anodal or cathodal stimulation; cathodal stimulation more effective
Richter et al., 1996	Epidural electrodes	480	0.08	0.00001–0.00003	0.000125–0.000375	0.06–0.18	Spreading depression suppressed by DC-stimulation, reoccurs 45–60 min following cathodal stimulation; minimum 30 μA
Scholfield, 1990	Implanted electrodes	4	0.000012564	0.000000025	0.0019898	0.0079592	Anodal stimulation results in depolarisation, cathodal in hyperpolarisation of presynaptical unmyelinated axons
Hattori et al., 1990	Epidural elektrodes sensori-motor cortex	1,800 10,800	0.0078525	0.0000003; 0.000003; 0.00003	0.00003820; 0.0003820; 0.003820	0.06876–41.256	30 min anodal stimulation with 3 μA increases cAMP-level. 0.3 μA decreases it. 3 h stimulation duration decreases cAMP under all conditions

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Islam et al., 1995a	Epidural elektrodes sensori-motor cortex	1,800	0.0078525	0.000003	0.000382	0.6876	Intraneuronal Ca-accumulation and dark neurones until 72 h after the end of anodal stimulation
Islam et al., 1995b	Epidural elektrodes sensori-motor cortex	1,800 10,800	0.0078525	0.000003; 0.00003	0.0003820; 0.003820	0.6876–41.256	NMDA-dependent c-Fos expression increased by anodal stimulation
Islam et al., 1997	Epidural elektrodes sensori-motor cortex	1,800 10,800	0.0078525	0.0000003; 0.000003; 0.00003	0.00003820; 0.0003820; 0.003820	0.06876–41.256	0.3 mA for 30 min, 3 mA for 30 min and 3 h anodal stimulation are elevating PKCg. All other combinations are not effective; begin 1 h, maximum 3 h after stimulation. Vanished after 72 h
Functional							
Albert, 1966	Medial cortex epidural elektrodes	60 repetitively	0.015	0.000012	0.008	0.48	Interhemispheric transfer task; transfer enhanced by anodal, diminished by cathodal stimulation
Hayashi et al., 1990	Implanted electrodes subst. nigra	1,800	0.0003141	0.000003	0.009551	171918,0	During anodal polarisation no effect. After polarisation enhanced contralateral rotation up to 10 days
Hori et al., 1975	Intracranial electrodes (in the bone) over the sensori-motor cortex	1,800 repeated	0.017635–0.17635	0.000001–0.00001	0.00001239–0.0001239	0.023302–0.23302	Enhanced flight-reflex reminding spontaneous movements after anodal polarisation elicited by acoustic or visual eue for hours and days. “dominant focus”
Kupfermann, 1965	Visual cortex, implanted epidural electrodes	400 (proposed)	0.2	0.0002	0.001	0.4	Cathodal stimulation diminishes learning, but not performance; anodal stimulation not effective

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Kyazimova, 1999	tDCS motor cortex	900–2,400					Changing dominance of two dominant foci shows that they are connected
Lu et al., 1994	tDCS, electrodes implanted in the bone over the sensori-motor cortex	1,800 ten times repeated in 3 days	0.0078525	0.0000003; 0.000003; 0.00003	0.00003820; 0.0003820; 0.003820	0.06876–6.876	Between 1–3 μA anodal stimulation increased spontaneous movement of forelimb. decreased forelimb struggle at 10 and 30 μA.
Luchkova, 1979	Implanted electrodes hypothalamus, thalamus	900–1,800					Anodal stimulation prevents conditioning and EEG-synchronisation
Morrell and Naitoh, 1962	Epidural electrodes visual cortex	600 and more	0.05	0.00005	0.001	0.6	Cathodal stimulation impairs performance. anodal improves it the next day with regard to learning
Murik, 1996	Epidural electrodes visual and auditory cortices	600 and more	0.2	0.00014	0.0007	0.42	Anodal stimulation results in less movement in new environment (positive emotion), cathodal in increased (distress, fear)
Proctor et al., 1964	Epidural electrodes visual and auditory cortices	30 (proposed)	0.0706725	0.0000706725	0.001	0.03	Auditory learning disturbed by cathodal stimulation; anodal stimulation not effective
Rosen and Stamm, 1972	Dorsolateral prefrontal, epidural electrodes	Up to 1,920	0.0078525–0.015705	0.00001–0.00004	0.000637–0.00255	1.22304–4.896	Improved learning in delayed reaction task by anodal stimulation, diminished by cathodal stimulation; continuous stimulation acts best

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Rusinova, 1988	Epidural electrodes sensorimotor cortex	No information available					Induction of dominant focus by anodal stimulation; changes in EEG and behavior are detectable even after cessation of stimulation, but extinguish able, it is possible to re-activate them
Rusinova, 1999	Epidural electrodes sensorimotor cortex	No information available					Anodal stimulation results in EEG coherence changes; reduction of alpha and delta-bands and isolation
Rusinova, 1989	Epidural electrodes sensorimotor cortex	No information available					Motor behavior contralateral to stimulation changes, CA3-EEG changes ipsilaterally
Stamm and Rosen, 1971	Dorsolateral prefrontal, epidural electrodes	Up to 1,920	0.0078525–0.015705	0.00001–0.00004	0.000637–0.00255	1.22304–4.896	Improved learning in delayed reaction task by anodal stimulation, diminished by cathodal stimulation; continuous stimulation acts best
Szeligo, 1976	Epidural electrodes occipital	45			0.0009	0.0405	Increased negative VEP-waves by anodal stimulation; more effective with repetitive stimulation, less time to learn needed in visual avoidance task
Vartanyan et al., 1980	Implanted electrodes cortex, Caudate, reticular formation	1,800 repetitively		0.0000004–0.00018	0.00008–0.0003	0.144–0.54	Motor learning and recall can be improved by stimulation of cortex, hippocampus, Ncl. caudatus and mesencephalic reticular formation

TABLE 2. Continued.

Authors	Electrode position	Electrode size (cm^2)	Stimulation duration (s)	Current strength (A)	Current density (A/cm^2)	Total charge ($A*s/cm^2$)	Effects
Ward, 1969	Epidural electrodes visual cortex	1,800					Visual discrimination decreased by anodal stimulation during and after stimulation; effect depends on stimulation duration and intensity
Weiss et al., 1998	Implanted electrodes amygdala	300–900 7–14 days					Epileptic seizures and after-discharges reduced for 1 month after stimulation
Yamaguchi et al., 1975	Implanted electrodes pre-motor cortex	No information available					Increased spontaneous movement contralaterally for 4–100 days after repeated anodal stimulation; similar to flight-flexes

neurons were modulated conversely. Thus, in the cat motor cortex neurons situated in deep cortical layers were often de-activated by anodal and activated by cathodal stimulation (Creutzfeldt et al., 1962). The same was found for superficially situated motor cortical non-pyramidal tract (PT) neurons (Purpura and McMurtry, 1965). It was argued that these neurons were spatially oriented in a way that reversed current flow direction through the neuron compared to the dominant type of neuron, which would result in an opposite-direction polarisation.

Moreover, the type of neurons modulated by DC stimulation seems to depend on stimulation strength: whereas total charges up to 0.008 μC/cm^2 modulated predominantly non-PT cells, higher intensities were necessary to change spontaneous activity of PT neurons (Purpura and McMurtry, 1965).

Apart from changes of spontaneous discharge rate, subthreshold DC stimulation modulated the cortical response to thalamic stimulation in the cat: anodal stimulation enhanced the positive and reduced the negative component of the respective electro-cortico potentials, whilst cathodal stimulation resulted in opposite changes (Landau et al., 1965; Purpura and McMurtry, 1965). Conversely, with regard to sensory-evoked potentials in the rat, anodal stimulation decreased the positive waves, while increasing the negative ones; again, cathodal stimulation resulted in reverse effects (Bindman et al., 1964). Because stimulation intensities were similar in both cases and the position of the reference electrode was proved to be unimportant (Bindman et al., 1964; Purpura and McMurtry, 1965), these discrepancies may be due to spatially differently organised cortices of the species.

Taken together, the reported studies show that during cortical DC stimulation, spontaneous neuronal activity and processing of afferent signals are modulated by polarity-specific shifts of resting membrane potential in a de- or hyperpolarising direction. Those effects can be obtained in motor, as well as, visual cortices. The direction of change depends on an interaction of current flow and neuronal orientation in space, and the type of neurons involved on phase density.

2.3. After-effects of DC stimulation on cortical excitability and activity

It was shown recently in humans that tDCS which exceeds a certain threshold of stimulation duration and intensity, results in motor cortical excitability modifications that continue after the end of stimulation: depending on total charge, after-effect durations from a few minutes (0.0087 C/cm^2) up to 1 h after the end of stimulation (0.022 C/cm^2) were accomplished (Fig. 1a, b; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). The respective excitability shifts are in the range of 40–50% compared to baseline. This stimulation paradigm does not only shift cortical excitability but also activity (Baudewig et al., 2001), and the effects are localized intracortically. As shown by a pharmacological study, the evolving after-effects depend on changes of NMDA receptor-efficacy (Liebetanz et al., 2002). The efficacy of tDCS in eliciting after-effects is not restricted to the human motor cortex: As shown recently, occipital stimulation can modulate visual cortical function (Antal et al., 2001, in press), and the directions of those changes are identical to those in the motor cortex with regard to tDCS polarity.

In animal experiments, the capability of DC stimulation to elicit prolonged cortical excitability and activity changes has been known for some time. Given a total charge of 0.03 C/cm^2, anodal stimulation of the rat sensorimotor cortex induced long-lasting increases in the negative wave amplitude of sensory-evoked potentials and spontaneous discharge rates, whilst cathodal stimulation resulted in reverse effects (Fig. 2a, b; Bindman et al., 1964). These shifts were stable at least for some hours after the end of stimulation. Somewhat shorter after-effect durations (about 20 s) were seen in the cat for a total charge of 0.06 C/cm^2 (Purpura and McMurtry, 1965). Because stimulation duration differed between the experiments, being much shorter in the second one, it is likely that stimulation duration beyond total charge is an important separate parameter for inducing after-effects. Alternative explanations could be inter-species or anesthetic differences, which might have prevented long-lasting modifications in the latter experiment.

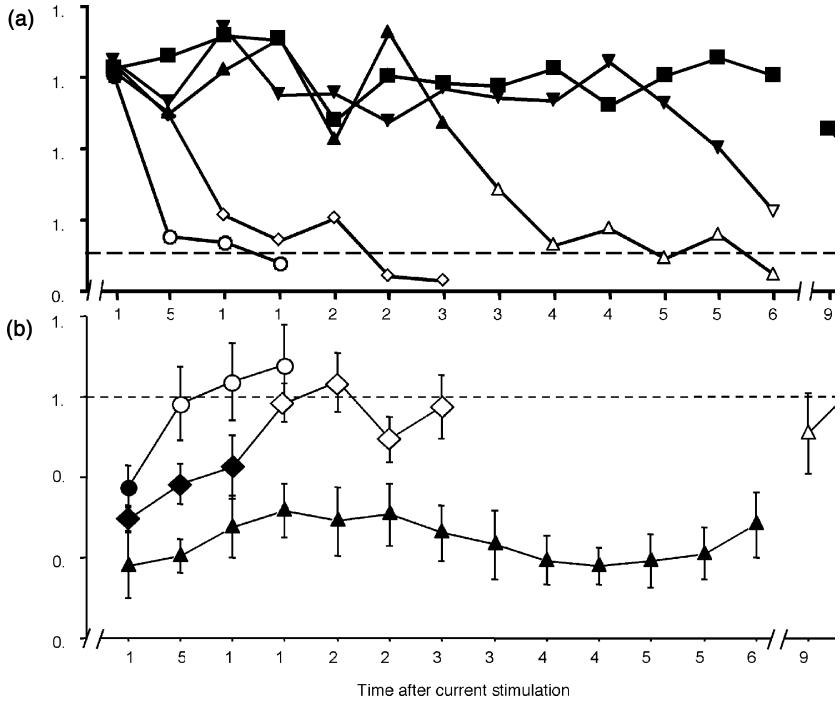

Fig. 1. tDCS of the human motor cortex modulates the MEP-amplitudes after stimulation duration-dependently for up to an hour after tDCS. Anodal stimulation (a) enhances, while cathodal (b) diminishes cortical excitability. Note that 5–7 min stimulation results in short-lasting after-effects, while prolonged tDCS increases the duration of the after-effects over-proportionally (Nitsche and Paulus, 2001; Nitsche et al., 2003a, with permission of *Neurology and Clin. Neurophysiol.*).

Further animal experiments revealed some of the mechanisms that lead to these effects. These are not just electrical phenomena, since intermittent complete cortical inactivation by cooling or application of Kcl did not eliminate them (Gartside, 1968a), but depend on protein-synthesis (Gartside, 1968b). As revealed by histological studies, anodal stimulation modified intracellular cAMP-level dependend on noradrenaline and increased the intracellular calcium level as well as early gene expression, the latter was shown to be NMDA receptor-dependent (Hattori et al., 1990; Islam et al., 1995a, b, 1997). These changes were elicited by a total charge between 0.068–0.68 C/cm^2, however, lower stimulation intensities were not tested. Remarkably, the modulation of cAMP level dependend on total charge: whereas 0.068 C/cm^2 decreased cAMP-level, 0.68 C/cm^2 increased it.

Thus, in humans, as well as in animals, weak DC stimulation is capable of eliciting long-lasting changes of cortical excitability and activity at similar charge densities. These changes depend on protein-synthesis and involve NMDA receptors as well as modifications in intracellular calcium and cAMP concentration, and early gene expression.

2.4. Functional effects of DC-stimulation

2.4.1. Human experiments

Human studies exploring a possible functional relevance for DC stimulation can be divided into two categories: those modulating cognitive or neurophysiological functions, and clinical studies.

With regard to the first group, it was shown that anodal stimulation of the motor cortex with a total charge similar to that known to result in cortical

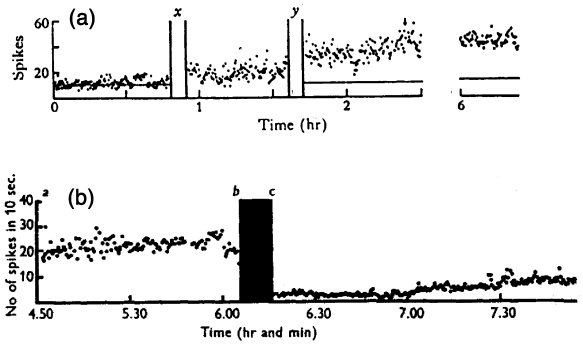

Fig. 2. In vivo weak direct current stimulation of the rat sensori-motor cortex induces prolonged shifts of spontaneous neuronal activity. The time-course of the number of spontaneous discharges before and after stimulation recorded by extracellular field potential measures is depicted. Here, 20 min anodal stimulation (a) results in an prolonged activity enhancement, while 10 min cathodal stimulation (b) reduces it. Vertical bars indicate stimulation phases (Bindman et al., 1964, with permission of *J. Physiol*.).

excitability changes (Table 1) optimised performance in a choice reaction time task (Elbert et al., 1991; Jaeger et al., 1987) and improved implicit motor *learning* in its aquisition phase (Fig. 3; Nitsche et al., in press), most probably due to an excitability enhancement. Moreover, at this total charge tDCS with both polarities reduced *training*-induced changes of motor cortical excitability patterns and re-established the pre-use dominant excitability pattern of a given cortical area (Rosenkranz et al., 2000). The most parsimonous explanation for the latter result is a de-activation of transiently use-dependently activated networks by cathodal and a re-activation of transiently use-dependently inhibited networks by anodal tDCS, thus, both tDCS-conditions would shift the focus of excitability back to the pre-use dominant one. Furthermore, these results imply that the functional effects of tDCS may depend on task characteristics.

For the visual cortex it was shown that relatively strong (up to 3.06 C/cm^2) anodal stimulation worsened visual perception in a brightness discrimination task during, and after, the end of stimulation (Korsakov and Matveeva, 1982). However, by use of a different electrode montage and much weaker stimulation (0.012 C/cm^2), cathodal stimulation, which hyperpolarises the cortex, increased perception threshold, whilst anodal stimulation had no effect (Antal et al., 2001). The surprising difference could be, at first glance, caused by a maximum activation of visual cortical neurons by strong anodal stimulation in the first experiment, which would make it difficult to perceive small differences in brightness due to a ceiling effect, whereas, in the weak stimulation condition an inhibition of visual cortical neurons would diminish perception at a given contrast intensity. As was shown recently, anodal and cathodal tDCS are able to modulate phosphene threshold stimulation polarity-dependently with a total charge similar to the latter study (Antal et al., in press), this explanation seems to be plausible. However, it cannot be ruled out that the modulation of different neuronal populations by the respective stimulation protocols caused the effects, since it is known that electrode position and stimulation intensity are critical for the tDCS-induced excitability modulation of specific neuronal populations.

Clinical studies have so far been largely confined to the treatment of psychiatric diseases, namely depression. Although these earlier experiments included some cortical stimulation, most probably the positioning of the electrodes (supraorbital-knee montage) primarily resulted in predominant brain stem stimulation. However, it was shown by Pfurtscheller (1970) that this kind of stimulation could change EEG patterns and evoked potentials at the cortical level (Table 1) and thus, has to be regarded as effective. Anodal (polarity referring to the frontal electrode) tDCS (14.4 C/cm^2) diminished depressive symptomatology (Constain et al., 1964), while cathodal stimulation of the same total charge reduced manic symptoms (Carney, 1969). In healthy subjects, anodal stimulation resulted in increased activity and elated mood, while cathodal stimulation was followed by quietness and apathy (Lippold and Redfearn, 1964). However, these effects could not be replicated by all follow-up studies, maybe because of different patient subgroups, or because measures

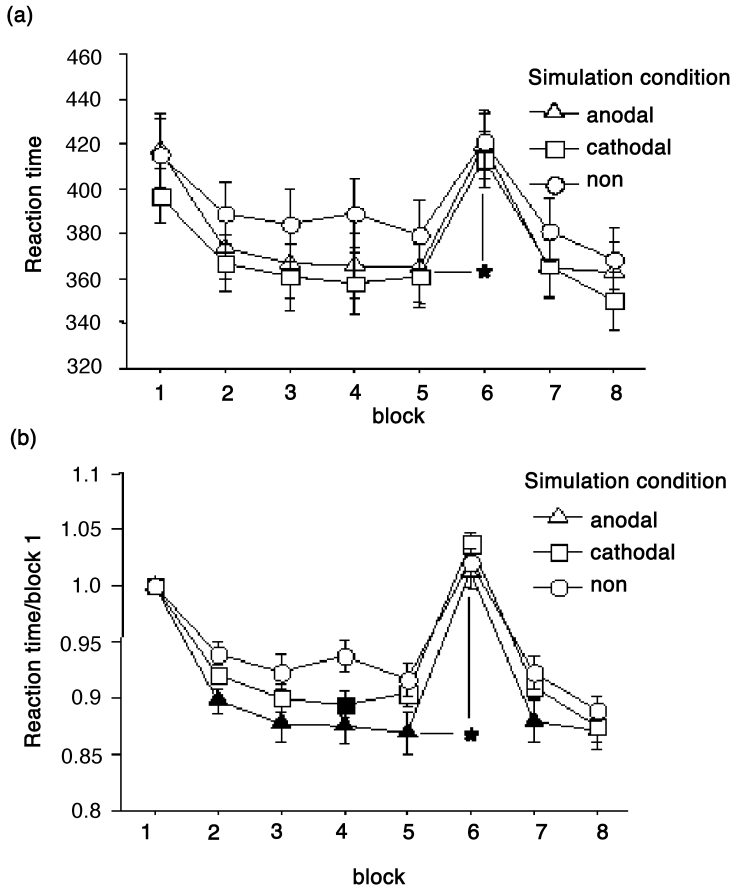

Fig. 3. Anodal tDCS of the primary motor cortex improves performmance in the Serial Reaction Time Task, a standard paradigm to test implicit motor learning. In this task, subjects have to perform a sequential finger movement task without being aware of a rehersal of the sequence. In blocks 2–5 and 7–8 the same sequence is presented 10 times, in block 1 and 6 a random sequence is presented. Reaction time differences between block 5 and 6 are selectively due to implicit motor learning. During anodal stimulation (given during the whole course of the experiment), subjects performed significantly faster during block 5 relative to block 6, as compared by a non-current condition. Figure (a) shows absolute reaction times, Fig. (b) those standardised to block 1 (Nitsche et al., 2003b, with permission of *J. Cog. Neurosci.*).

of changes or other factors that were not controlled systematically (for an overview see Lolas, 1977). In schizophrenic patients, applying direct currents seemed to be without effect in one study (Lifshitz and Harper, 1968). Other studies suggest that anodal stimulation of the frontal cortex (total charge between 0.06 and 0.72 C/cm^2) diminished electrophysiological and clinical symptoms of infantile cerebral palsy (Vartayan et al., 1981; Bogdanov et al., 1994), and that anodal DC stimulation of the amygdala with a similar charge density could prevent seizures, whilst cathodal stimulation elicited them (Wieser, 1998). Although these studies imply that tDCS could be helpful in some neurological and psychiatric diseases, the results are difficult to interpret, because, so far it has not been shown if the excitability changes resulting from tDCS of the frontal cortex or even subcortical stimulation are similar to those induced by motor cortical tDCS. This is not a trivial problem, since neuronal orientation relative to the flow of the

current determines the effects of stimulation and it is not improbable that the foldings of the frontal cortex and neuronal orientation in the amygdala result in stimulation effects different from those obtained by stimulation of the primary motor and visual cortices.

2.4.2. Animal experiments

Since learning requires functional changes in cortical architecture that involve excitability modulations, the induction of neuroplastic changes by weak direct current stimulation is an interesting potenital tool to modulate these processes. Indeed, it was shown in some early experiments that learning processes are influenced by DC stimulation: in the monkey, anodal stimulation of the dorsolateral prefrontal cortex improved performance in a delayed reaction time task, while cathodal stimulation of the same region worsened it (Fig. 4, Rosen and Stamm, 1972). The same pattern of results was found by Albert (1966) and Morrell and Naitoh (1962) for a conditioned avoidance task in the rabbit. Total charge varied between 0.48 and 4.8 C/cm^2 (Table 2). Thus, an externally induced increase of cortical excitability seems to be beneficial to learning processes, while decreasing it results in a more negative outcome. This is in accordance with current opinions that long-term potentiation, which could be enhanced by an excitability elevation and diminished by a respective reduction of excitability, is the crucial mechanism for the formation of memory traces (Rioult-Pedotti et al., 2000). With regard to visual and auditory cortex stimulation, the results are less conclusive so far: Kupfermann (1965) found decreased learning in a visual categorisation task caused by cathodal occipital lobe stimulation of 0.4 C/cm^2, whilst anodal DC stimulation was not effective. Proctor et al. (1964) describe similar results for an auditory learning task at a somewhat lower total charge of 0.03 C/cm^2. However, Szeligo (1976) describes improved learning by anodal visual cortex stimulation in a visual avoidance task at a total charge of 0.04 C/cm^2. Similar to the results achieved in the human motor cortex, most probably task differences or differences of stimulation intensity explain the conflicting results.

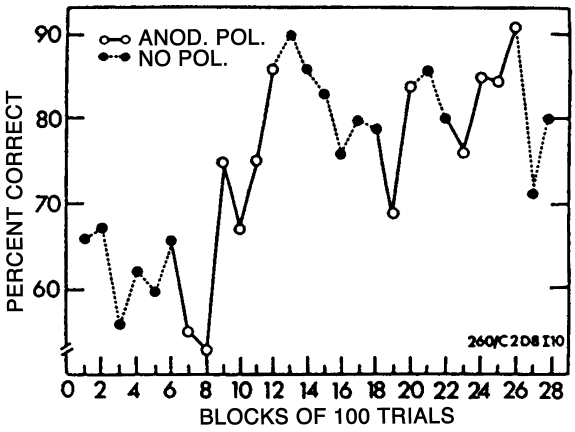

Fig. 4. In vivo anodal weak direct current stimulation of the monkeys dorsolateral prefrontal cortex enhances performance during learning of a delayed reaction time task. Filled symbols represent trials during anodal stimulation, open symbols without stimulation (Rosen and Stamm, 1972, with permission of *Exp. Neurol.*).

Another early branch of research dealt with the induction of a so-called dominant focus in the rabbit motor cortex: it was found that prolonged anodal direct current stimulation resulted in reflex-like motor reactions to sensory stimuli, and that these reactions could not be elicited before the stimulation (Hori et al., 1975; Lu et al., 1994; Rusinova, 1988). It was argued that an externally induced excitability enhancement facilitated the release of flight reflexes which were formerly actively inhibited (Hori et al., 1975). Interestingly, these behavioral modifications remained after the end of stimulation, and the neuronal activity of the stimulated region differed from that of the remaining cortex, which demonstates that neuroplastic changes are induced by this paradigm. Total charges were in the range of the learning experiments, as far as reconstructable (Table 2).

As shown by Richter et al. (1994, 1996), an excitability diminution elicited by cathodal stimulation of brain slices suppressed spreading depression, which is due to cortical hyperactivity and results in excitotoxic effects. Prolonged treatment resulted in sustained after-effects at a total charge from 0.002 to 0.18 C/cm^2. Perhaps the same mechanism is responsible for the reduction of after-discharges and

inductability of epileptic seizures by repetitive direct current stimulation of the rat amygdala, as reported by Weiss et al. (1998), however, these authors did not report stimulation polarity or the effects of stimulation onto spontaneous cortical activity or excitability. Interestingly, it was shown recently that depending on stimulation polarity direct current stimulation can enhance or diminish epileptic activity in slice preparations (Durant and Bikson, 2001).

2.4.3. Safety aspects

So far, virtually no systematic studies have been performed which are optimally suited to define criteria for safe transcranial direct current stimulation. However, some preliminary statements regarding safety aspects can be derived from available studies. It has to be kept in mind that they were originally developed and studied for relatively strong, suprathreshold pulsed stimulation.

Important possible features of electrical brain stimulation, which may cause brain damage, are electrochemically produced toxic brain products and electrode dissolution products on the one hand, caused by the (metallic) electrode-tissue interface (Agnew and McCreery, 1987). As stated by the authors, these factors are not important for transcranial stimulation – as performed by tDCS – with the exception of a possible skin injury, because by transcranial stimulation electrodes and brain tissue are not in direct contact. Since tDCS is performed with water-soaked sponge electrodes by our group, and thus, chemical reactions at the electrode-skin-interface are minimised, the only remaining possibility of a damaging effect to the skin will be the heating of the electrode (which has been tested not to happen), if our tDCS-protocols are used (Nitsche and Paulus, 2000). On the other hand, electrical stimulation could cause tissue damage by neuronal hyperactivity and brain tissue heating (Agnew and McCreery, 1987). Since the damaging effect due to cortical hyperactivity originally refers to the excitotoxic effect of near-tetanic suprathreshold stimulation and tDCS using our protocols induces only moderate changes of cortical excitability (about 40% as compared to baseline), has been shown in the animal to increase spontaneous firing rate also only to a moderate degree (Bindman et al., 1964), and does not elicit supra-threshold effects, a damaging effect by neuronal hyperactivity is improbable, if these protocols are used. The damaging effect of neuronal tissue heating can be ruled out keeping in mind that this was not the case directly under the electrodes (Nitsche and Paulus, 2000) and that only about 50% of charge/total charge, which could cause those effects, will reach the brain (Rush and Driscoll, 1968). However the situation could be different if the stimulation is applied above foramina, where current flow would be focused and thus, the effective electrode size diminished (Rush and Driscoll, 1968). Consequently, this should be avoided. Given total charge, which is the probably most appropriate parameter – but tested only for suprathreshold electrical stimulation (Yuen et al., 1981) so far – at least approximately comparable to tDCS, the stimulation intensity applied in our protocols so far (up to 0.02 C/cm^2) is much lower than the minimum total charge tested by Yuen et al. (1981) (216 C/cm^2), which only in cases of relatively strong suprathreshold stimulation elicited some damaging effects. Similarly, our stimulation protocols are below the minimum current density (25 mA/cm^2) resulting in brain tissue damage, as described by McCreery et al. (1990). Other parameters studied for suprathreshold electrical stimulation like, charge per phase and, charge density refer to only one pulse within a suprathreshold stimulation session lasting for several hours (Yuen et al., 1981, Agnew and McCreery, 1987) without including the overall applied charge – which determines the damaging effects on neuronal tissue substantially – in the formula. The fact that in regard to these parameters in contrast to suprathreshold electrical stimulation the whole stimulation session will be included in case of tDCS, because tDCS involves only one phase of stimulation, makes them unapplicable for defining safety limits of tDCS. Thus, in regard to the above-mentioned indirect criteria, tDCS should be regarded as safe with the protocols used by our group so far. Moreover, for these stimulation protocols further direct evidence for the safety of the protocols is available: it was shown

that they do not cause heating effects under the electrode (Nitsche and Paulus, 2000), do not elevate serum neurone-specific enolase level (Nitsche and Paulus, 2001; Nitsche et al., 2003), a sensitive marker of neuronal damage (Steinhoff et al., 1999) and do not result in changes of diffusion weighted or contrast-enhanced MRI or pathological EEG-changes (unpublished observations). Additionally, the accomplished excitability changes of about 40% compared to baseline should not result in excitotoxic effects, and the restricted duration of the effects seems not to induce stable (in terms of days or weeks) functional or structural cortical modifications, which could be dysfunctional in healthy subjects. This paradigm has been tested in about 500 subjects in our laboratory so far without any side-effects apart from a slight itching under the electrode and a short light flash if the stimulation was switched on or off abruptly. For this reason, and for the prevention of stimulation break effects, which have been shown to diminish the initial effects after the end of stimulation (Bindman et al., 1964), we now prefer ramping for switching the current on or off. Because it seems that current densities above 0.00002857 A/cm^2 (which refers to 1 mA/35 cm^2, again, it is important to realise that the current strength per area will cause this effect) could be painful (unpublished observations), we suggest that this value should not be exeeded. Nevertheless, for the extension of the after-effects, most probably inducible by a further prolongation of stimulation duration, which is needed for clinical applications, additional systematic safety studies are urgently needed and currently performed in our laboratory.

Some additional precautions should be considered for safe stimulation: electrode montages that could result in brainstem or heart nerve stimulation can be dangerous and should be ommitted. After stimulating the brainstem, Lippold and Redfearn (1964) describe one case of disturbed breathing, speech arrest and psychosis, and it cannot be ruled out completely that a current flow could modulate rhythmogenesis of the heart. Thus, according to currently available knowledge, not only the cortical stimulation electrode, but also the remote one should be positioned at a place preventing current flow through the brainstem. The stimulation device should guarantee a constant current strength, since current strength and not voltage is the relevant parameter for inducing neuronal damage (Agnew and McCreery, 1987) and a constant voltage device could result in unwanted changes of current strength, if resistance is unstable. Stimulation above foramina of the cranial bones should be avoided since this could result in a local excess of total charge and current density due to a focusing effect. Stimulation durations which are likely to result in excitability changes of more than an hour should be applied cautiously in healthy subjects, since excitability changes remaining for such a long time may be consolidated and stabilised (Abraham et al., 1993), and could be dysfunctional. For the same reason, long-term excitability changes should not be induced more than once a week, since repetitive daily stimulation result in excitabiltiy changes stable for weeks or even months in animals (Weiss 1998).

2.4.4. Perspectives

Transcranial direct current stimulation seems to be a promising method to induce acute as well as prolonged cortical excitability and activity modulations could thus evolve as a promising new tool in the field of neuroplasticity research.

If safety criteria involving stimulation strength per area, electrode positioning and duration of after-effects are met, the technique should be regarded as safe.

Future studies should evaluate systematically the effect of tDCS onto additional cortices, and should gather information about involved neuronal systems, receptors, ion channels and the dependancy of the effects on stimulation intensity.

For this tool to become relevant, not only for basic research purposes but also for clinical application, it must be shown to induce excitability changes in the human cortex which are stronger, and longer lasting, than those already achieved so far. Before these studies begin, safety-studies need to be performed to determine the maximum stimulation intensities and durations that can be applied without causing harmful effects.

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