Chapter 4
Current Methods and Approaches of Noninvasive Direct Current–Based Neuromodulation Techniques

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Introduction

In the last 20 years several techniques for inducing excitability changes based upon the delivery of direct current (DC) over the skin overlying different structures of the central nervous system became available to experimental and clinical neuroscientists. Transcranial direct current stimulation (tDCS) refers to DC delivery on the scalp over the cerebral cortex (Nitsche and Paulus 2000; Priori et al. 1998), cerebellar DC stimulation refers to delivering DC current over the cerebellum (Ferrucci et al. 2015), and transcutaneous spinal DC stimulation (tsDCS) refers to the delivery of DC currents over the spinal cord (Cogiamanian et al. 2012).

Electrodes

Any transcranial electric stimulation technique needs to transfer the electric current by at least two electrodes, a target electrode and a return electrode. Multiple electrodes may be used as well both for the target and for the return electrode in order to shape the current flow. The types of electrode used for tDCS encompass metal electrodes usually covered by sponges, conductive rubber electrodes or plastic electrodes providing some mm of space for being filled with a contact medium such as conductive cream or any combination of it. Electrode fixation is usually achieved

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by the aid of elastic straps, or head gears attached in various ways to the subject head. No ideal fixation system so far exists. The straps may still allow some movement over time during a tDCS session. Over-tightening the straps may lead to evacuation of saline from the electrode sponges. At the conductive electrode electrochemical reactions take place. Therefore the electrode should contact the skin by intermediate gel or saline solution in a sponge as a buffer between electrode and skin – with sufficient electrolyte volume preventing chemicals formed at the electrode from reaching the skin (Palm et al. 2014). In order to confine the electrode surface to the size of the electrode neither too much gel nor too much saline solution should be applied. In general, precise location of electrodes needs to be documented and kept constant to minimize variability (Saturnino et al. 2015). For example, even the position of the connecting electrode wire should be documented to provide maximum potential for replication (e.g., wire oriented to back of head, behind the ear, etc.).

The shape and the size of electrodes and/or sponges significantly alters the distribution of current delivered to the scalp and the brain (Saturnino et al. 2015). Small electrodes enable a more focused stimulation of smaller brain areas ending up e.g. in selective modulation of muscles targeting thenar or hypothenar (Nitsche et al. 2007). Large electrodes such as those conventionally used (Nitsche and Paulus 2000) with an area of 35 cm^2 provide the advantage that at first glance a not so precise allocation of the electrode position is needed. However in the light of the calculations made by Saturnino (Saturnino et al. 2015) and others small deviations from a standard electrode allocation may result in a substantial variability. Variability may be further enhanced and complicated by local thinnings of the skull which as a current running pathway may guide current through areas of locally reduced resistance somewhat independent of the location of larger electrodes (Opitz et al. 2015) (Fig. 4.1).

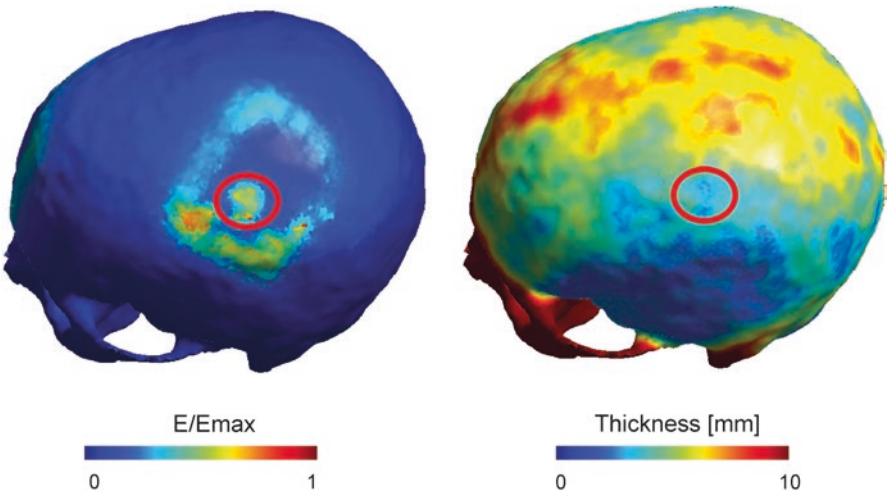

Fig. 4.1 Skull thickness (right). Red areas mark thick skull, blue areas thin skull ("temporal window" also used in ultrasound investigation). Red circle marks local thinning. On the left side electrical flow induced by a 7*5 cm electrode is calculated. Current drawn to the electrode edges is seen as well as a current pathway caused by the local thinning (red circle)

This problem can be circumvented by smaller electrodes which however need higher allocation precision (Woods et al. 2015) (*see also* Chap. 7, "Methodological Considerations for Selection of tDCS Approach, Protocols and Devices").

At the motor cortex this can be comparatively easy achieved by transcranial magnetic stimulation, other methods incorporate the International 10-20 (or 10-5) Electrode Placement System or commercially available neuronavigation systems.

With larger electrodes one should keep in mind that the conducting gel in larger electrodes guides electric current towards the edges of the electrodes, in fact a kind of ring stimulation may be taking place – although this scenario might particularly apply for the skin, but not the brain level. While other electrodes have been designed for defibrillation purposes with decreasing conductivities towards the electrode edges to enforce a more homogeneous current distribution, these electrode types have so far not been employed in transcranial stimulation techniques (Saturnino et al. 2015).

Usually the target electrode is placed above the target area. The return electrode(s) play a decisive role for guiding electric current through the intended brain or spinal cord areas. The early study by Nitsche and Paulus (2000) already showed that out of a number of different return electrodes only the one placed at the contralateral forehead provided effects during stimulation (Nitsche and Paulus 2000). In the spinal cord, the position of the return electrode influences the level of distribution of the maximum current density (Parazzini et al. 2014a) (Figs. 4.2 and 4.3).

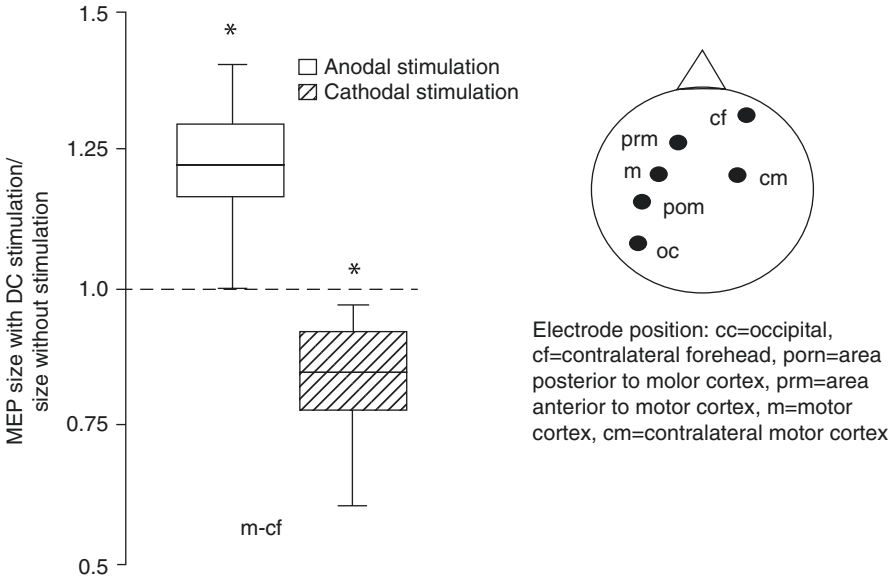

Fig. 4.2 Cortical excitability change during current flow showing rapidly induced effects of weak DC stimulation on the size of the motor evoked potential (MEP) in the right abductor digiti minimi (ADM) muscle, revealed by transcranial magnetic stimulation (TMS), using the motor cortex—contralateral forehead arrangement. MEP amplitudes during stimulation are normalized by division by MEP amplitudes without stimulation. During DC stimulation, the MEP amplitude increased with anodal and decreased with cathodal current stimulation. An effect was only seen with the m-cf montage. (Taken from Nitsche and Paulus 2000; with permission)

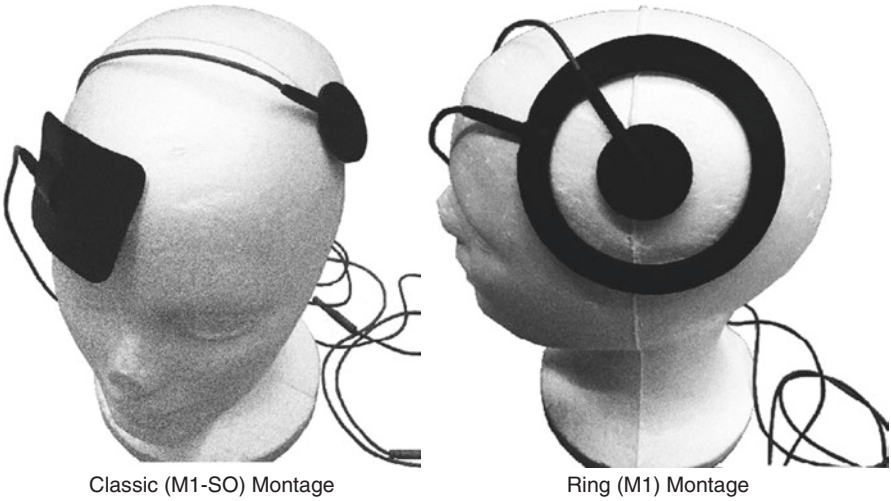

Fig. 4.3 Electrode montages can be realized in a conventional "bipolar" (top) or "center-surround" mode (bottom). (From Heise et al. 2016). The outer ring has the disadvantage that current flow cannot be controlled for compensation at thinner or thicker skull areas

Large return electrodes with an area of about 100 cm^2 have been suggested as a tool to dilute current intensity below threshold for excitation of brain tissue (Nitsche et al. 2007). Extracephalic electrodes have been discussed as another means to circumvent stimulation of the brain areas beneath cephalic return electrodes. In order to achieve comparable after effects sizes however stimulation intensity has to be doubled, at least with a return electrode at the arm (Moliadze et al. 2010b). Many modelling studies have suggested optimized current flows by the use of multichannel electrode arrays e.g. (Minhas et al. 2010; Ruffini et al. 2014). These arrays need individual calculations of electrode positions, commercial programs as well as shareware programs (e.g. www.simnibs.de) are available. It should be noted that these models have not been physiologically validated in most cases (Fig. 4.4).

Stimulation Protocols

In contrast to tACS with its capability for on-line entrainment of brain function, tDCS is essentially a method for induction of plastic after effects, although it was shown very early that 4 s of anodal tDCS increases and cathodal tDCS decreases excitability (Nitsche and Paulus 2000). Most of the available literature has dose-titrated systematically required physical parameters by single pulse TMS at the motor cortex. At least 0.6 mA intensity with a stimulation duration of at least 3 min was necessary to induce after effects (Nitsche & Paulus, 2000). In order to achieve an anodal excitatory after effects of 1 h a stimulation duration

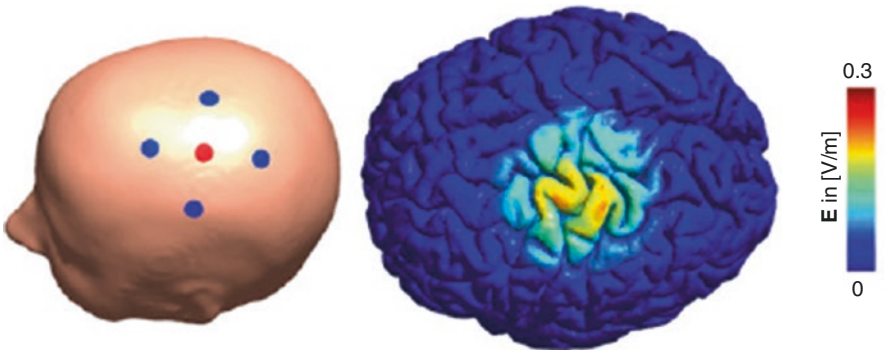

Fig. 4.4 A specific form of center-surround stimulation encompasses 4 surrounding electrodes called high-definition tDCS by (Minhas et al. 2010). Any other combination of (more) electrodes in the centre or both more or less electrodes in the surround is possible. If a constant current flow of 25% in each of the surround electrodes is to be guaranteed then a split channel connecting 4 electrodes must be used summing up to 100% in the center, with consistent impedance for the 4 electrodes. (Taken from Saturnino et al. 2015)

of 13 min is required (Nitsche and Paulus 2001), for cathodal inhibition 9 min are sufficient (Nitsche et al. 2003b). The original expectation that longer stimulation durations inevitably lead to longer plastic after effects is not true. After 26 min of continuous anodal stimulation the excitatory after effects switch into inhibition (Monte-Silva et al. 2013). Excitatory after effects can be achieved if the 26 min stimulation duration is interrupted by an either 3 min or 20 min interval, in these cases extending into the 24 h range (Monte-Silva et al. 2013). Also variation of stimulation intensity may induce a reversal of the sign of the after effects. While 1 mA cathodal stimulation intensity leads to inhibition a switch to 2 mA amplitude causes cathodally induced excitation (Batsikadze et al. 2013). All these data were derived from and are confined to resting relaxed subjects. In case of attentional challenge the after effects collapse and tend to reverse; anodal tDCS under finger tapping leads to reduction of MEP after effects sizes below baseline (Antal et al. 2007). A possible explanation for this behaviour might be that in activated neurons channels may open leaving a smaller range of membrane potential alteration induced by transcranial electrical stimulation methods (Paulus and Rothwell 2016). In line with these MEP results, also behavioural data show deviations from the simple rule – anodal tDCS~ excitation, cathodal tDCS ~inhibition. Furthermore, excitation and inhibition from tDCS may not be synonymous with functional changes in task performance (e.g., excitation may not equal faster reaction time in all cases and may be dependent on the inherent systems engaged in a given behavioural task). For example, in an implicit motor learning paradigm involving motor reaction times anodal tDCS improved reaction times, at odds with the MEP inhibition by anodal tDCS during finger tapping. Furthermore, cathodal tDCS also improved reaction times, albeit non-significantly (Nitsche et al. 2003c). Hence, the application of anodal current

does not mean necessarily facilitation of a given function and vice versa for cathodal polarity. Some effects may be related to much more complex neurochemical, metabolic and plastic changes occurring in the central nervous system often uncoupled from excitability changes at least as assessed by TMS. Thus, operating on the simple assumption that anode equals excitation and cathode equals inhibition may be ill advised.

As a corollary, the stimulation parameters obtained effectively at the motor cortex provided a gross impression which intensities and stimulation durations might be best suited for stimulation of other areas. However, in the case of patients every item has to be reconsidered. Stroke patients having had loss of brain tissue being replaced by CSF will probably need very different tDCS in terms of electrode placement and stimulation parameters. Thinner CSF will lead to higher electric fields in the underlying brain (Opitz et al. 2015), hence in older patients with brain atrophy (i.e, more CSF) it may be the case that current levels reaching the brain are less than would be achieved in younger adults. This however awaits experimental verification. As a consequence each new specific experimental protocol should incorporate a titration of stimulation parameters. Furthermore individual efficacy varies considerably even with the standard TMS protocol at the motor cortex. A substantial number of subjects behave in an opposite direction when compared to the overall group level, both in tDCS and other neurostimulation applications. Individual adjustment of stimulation protocols by current flow calculations may end up at a theoretical limit when cortical folding is taken into account. Suppose a target area incorporates a cortical gyrus including the crown and both opposing walls, anodal stimulation at one side will by opposed by cathodal stimulation at the opposite wall. Thus, current flow direction in relation to neuronal orientation will be in opposite directions. Switching to tACS or tRNS, which may end up with after effects similar to tDCS might provide an improvement in the present context (Moliadze et al. 2010a, 2012; Terney et al. 2008). Another way to guide tDCS after effects in a wanted direction will be the combination with neuropharmacology. If the sodium channel blocker carbamazepine is combined with tDCS only inhibitory effects survive (Nitsche et al. 2003a). L-Dopa in a medium dosage of 100 mg switched anodal excitation into inhibition, and stabilized excitability-diminishing effects of cathodal tDCS (Kuo et al. 2008), vice versa serotonin reuptake inhibition guides inhibitory cathodal after effects into excitation, and enhances excitatory effects of anodal tDCS (Nitsche et al. 2009). Boosting tDCS after effects by co-application of citalopram in the treatment of depression has been confirmed in a large multi-center study (Brunoni et al. 2013). Many more effects of these and other drugs have been published beyond the scope of this contribution (Nitsche et al. 2012). Nonetheless, drugs may substantially affect the effects induced by DC-based transcutaneous techniques and pharmacological influences should be carefully considered in designing and interpreting the results of clinical studies in patients. Different results obtained with tDCS by different groups, can be explained by differences in ongoing pharmacological treatments.

Sham Stimulation

In a large study on depression encompassing 120 patients the placebo response with 2 mA anodal tDCS amounted to − 18.2% on the Montgomery Asberg Rating Scale as compared with the tDCS response of – 39.5% (Brunoni et al. 2013). As in any drug or other interventional study proper control for sham stimulation effects is a big issue. Usually a fade in fade out protocol is used to imitate some initial skin sensation in order to assure a subject's or patient's feeling real stimulation. In any case the subject should be questioned after the stimulation about his own rating if sham or real tDCS has been applied. A few issues have to be considered. Up to about 1 mA amplitude it is difficult for unexperienced subjects to differentiate between sham and real tDCS (Ambrus et al. 2012). With 2 mA current strength tDCS stimulation comfort is lower at stimulation onset in young and older adults and, overall, lower for young participants (Wallace et al. 2016).

With conventional 35 cm^2 electrodes active stimulation at 2 mA can be identified at above chance levels with an accuracy never exceeding 65% (Wallace et al. 2016). Stimulators will have to be modified in order provide some itching during the whole stimulation procedure at higher intensities for proper blinding. With 3 mA tDCS intensity stimulation starts to become painful. Smaller electrodes per se do not increase skin sensations (Turi et al. 2014). Other issues of importance for blinding (parallel design, skin erythema, double blinding, repeated measures conditions and others) have been discussed recently (Woods et al. 2016).

The usual approach of blinding participants for plasticity-inducing protocols is to apply a "sham" stimulation protocol, which encompasses ramping stimulation up and down like in the real stimulation condition, but to stimulate with the target intensity only for a few seconds. Participants will feel the initial itching/tingling sensation, but the stimulation duration is too short to induce after effects. For 1 mA tDCS with an electrode size of 25 cm^2, this method has been shown to reliably blind participants (Gandiga et al. 2006). Stronger stimulation will induce larger sensations, and thus compromise blinding, especially under repeated measures conditions (Nitsche et al. 2003b; Opitz et al. 2015). In crossover studies, this might however not be a relevant problem (Palm et al. 2014). Alternative approaches are application of topical anaesthetics to abolish skin sensations (Parazzini et al. 2014a) or an active control condition (i.e. stimulation over an area irrelevant for the task under study). Since the occurrence of skin damage seems to be not reliably associated with cutaneous sensation (Parazzini et al. 2013), local anaesthetics should not put participants specifically at risk. Blinding of the experimenter with regard to the specific stimulation protocol is accomplished by use of stimulators that include a sham stimulation function, thus keeping the experimenter unaware of the specific stimulation condition. Even here, however, the presence of skin erythema, which is due to tDCS-induced vasodilation (Parazzini et al. 2014b), can compromise blinding. Skin erythema is reliably reduced by acetylsalicylate, or topical application of ketoprofen (Parazzini et al. 2014b; Paulus and Rothwell 2016). Thus, for reliable double-blinding, a couple of approaches are available, which should be chosen care-

fully due to the specific experimental design. Other approaches for testing the specificity of the effects are assessing the effects of opposite stimulation polarities, or testing the effect on different central nervous system areas.

Cerebellar Direct Current Stimulation

In the last 10 years several pieces of evidence demonstrated that delivering DC over the cerebellum can modulate its functions. Ferrucci et al. (2008) firstly reported that delivering DC with one electrode over the cerebellum and the other over the right shoulder (Fig. 4.5) for few minutes at 2 mA, specifically decreased the rate of improvement of a working memory task. Interestingly, stimulation over the dorsolateral prefrontal cortex induced the opposite effect, whereas sham stimulation failed to induce any change. Additionally, cerebellar stimulation did not influence the visual evoked potential, therefore ruling out any possible effect through influence over the visual system. Though indirect, this was the first report about the behavioural and cognitive effects of DC stimulation of the cerebellum. A further step forward were the physiological experiments reported by Galea et al. (2009) who observed that cathodal cerebellar DC stimulation (2 mA) can modulate cerebellar-brain inhibition assessed by transcranial magnetic

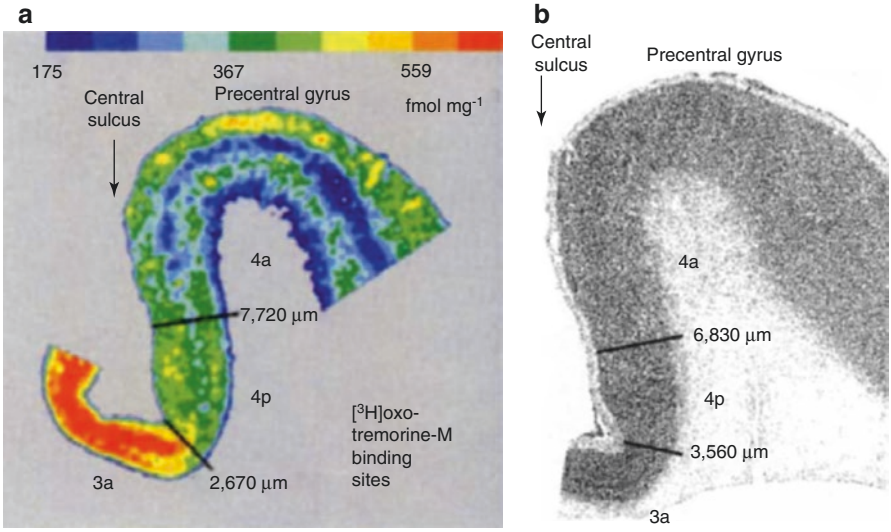

Fig. 4.5 (**a**, **b**) Allocation of the motor cortex area 4a and 4p in the anterior wall of the human motor cortex. (Taken from Geyer et al. 1996). Current flow may be more perpendicular in the sulcus than at the crown, favouring tDCS effects in a sulcal as compared to a crown located area. However, this is currently a hotly debated notion. In contrast, it is accepted that the same electric field will result in different current flow directions regarding neuron positions at the crown or the skull. The human motor cortex, area 4a and 4p, a mostly allocated in the anterior wall of the precentral gyrus and not at the crown

stimulation. Again, sham stimulation failed to induce any physiological change. These two seminal papers prompted several groups to test the effects of cerebellar DC stimulation on different behavioural and neurophysiological variables (for recent reviews see Ferrucci and Priori 2014; Grimaldi et al. 2014, 2016). The hypothesis is that in spite of the highly folded pattern DC stimulation can influence the excitability of cerebellar cortex, ultimately modulating its inhibition over the cerebellar nuclei, and therefore their efferent output projections to the brain. Modelling studies showed that the electric field generated by cerebellar DC stimulation variably goes deep into the posterior cranial fossa in relation with gender and age: the field apparently is deeper in children and woman (Parazzini et al. 2013, 2014b) (Fig. 4.6).

Besides the observations of the effects induced by cerebellar DC stimulation in normal subjects, there are also interesting studies in patients with ataxia and Parkinson's disease. Benussi et al. (Benussi et al. 2015) reported that in 19 patients with ataxia of different etiologies, a single session anodal cerebellar DC stimulation (20 min, 2 mA) –but not sham stimulation— transiently improves symptoms and motor coordination in patients with ataxia. The cerebellum is also involved in the pathophysiology of movement disorders other than cerebellar ataxia as for instance Parkinson's disease (Mirdamadi 2016; Wu and Hallett 2013). With the hypothesis of modulating the motor cortical excitability during levodopa induced dyskinesias, Ferrucci et al. (2016) tested a group of 9 patients with Parkinson's disease with anodal and sham DC stimulation (20 min, 2 mA) either over the cerebellum or over the motor cortical areas for 5 days: anodal –but not sham-- DC stimulation over both sites failed to change the UPDRS III but significantly improved the UPDRS IV related to involuntary movements. Minichino et al. (2014) assessed sleep quality of a group of 25 euthymic patients with bipolar disorder and found that sleep distrurbance-dependent daytime dysfunction significantly decreased after 3 consecutive weeks of treatment (20 min, 2 mA). In 14 patients with depression cerebellar DC stimulation with the other electrode over the prefrontal cortex was also found effective (Ho et al. 2014). Ten-session anodal cerebellar tDCS (twice a day, 20 min 2 mA) with the other electrode over the prefrontal cortex in treatment resistant obsessive compulsive disorder improved obsessive symptoms but not depression by some 26% for 3 months, thus making DC stimulation an attractive possibility in the management of obsessive compulsive disorder (Bation et al. 2016).

Transcutaneous Spinal Direct Current Stimulation

The third target for DC based non invasive neuromodulation techniques is the spinal cord. Eccles et al. in the sixties observed that polarizing DC currents delivered over the exposed cat spinal cord elicited consistent and remarkable changes in motoneuronal function in the ventral horn (Eccles et al. 1962).

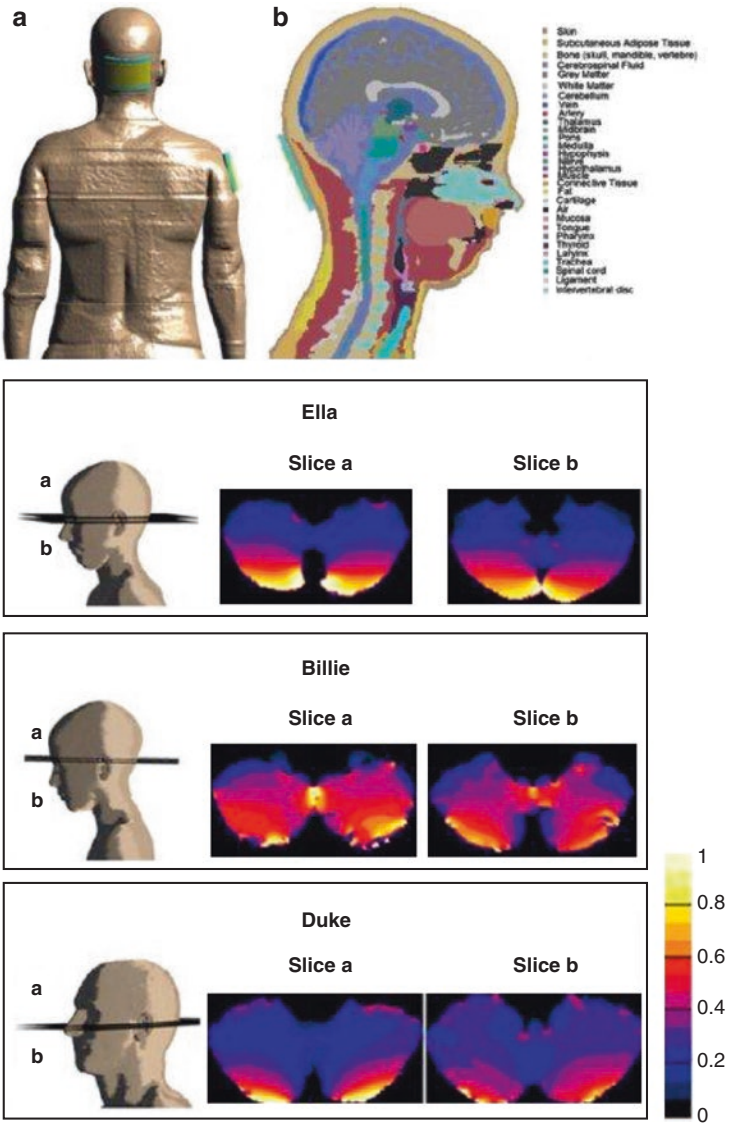

Fig. 4.6 Position of electrodes for transcutaneous cerebellar DC stimulation shown on a model used for current estimation. (From Parazzini et al. 2014a, b. with permission). Top, (**a**) electrode (green and light blue) position viewed from the back; the active electrode is over the cerebellum and the return electrode over the left shoulder. The active electrode can also be smaller and placed over a single cerebellar hemisphere, the return electrode can also be placed in other position over the head or face (not shown). Top, (**b**) a sagittal MRI reconstruction showing the tissues below the electrode; different tissues are identified by different colours shown on the right. Bottom: current density amplitude distributions below the electrode for cerebellar DC stimulation in three different subjects (Ella, Billie, Duke) modelled on a transversal MRI slice passing through the electrode; current density is plotted according to the colour scale on the right. Note that the current density distribution varies in different subjects and tends to spread anteriorly in the adolescent Billie (middle), whereas remains localized to cerebellar hemispheres in the adult male subject Duke (bottom) and has an intermediate distribution in the adult female Ella (top)

Starting from the observation by Eccles and coworkers, the Milano group assessed the effects of delivering DC over the thoracic human spinal cord (Cogiamanian et al. 2008) by transcutaneous thoracic spinal DC stimulation (Fig. 4.6). The conduction along the lemniscal system was assessed by somatosensory evoked potentials (SEP) elicited by stimulation of the tibial nerve in healthy subjects. The SEP amplitude decreased after anodal DC stimulation and increased (not significantly) after cathodal DC stimulation. Interestingly thoracic DC stimulation failed to change the SEP evoked by median nerve stimulation, thus demonstrating that the effect of DC was spatially restricted to the sensory fibres travelling in the spinal cord below the stimulating electrode but not in other places. Further studies found that a similar effect appeared for the spinothalamic system (Truini et al. 2011) and corticospinal fibers (Bocci et al. 2015). Nierat et al. (2014) found that cathodal tsDCS at cervical level increased significantly the volume of air inhaled or exhaled in a single breath (Tidal Volume) in a group of healthy subjects, possibly modulating the descending input over phrenic motoneurones. Several other studies tested the effects of tsDCS on segmental reflexes. For instance, Winkler et al. (2010) found that tsDCS modulated the H-reflex post-activation depression in a polarity dependent manner, Cogiamanian et al. (2011) found that tsDCS modulated the nociceptive flexion reflex in humans. Bocci et al. (2014) tested the effects of tsDCS on spinal motorneuron excitability: they found that cathodal-tsDCS dramatically increases motor unit number estimation (MUNE) values following cervical polarization, while sham and anodal polarization had no significant effect. At the same time, cathodal-tsDCS dampened the peripheral silent period in respect to sham and anodal conditions. The authors concluded that tsDCS, possibly also through supraspinal effects, could provide a novel therapeutic tool in managing several pathological conditions characterized by reduced motor unit recruitment (Fig. 4.7).

Anodal tsDCS in restless leg syndrome decreased for a short time symptoms on the VAS, whereas application of sham stimulation had no effects (Heide et al. 2014) supporting the pathophysiological concept of spinal cord hyperexcitability in RLS. Hubli et al. (2013) assessed the effects of tsDCS on spinal reflexes in patients with complete spinal cord injury reporting that reflexes improved after anodal tsDCS concluding that anodal tsDCS can modulate spinal neuronal circuitries after SCI.

Direct Current–Based Noninvasive Neuromodulation Techniques at Home

Among various advantages of tDCS over rTMS, there is the possibility of delivering stimulation at home. Yet, DC-based techniques are relatively cheap, safe, and the devices are small, easily portable, and wearable. The patients and their caregivers

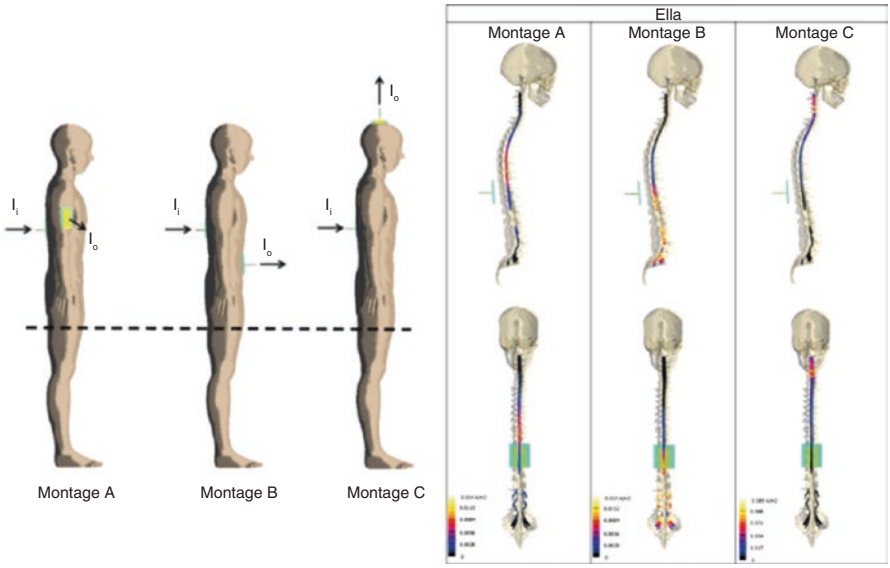

Fig. 4.7 Position of electrodes for transcutaneous spinal DC stimulation shown on a model used for current distribution estimation. (From Parazzini et al. 2014a). Left: with the active electrode over the lower thoracic spinal cord, three different positions of the return electrode (I0) are shown from the left to the right: left shoulder, abdominal wall, and vertex. Right: current density distribution (top: lateral view, bottom: viewed from the back) within the spinal cord keeping the green active electrode over the lower thoracic spinal cord, with three different positions of the return electrode shown from the left to the right: left shoulder, abdominal wall, and vertex. Current density is graphically expressed according to the colour scale. Note that when the return electrode is placed over the right shoulder the maximum current density is in the thoracic spinal cord above the level of the electrode, when the return electrode is on the abdominal wall the maximum current density is below the lower half of the stimulating electrode, and when the return electrode is on the vertex the maximum current density is in the cervical spinal cord. Hence, different positions of the return electrode can focus the current distribution at different spinal cord levels

can easily learn how to place the electrodes for different types of brain, cerebellar and spinal cord DC stimulation. At difference from TMS related techniques, though the great feasibility and accessibility of DC-based techniques can be dangerous because it makes it easy using tDCS as a "toy", without medical supervision, the simplicity of the technique and of the devices allows the treatment of large populations of patients at home (Priori et al. 2009). Andrade (2013) effectively and safely used tDCS at home in a patient with clozapine refractory auditory hallucinations. Mortensen et al. (2016) found that tDCS at home is well-tolerated by patients with upper limb impairment following intracerebral hemorrage and the authors found that anodal tDCS increased the grip strength thus representing a feasible add-on treatment for home rehabilitation. Kasschau et al. (2016) reported the use of a telemedicine platform to monitor the use of tDCS at home in a group of patients with

multiple sclerosis concluding that remotely supervised tDCS can be safe and reliable in multiple sclerosis, further expanding the patient access to the technique. Hyvarinen et al. (2016) found domiciliary tDCS safe and feasible for tinnitus. In conclusion, the possibility of home delivery of tDCS opens the avenue to a treatment that will be feasible in large population of patients without entering a hospital. This has also obvious implications for developing countries or countries where there are great distances to be covered before finding a hospital.

Conclusions

Available evidence shows that non-invasive DC-based neuromodulation techniques can influence the function of different structures in the human brain, cerebellum, and spinal cord. Although the effects can vary from subject to subject in relation with different factors (age, gender, concomitant drug consumption), the excitability changes induced have potential clinical relevance for therapeutic purposes. In addition, the techniques discussed above share feasibility for use at home and the safety that warrant their possible use in large population of patients. Much remains to be done, especially for the development of standardized protocols of DC stimulation in different neuropsychiatric disorders.

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