REVIEW

Electrifying the motor engram: effects of tDCS on motor learning and control

Jean-Jacques Orban de Xivry · Reza Shadmehr

Abstract Learning to control our movements is accompanied by neuroplasticity of motor areas of the brain. The mechanisms of neuroplasticity are diverse and produce what is referred to as the motor engram, i.e., the neural trace of the motor memory. Transcranial direct current stimulation (tDCS) alters the neural and behavioral correlates of motor learning, but its precise influence on the motor engram is unknown. In this review, we summarize the effects of tDCS on neural activity and suggest a few key principles: (1) Firing rates are increased by anodal polarization and decreased by cathodal polarization, (2) anodal polarization strengthens newly formed associations, and (3) polarization modulates the memory of new/preferred firing patterns. With these principles in mind, we review the effects of tDCS on motor control, motor learning, and clinical applications. The increased spontaneous and evoked firing rates may account for the modulation of dexterity in non-learning tasks by tDCS. The facilitation of new association may account for the effect of tDCS on learning in sequence tasks while the ability of tDCS to strengthen memories of new firing patterns may underlie the effect of tDCS on consolidation of skills. We then describe the mechanisms of neuroplasticity of motor cortical areas and how they might be influenced by tDCS. We end with current challenges for the fields of brain stimulation and motor learning.

Keywords tDCS · Motor cortex · Motor control · Motor learning

Introduction

The survival of a biological entity depends on its ability to accurately control the motion of its limbs, head, and eyes. Our nervous system provides us with the ability to learn this control and the ability to maintain calibrated and accurate movements despite interactions with a changing body (e.g., fatiguing muscles) and a changing environment (e.g., variable tools and terrains). Motor learning is a general term that corresponds to these abilities: the ability to adapt to a change in the environment by forming an internal model that accurately predicts the sensory consequences of motor commands (termed motor adaptation, Lackner and DiZio 1994; Shadmehr and Mussa-Ivaldi 1994; Shadmehr et al. 2010) and the ability to become more skilled at a task by reducing the variability of motor commands and increasing accuracy (termed skill learning, Shmuelof et al. 2012). What is the neural basis of motor learning?

Until recently, the tools available to answer this question in humans were limited. One could study patient populations with focal deficits in the cerebellum (Martin et al. 1996; Smith and Shadmehr 2005; Donchin et al. 2012; Izawa et al. 2012) or the parietal cortex (Mutha et al. 2011), one could disrupt motor cortex function with transcranial magnetic stimulation (Muellbacher et al. 2002; Richardson et al. 2006; Hadipour-Niktarash et al. 2007; Censor et al. 2010; Orban de Xivry et al. 2011a; Villalta et al. 2013), or one could use functional brain imaging in

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healthy populations (Shadmehr and Holcomb 1997; Della-Maggiore et al. 2009; Landi et al. 2011; Hardwick et al. 2012; Lohse et al. 2014). However, in the past decade, a noninvasive method of investigation, transcranial direct current stimulation (tDCS; Priori et al. 1998; Nitsche and Paulus 2000), has become increasingly popular, allowing for electrical modulation of the neural tissue in the living human brain, resulting in the ability to alter function of specific regions, providing possibilities in terms of accelerating learning and/or retention, as well as quantifying the contributions of each brain region to the process of motor learning.

For example, consider a well-studied example of motor adaptation, holding a novel tool and attempting to reach to a target (Shadmehr and Mussa-Ivaldi 1994). The tool's dynamics will be unfamiliar to the brain, and the motor commands to the arm will produce a motion that will be different than predicted, resulting in sensory prediction errors. The error also produces learning, as evident by the fact that on the next movement the brain alters the motor commands to partially compensate for the novel dynamics of the tool (Thoroughman and Shadmehr 2000). With training, some of the modifications to the motor commands become a motor memory (Shadmehr and Holcomb 1997; Criscimagna-Hemminger and Shadmehr 2008; Joiner and Smith 2008). Formation of this motor memory appears dependent on the integrity of the cerebellum (Smith and Shadmehr 2005; Criscimagna-Hemminger et al. 2010; Izawa et al. 2012; Taig et al. 2012; Gibo et al. 2013), the cerebellar output to the motor cortex via the thalamus (Chen et al. 2006), and the motor cortex (Li et al. 2001; Paz et al. 2003; Richardson et al. 2006; Arce et al. 2010a; Orban de Xivry et al. 2011a, 2013).

Remarkably, this form of motor adaptation in humans can be readily up-regulated or down-regulated by noninvasive stimulation of either the motor cortex or the cerebellum. Transcranial direct current stimulation (tDCS) of the brain, a technique where low current is delivered through the skull via two small electrodes, can indeed alter the excitability of the underlying tissue (Nitsche and Paulus 2000). When placed on the motor cortex, tDCS can strengthen the motor memory formed during motor adaptation (Hunter et al. 2009) and alter the generalization patterns of the learning (Orban de Xivry et al. 2011b). The same stimulation method can facilitate the rate of motor adaptation if the anode is placed on the cerebellum (Galea et al. 2011; Herzfeld et al. 2014) and can inhibit the rate of motor adaptation if the cathode is placed on the cerebellum (Herzfeld et al. 2014).

With repetition of a learned behavior (Huang et al. 2011), variability of movements declines and speed of execution increases (Shmuelof et al. 2012). With repetition of motor commands, the neurons in the motor cortex undergo plasticity, forming new synapses and dendritic spines (Xu et al. 2009; Yang et al. 2009). This reorganization of the motor cortex is part of the motor engram, i.e., the neural substrate of the motor memory. Interestingly, tDCS of the motor cortex facilitates the ability to retain motor skills (e.g., Reis et al. 2009).

The effects of tDCS on the motor engram are the major topics of this review in which we will attempt to describe the mechanisms of action of tDCS at the neuronal level and then consider the possibility that these mechanisms can explain behavioral effects found in modern tDCS studies and in clinical applications. Finally, we turn to the synaptic events observed during motor learning and their modulation by direct current stimulation. We conclude by laying out limitations of tDCS and consider a few open questions whose answer would push the field forward.

Early use of direct current polarization

Research on application of direct current (DC) polarization of the brain began in the 1950s with the aim of shifting the 'steady potential' of the brain. In early experiments (Bishop and O'Leary 1950), DC polarization was applied in vivo on the dorsal nucleus of the lateral geniculate of the cat. One electrode was placed on the top surface and the other on the bottom. In this setup, all the neurons in the middle layer of the nucleus that were perpendicular to the surface were anodally stimulated in the dendrites while their axon was cathodally stimulated or vice versa. The experiment in the thalamus, and later in the cerebellum (Chan and Nicholson 1986; Chan et al. 1988), demonstrated that polarization of the dendrites could alter the response of the neuron to a synaptic input: Anodal polarization of the dendrites increased the firing rate of neurons as evoked by a given input, whereas cathodal stimulation decreased this rate.

Later studies investigated the effect of DC polarization at the cellular and behavioral level in vivo. A key experiment was performed by Morrell (1961). In this experiment, small polarizing electrodes were placed subdurally on the surface of the cortex while the reference electrode was attached to the mouth or the ears of the animal. DC polarization of the motor cortex of the rabbit or cat did not produce a movement. However, it facilitated the production of movements in response to a startling sensory stimulus (flash of light or sound). This behavioral effect of anodal polarization was termed 'dominant focus of excitation' (Morrell 1961). In addition, there was a residual low-voltage EMG activity in the limb related to the region of M1 that was stimulated.

Morrell made several observations from which we draw three principles. As we will see, these principles may account for most of the behavioral effects reported since the modern era of tDCS started.

First principle: firing rates are increased by anodal polarization and decreased by cathodal polarization

The enhanced behavioral response to the startling stimulus was paralleled at the neural level in the motor cortex (Morrell 1961): neurons that did not fire in response to the stimulus before anodal polarization started to fire in response to the same stimulus (Fig. 1a). That is, anodal polarization of the cortex increased both the spontaneous and the evoked

A   **First principle: polarization modulates firing rates**

Before polarization   After polarization

B   **Second principle: anodal polarization strengthens newly formed associations**

Before polarization

After polarization

C   **Third principle: DC polarization modulates the memory of new firing patterns**

Before polarization   After polarization and repetitive visual stimulation

Fig. 1 Illustration of the three main principles of the action of tDCS on neural activity and motor behavior. In *all panels*, *light*, and *dark gray* neurons are associated with slightly active and very active neurons. Sun and music notes are associated with visual and auditory stimulus, respectively. In **a** and **c**, *vertical black traces* represent action potentials over time. In **b**, *black traces* on the far right schematically illustrate the degree of muscle activity. In **a**, *dark gray* neurons representing polarized neurons exhibit higher spontaneous (*top*) or evoked (*bottom*) discharge rate. In **b**, before polarization, neither a flash of light nor a tone elicited a movement when presented (*top*). After a period of polarization during which a flash of light was repeatedly presented, the light now elicited a motor response while the tone did not. In **c**, a flash of light did not elicit a response in a neuron of the visual cortex. After polarization of the visual cortex and 3 Hz visual stimulation, a single flash of light elicited a 3 Hz response in the neurons

discharge rates (see also Creutzfeldt et al. 1962; Brazovskaya et al. 1972). Therefore, anodal polarization of the motor areas sensitized the animal to the stimulus that was presented during polarization.

Second principle: anodal polarization strengthens newly formed associations

As summarized by Sokolov (1977), the results above suggest that polarization had the ability to 'couple the conditioned (tone) and unconditioned (polarization) inputs' at the neural level (Fig. 1b). This after-effect was specific to the stimulus used during training. The neural response outlasted the polarization interval by 20 min (Morrell 1961). For example, if sounds were used to elicit movements during DC polarization, a sound was still able to elicit a movement up to 20 min later. Critically, during the same period, a flash of light was not able to elicit such a movement if it was not used to condition the motor response. This effect of modality suggests that anodal polarization specifically stabilizes newly formed associations in the cerebral cortex. Similar after-effects were observed in another study (Bindman et al. 1962) where an electrode was placed at the surface of the sensory cortex and another electrode was placed on a distal muscle. They observed an increase in the spontaneous and evoked electrical activity of neurons compared with pre-polarization levels during and for several hours after 5 min of anodal polarization.

In both studies (Morrell 1961; Bindman et al. 1962; see also Landau et al. 1964), the neural effect was limited to the area surrounding the polarizing electrode and decreased with the distance between the neuron and this electrode (Morrell 1961) or was restricted to the stimulated cortex and not found in the thalamus where evoked and spontaneous firing rates did not change (Bindman et al. 1962).

Third principle: DC polarization modulates the memory of new/preferred firing patterns

Lastly, anodal polarization facilitated the formation of a memory of an input pattern (Morrell 1961). For instance, when a flash of light was repeatedly presented (3 Hz) during anodal polarization of the visual cortex, it made visual cortex neurons fire repetitively at this frequency. At the end of the polarization period, a single flash of light entrained the same neuron to fire again at 3 Hz (Fig. 1c). The propensity of neurons to fire at 3 Hz after a single flash of light decreased over the next 20 min following the stimulation period. Therefore, anodal polarization conferred upon these neurons the property of retaining a pattern of discharge for a short period of time.

In summary, spontaneous and evoked firing rates are increased by anodal polarization and decreased by cathodal
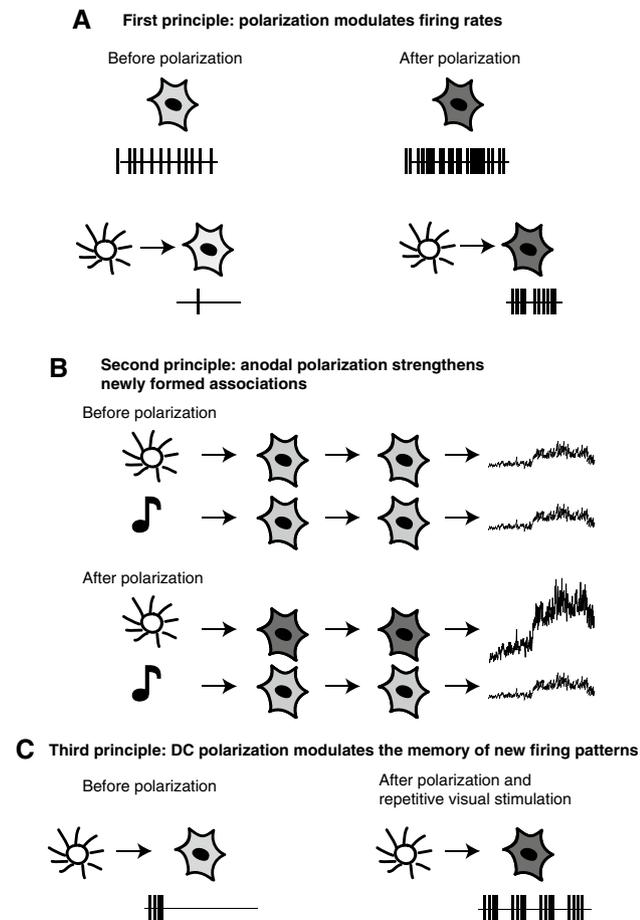
polarization. Anodal polarization reinforces the coupling between the conditioned and unconditioned inputs at the neural level. That is, learning is facilitated by anodal DC polarization (Sokolov 1977). Finally, DC polarization modulates the memory of new/preferred firing patterns.

Application of the three principles of polarization

Effect of tDCS on motor control and motor learning in healthy participants

In the absence of any learning requirements, humans are able to perform accurate movements that are under control of an extensive network of brain areas (Shadmehr and Krakauer 2008). The motor cortex is at the heart of this network as its dynamics sculpts motor behaviors (Churchland et al. 2010, 2012; Shenoy et al. 2013). Therefore, it is not surprising that modulation of neuronal firing by motor cortex polarization (first principle) directly influences simple motor behaviors in the absence of any learning or adaptation. In this context, increases in M1 neuronal firing rates induced by anodal tDCS increase the maximum voluntary force that the subjects can produce (Tanaka et al. 2009; Salimpour and Shadmehr 2014) when the reference electrode is supra-orbital (cephalic montage) but not when this reference electrode was placed on the shoulder (Cogiamanian et al. 2007; Lampropoulou and Nowicky 2013). In addition, anodal tDCS of M1 enhances dexterity such as measured by the Purdue Pegboard (PPT) or the Jebsen–Taylor (JTT) tests (Antal et al. 2004; Boggio et al. 2006; Hummel et al. 2010; Williams et al. 2010; Matsuo et al. 2011; Sohn et al. 2012; Kidgell et al. 2013; Bastani and Jaberzadeh, 2014; Convento et al. 2014). The improvement in motor function is even more marked for fine motor skills compared with grosser skills (Hummel et al. 2010). In contrast, cathodal stimulation of M1 can improve the specificity of muscle activation in the ipsilateral arm (McCambridge et al. 2011). These effects could likely be attributed to the effect of tDCS on spontaneous firing rate. Given that motor cortex polarization also modulates the evoked neuronal population response, it is expected that reaction time to a sensory stimulus would be modulated by polarization. However, the data on reaction time are mixed. Some studies reported a reduction in reaction time with anodal polarization of M1 (Elbert et al. 1981) and an increase in reaction time with cathodal polarization (Leite et al. 2011). However, in the absence of learning, most studies reported no modulation of reaction time with brain polarization (Kuo et al. 2008; Tanaka et al. 2009; Stagg et al. 2011b). In summary, it is suggested that the first principle of tDCS accounts for the effect of tDCS on motor behavior that do not involve learning.

It is possible that the second and third principles can be linked to the two phases of motor learning: respectively, learning and consolidation. Most motor learning experiments follow three steps: a baseline period where normal motor behaviors are quantified in order to get some reference data on the behavior at hand. Then, the manipulation of the task is introduced which will induce learning. In the case of motor adaptation paradigms, a perturbation is introduced. During this initial phase, behavior is adapted from trial-to-trial in order to increase the performance at the task (learning phase). Finally, in the last phase, the behavior stabilizes and the learned or adapted motor behavior is stored in memory (consolidation phase). Several mechanisms are thought to drive the two learning phases described above. These mechanisms are either a fast and slow version of the same process (Smith et al. 2006), or different components of motor learning altogether (Haith and Krakauer 2013) or a single component of motor learning (Reis et al. 2009). In addition, motor learning can affect motor behavior in at least three different ways: It can link different action phases (Sailer et al. 2005; Safstrom et al. 2013), it can shift the speed-accuracy trade-off (Reis et al. 2009; Lefebvre et al. 2012a; Shmuelof et al. 2012), and it can adapt the motor commands to the new environment (Shadmehr et al. 2010; Huang et al. 2011). Clearly, the effect of tDCS on learning depends on the mechanisms that govern it.

Linking of different action phases is particularly important to for sequence learning and for navigating a cursor smoothly. During the learning stage, such linking of action phases has been associated with the formation of new spatiotemporal patterns of neural activity in the motor cortex (Lu and Ashe 2005; Matsuzaka et al. 2007; Peters et al. 2014). The observation that such formation of new patterns of motor activity is facilitated by tDCS would be accounted for by the second principle. Anodal tDCS of the motor cortex is particularly effective in augmenting learning in sequence learning tasks (Nitsche et al. 2003; Vines et al. 2006, 2008a, b; Kuo et al. 2008; Kang and Paik 2011; Stagg et al. 2011b; Cuypers et al. 2013; Karok and Witney 2013; Waters-Metenier et al. 2014). In sequence learning tasks, the benefits of tDCS are restricted to the learning phase (Marquez et al. 2013a, b). In contrast, in skill learning tasks where a shift in speed-accuracy trade-off is required for improvements in performance (cursor navigation), tDCS mostly affects the time-dependent consolidation of the skill (Reis et al. 2009, 2013; Fritsch et al. 2010; Marquez et al. 2013a, b; Prichard et al. 2014) although one studies also reported online effects for a cursor navigation task (Lefebvre et al. 2012b). Interestingly, for both types of skill learning tasks, tDCS also improves the skilled performance in untrained tasks (Lefebvre et al. 2012b; Waters-Metenier et al. 2014).

Several studies have demonstrated that tDCS of M1 does not alter the rate of motor adaptation (Galea et al. 2011; Orban de Xivry et al. 2011b; Herzfeld et al. 2014). In accordance with the third principle, M1 tDCS may affect the retention of the memories acquired during adaptation training, although this remains controversial. Some studies reported that anodal stimulation of M1 slowed the decay rates of motor output (Hunter et al. 2009; Galea et al. 2011) or improved the spatial generalization of these memories (Orban de Xivry et al. 2011b). However, Herzfeld et al. (2014) repeatedly measured the decay rates during acquisition with anodal M1 stimulation and observed no significant changes and also found no effects on retention as measured at 24 h. However, each of these three studies adopted very different paradigms (number of targets, length of training, etc.) and measured retention differently. Therefore, the effect of tDCS on M1 during motor adaptation tasks remains unclear.

Restoration of motor performance with tDCS

In motor learning tasks, a manipulation (e.g., introduction of a sequence or a perturbation) affects motor performance and the subjects learn to improve their motor performance. As described in the previous section, tDCS facilitates learning in these artificial tasks. However, motor performance can also be affected by aging (Leversen et al. 2012), brain lesion (Coderre et al. 2010; Tyryshkin et al. 2014), or brain disease (Mazzoni et al. 2012) and produces a decrease in motor performance. The potential of tDCS to restore motor performance in these more natural contexts has been investigated in the recent years.

Aging is associated with a decrease in motor performance (Smith et al. 1999; Carmeli et al. 2003) that is accompanied by a larger recruitment of brain areas (Ward 2003; Heuninckx et al. 2008). Several studies suggest that anodal tDCS can restore normal motor performance in healthy older subjects (Hummel et al. 2010; Parikh and Cole 2014). In addition, this age-related decline in motor performance is also accompanied by an age-related decline in motor learning/motor adaptation (Seidler 2007; Lustig et al. 2009). Interestingly, anodal stimulation of M1 is able to compensate this deficit in skill learning (Goodwill et al. 2013; Zimerman et al. 2013) even when tDCS does not modulate the same learning process in younger adults (Zimerman et al. 2013). Cerebellar stimulation is also able to increase the rate of motor adaptation in older subjects (Hardwick and Celnik, 2014).

For stroke patients, the effects of tDCS on motor functions are generally positive (see Bastani and Jaberzadeh 2012; Kandel et al. 2012; Butler et al. 2013; Marquez et al. 2013a, b for systematic reviews and meta-analyses). Many studies have found improvements in motor function

in stroke patients as measured by clinical scales or the JTT (Fregni et al. 2005; Hummel et al. 2005; Lindenberg et al. 2010; Mahmoudi et al. 2011; Khedr et al. 2013; Lefebvre et al. 2013) and an increase in pinch or grip force and a decrease in reaction times (Hummel et al. 2006; Stagg et al. 2012; Lefebvre et al. 2013). The improvement in reaction time with the ipsilesional stimulation protocol was correlated with the change in movement-related activity under the anodal electrode (M1) and in the ipsilesional premotor cortex (Stagg et al. 2012). Finally, in one patient, tDCS had the ability to decrease spasticity of the affected limb and, therefore, to improve motor function (Vandermeeren et al. 2013). A similar decrease in rigidity by tDCS was noted in PD patients (Fregni et al. 2006). The principles of tDCS governing these effects are unclear. Decrease in GABA concentration is probably helpful for motor-related activity in the ipsilesional cortex (Clarkson et al. 2010). An increase in spontaneous/evoked firing rates might also drive some of the effects such as increase in pinch force (Hummel et al. 2006) and the increase in movement-related activity (Stagg et al. 2012). The long-lasting effect of tDCS on motor function is likely due to the after-effect of tDCS and its ability to engrave new firing patterns in memory. Finally, in the same way it improves motor function in these patients, tDCS has also the ability to improve the acquisition and the memory of a new skill as it does in healthy subjects (Madhavan et al. 2011; Lefebvre et al. 2012b; Zimerman et al. 2012).

In contrast, the application of tDCS in Parkinson's disease (PD) has produced puzzling results that are partly due to the apparent effect of dopaminergic medication on stimulation results. In patients who were taken off their dopamine medication, anodal tDCS of M1 significantly improved clinical scores and performance in a reaction time task (Fregni et al. 2006). Slight improvements were also observed with cathodal stimulation, making the comparisons between anodal and cathodal stimulation sessions often inconclusive (Fregni et al. 2006). In another study (Benninger et al. 2010), patients performed a walking test, and tests of arm function during 'on' and 'off' medication sessions. The authors found that anodal stimulation decreased walk time (the primary outcome) compared with sham stimulation, but only when tested off medication. In addition, the time to perform sequential arm and hand movements (a measure of bradykinesia) was reduced by anodal stimulation for patients both in the on and off medication states. However, clinical motor symptoms were only slightly reduced by active stimulation. Similar results were obtained in a study where anodal stimulation of M1 improved both the gait and clinical motor symptoms of PD patients in the 'on' medication state (Valentino et al. 2014). However, in a recent double-blind study of PD patients who were 'on' medication, participants were compared to

themselves when receiving either anodal or sham stimulation of M1 (Verheyden et al. 2013). The authors found no significant effects of stimulation in all but one measure (time for walking a 10 m distance) and noted that this statistical significance may have been due to chance. While all the above-mentioned studies focused on anodal stimulation of the ipsilesional motor cortex, a recent study on rats suggests that cathodal stimulation of the contralesional motor cortex may be beneficial for PD patients. Indeed, cathodal stimulation of the frontal motor areas produced robust and sustained increases in striatal dopamine concentrations, whereas anodal stimulation produced little or no change (Tanaka et al. 2013). This observation raises interesting avenues for improvements in motor functions of PD patients with cathodal tDCS of M1. For instance, in a study of patients with PD 'on' medication, Salimpour et al. (2013) found improvements in clinical motor symptoms and in a bimanual isometric force production task with cathodal M1 stimulation.

Because hand dystonia is associated by increased excitability of hand area of the motor cortex, it has been postulated that decreasing this excitability would alleviate the symptoms of dystonia. Given that a reduction in excitability of M1 via inhibitory 1 Hz rTMS helps focal hand dystonia (Siebner et al. 1999), it was expected that cathodal tDCS of the affected M1 would have the same effect. A recent study that used bi-hemispheric tDCS (cathodal polarization of the affected hemisphere and anodal polarization of the unaffected hemisphere) concurrently to a training procedure reveals that motor function of the dystonic hand was improved after 5 days of training (Furuya et al. 2014). Such improvement was absent after sham or unilateral stimulation, which is consistent with the absence of effect found in earlier studies with unilateral tDCS montage (Buttkus et al. 2010; Benninger et al. 2011). Furthermore, these results demonstrate the importance of electrode montage for clinical applications of tDCS but require further confirmations.

Alternative models for the effect of tDCS on motor control and motor learning

In the recent years, several alternative models have been proposed to account for the effects of tDCS on cognitive or motor functions. Here, we discuss these alternatives models, what they can and cannot explain. However, it is likely that the actual picture is a mixture of them as they are not completely independent.

Some authors suggest that tDCS mediates motor control/learning process by modulating long-term potentiation (Reis and Fritsch 2011). Support for this idea stems from the impact of tDCS on motor learning, for which LTP is essential (Rioult-Pedotti et al. 2000), and from detailed

neurophysiological study in animals (Fritsch et al. 2010) and in humans (Cantarero et al. 2013a, b). However, the LTP model does not account for the simple effect of tDCS on motor behaviors independently of any learning process, nor does it account for the effect of cathodal stimulation on motor learning or control.

An alternative model, quite opposite to the previous one, might suggest that all the effects of tDCS might be due to the observed decrease in GABA due to anodal tDCS (Stagg et al. 2009). Indeed, it is known that a decrease in GABA is required for long-term potentiation in the motor cortex (Hess et al. 1996). Therefore, such a decrease in GABA concentration would be sufficient to account for most of the effects accounted for by the second principle. However, a decrease in GABA would be associated with less precise movements, hence a decrease in motor function, and not an improvement in motor function such as found in numerous tDCS studies. Indeed, animal studies have shown that polarization (Morrell 1961) or application of a GABA antagonist (Castro-Alamancos and Borrell 1993) results in involuntary muscle activity. In addition, decreasing GABA concentration through application of $GABA_A$ antagonist reduces the ability to contract muscles individually (Matsumura et al. 1992; Kubota 1996; Schieber and Poliakov 1998). In contrast, anodal stimulation of the motor cortex improves individuation of the fingers (Waters-Metenier et al. 2014). This observation is probably related to the importance of inhibition in shaping the output of the M1 (Merchant et al. 2008; Isomura et al. 2009).

Finally, an interesting model that was devised on the effects of tDCS in cognitive tasks suggests that both TMS and tDCS modulate cognitive functions through increasing or decreasing the level of noise in the system (Miniussi et al. 2013). In this model, anodal tDCS injects noise to the neural activity while cathodal tDCS filters out some of the noise. The effect of noise injection on task performance depends on the state of the neural population, the characteristics of the stimulation, and the task performed. This state-dependency reflects co-activation of the neuronal population by its input and by polarization. In the motor domain, anodal tDCS of M1 increased motor cortical excitability before but not after motor learning (Cantarero et al. 2013a). However, a bimanual coordination study that investigated how tDCS could affect the contribution of each arm found that tDCS could increase the unimanual maximum voluntary force but tended to reduce the unimanual variability of the force produced during a unimanual isometric force production task (Salimpour and Shadmehr 2014). There is no explanation for how an increased in noise in the neural population would tend to reduce noise in the motor output. In addition, as acknowledged by the authors (Miniussi et al. 2013), this model can only account for the online effects of tDCS but not for its offline effects.

Effects of tDCS not accounted for by the three principles

Indirect effect of tDCS on the contralateral hemisphere

The effect of tDCS on the ipsilesional motor cortex on motor function has been explored in studies that show that skill learning or hand function can be improved by reducing the excitability of the ipsilateral motor cortex that controls the non-dominant hand (Vines et al. 2006, 2008b) or the contralesional motor cortex of stroke patients (Fregni et al. 2005; Zimerman et al. 2012). The neurophysiological mechanisms underlying this effect are unclear because long periods of cathodal stimulation on one motor cortex do not affect the excitability or inhibition of the other motor cortex (Di Lazzaro et al. 2012).

Common effects of anodal and cathodal polarization

In a few studies (Orban de Xivry et al. 2011b; Stagg et al. 2011b), anodal and cathodal stimulations of the motor cortex were found to have the same effects. In addition, the difference between the effects of anodal and cathodal stimulation on learning was weak (Nitsche et al. 2003). Clearly, none of the three principles could account for effects that are independent of the polarity.

Cerebellar tDCS influences motor learning

Behavioral effects of cerebellar stimulation have been recently uncovered in motor adaptation tasks. In these tasks, anodal polarization of the ipsilateral cerebellum increases the speed of learning of a reaching task (Galea et al. 2011; Hardwick and Celnik 2014; Herzfeld et al. 2014) or a split-belt treadmill walking adaptation task (Jayaram et al. 2012). Cathodal cerebellar stimulation decreases the speed of learning the reaching task (Herzfeld et al. 2014).

Forming memories in the motor cortex

With motor learning, there are changes in the firing rates of M1 neurons and/or the output of M1 neuronal ensembles. This is true for adaptation tasks (Gandolfo et al. 2000; Li et al. 2001; Paz et al. 2003, 2005; Paz and Vaadia 2004; Arce et al. 2010a, b; Mandelblat-Cerf et al. 2011; Richardson et al. 2012) and in skill learning tasks (Kargo and Nitz 2003, 2004; Cohen and Nicolelis 2004; Costa et al. 2004; Lu and Ashe 2005; Jackson et al. 2006; Matsuzaka et al. 2007; Kilavik et al. 2009; Komiyama et al. 2010; Nazarpour et al. 2012; Huber et al. 2012; Picard et al. 2013; Peters et al. 2014).

Kleim et al. (1998) examined the reorganization of M1 during skill learning in rats. In a reaching task, the animals used their paw to retrieve a single pellet of food through a small aperture (Buitrago et al. 2004). Initially, rats were successful on 10–15 % of the attempts. Performance increased during several days of training before plateauing around a success rate of 50–60 %. In an acrobatic task (Kleim et al. 1996), rats had to reach a platform through obstacles as fast as possible. With training, performance improved so that trial duration decreased from 15 to 5 s. During these tasks, there were long-term potentiation (LTP) and depression (LTD) of synapses in the motor cortex (Rioult-Pedotti et al. 2000; Hodgson et al. 2005), as well as LTP of existing but masked horizontal synapses (Rioult-Pedotti et al. 1998). There are a number of factors that contribute to formation and maintenance of synaptic plasticity in the motor cortex during motor learning (see reviews Luft and Buitrago 2005; Monfils et al. 2005):

- Protein synthesis is important for long-term potentiation (LTP) of synapses (Krug et al. 1984; Teyler and DiScenna, 1987; Grzegorzewska et al. 2004; Hess, 2004; Mei et al. 2011), for acquisition of new motor behavior (Kleim et al. 1996; Luft et al. 2004; Derksen et al. 2007), and for maintenance of the existing motor repertoire (Kleim et al. 2003). It has been found that protein kinase Mzeta secretion (an atypical and autonomously active form of protein kinase C), which is essential for the maintenance of spatial memories (Serrano et al. 2008), is also critical for the maintenance of motor memories (von Kraus et al. 2010). This protein is also necessary and sufficient for LTP maintenance (Ling et al. 2002). BDNF plays a key role in LTP and in motor learning: BDNF concentration is modulated by motor learning in rats (Klintsova et al. 2004) and diminished secretion of BDNF in mice and in humans due to a genetic mutation appears to impair motor learning in a variety of tasks (Kleim et al. 2006; Fritsch et al. 2010; McHughen et al. 2010, 2011).
- Neurotransmitter concentrations are critical for synaptic transmission. The modulation of these concentrations can affect motor cortex plasticity, hence learning. This is true for dopamine (Hosp et al. 2009, 2011; Molina-Luna et al. 2009) and for GABA (Jacobs and Donoghue, 1991; Trepel and Racine, 2000).
- Motor learning is correlated with the number of new synapses that have been formed in the motor cortex (Xu et al. 2009; Yang et al. 2009; Fu et al. 2012). During early training, many new synapses are formed, but some of them are later pruned away (Xu et al. 2009). Synaptogenesis is especially present in neurons that control the trained limb (Wang et al. 2011).

Whether these events occur in parallel, in series, or both is not yet known. However, they may interact. For instance, in the hippocampus, LTP can increase the survival rate of new spines (Tanaka et al. 2008; Hill and Zito 2013) while in the motor cortex, LTP is accompanied by an increase in the number of spines (Ivanco et al. 2000).

The components of the motor engram described here could be influenced by a small current flowing on the surface of the brain such as during tDCS, which is known to modulate motor performance.

The effects of DC polarization on the neurons and on motor memories

The effect of DC polarization on neural firing was analyzed by Bindman et al. (1964). Using the same electrode to polarize and record neuronal activity (but at different time), these authors found that both the discharge rate and the number of active units were increased by anodal polarization (units that were silent became active due to polarization). Importantly, they noted that evoked potentials did not change immediately. Rather, the effect of DC polarization built up in several minutes before a peak of the effect was reached but this effect persisted once the current was stopped. The effect of polarization continued to increase for the next 15–30 min. Finally, as a precursor of transcranial alternate current stimulation (tACS), they observed that intermittent passage of current from one polarity to the other enhanced the effect of polarization.

Further insights were gained by intracellular recordings of motor cortex cells during anodal polarization (Purpura and McMurtry 1965). Short periods of polarization (max 40 s) and weak currents (40–80 mA/mm^2) modulated the evoked responses of cells measured by electrocorticogram without modifying the membrane potentials. In contrast, larger currents elicited similar change in cortical waves but also in membrane potentials in response to an input (see also Denney and Brookhart 1962; Voronin 1968). Strong anodal polarization of the cortical surface depolarized while cathodal polarization hyperpolarized the soma membrane of pyramidal tract cells. This finding was confirmed by more recent in vitro studies that found that modulation of the neural membrane is time (Bikson et al. 2004) and localization specific (Bikson et al. 2004; Rahman et al. 2013) and is affected by polarization of afferents (Rahman et al. 2013), by cell type and morphology (Radman et al. 2009), and by the orientation of axons (Kabakov et al. 2012). Therefore, neurons in a single cortical column could be affected completely differently by direct current stimulation because of their diverse orientations.

Finally, membrane oscillation and fast pre-potentials appeared during anodal polarization. Interestingly, those two features might be important for learning and memory. Membrane oscillation can improve the precision of an action potential (Gross 2006; Schaefer et al. 2006). The presence of fast pre-potentials during anodal polarization suggests that surface polarization changes the properties of the dendrites and thus alters how the cells respond to synaptic input. These fast pre-potentials represent a powerful mechanism to boost the output of neocortical neurons in response to given inputs (Crochet et al. 2004). Fast pre-potentials were also observed in another study in the rabbit (Voronin 1968). In that study, a decrease and an increase in EPSPs were reported with anodal and cathodal polarization, respectively. This surprising finding could be explained by a shift in the membrane potential at rest (increase and decrease for anodal and cathodal stimulation). More action potentials were elicited in response to tone or flash during anodal polarization.

To test the nature of the DC polarization after-effects, Gartside (1968a) cooled the brain to inhibit firing but found that when it warmed up, it went back to the post-polarization level and not to the pre-polarization levels. That is, the after-effect cannot stem from reverberating loops. LTP of synapses might account for this long-lasting effect. Recent studies found that anodal but not cathodal tDCS accompanied by ongoing activity gave rise to LTP of synapses both in motor cortex slices (Fritsch et al. 2010) and in hippocampal slices (Ranieri et al. 2012). Maintenance of long-term potentiation depends on protein synthesis and so does the after-effect of tDCS. Indeed, blocking protein synthesis 30 min before anodal polarization abolished the after-effect but not the increase in firing rates during the polarization itself (Gartside 1968b).

Protein kinase C is increased in several cortical areas after 30 min of 3 µA anodal polarization (Islam et al. 1994). This increase lasts for 3 h after polarization and then decreases in 72 h. An atypical form of this protein is essential for motor memories (von Kraus et al. 2010). In addition, there is an increase in c-fos expression in the 30 min after anodal stimulation (but not 15 min) in many brain areas but especially surrounding the electrode (Islam et al. 1995). In addition, Ranieri et al. (2012) noted an increase in c-fos with potentiation elicited by anodal current stimulation. These studies suggest that NMDA receptors are involved in the effects of anodal polarization, C-fos is required for the stabilization of LTP in dentate gyrus (Demmer et al. 1993) but not necessary for induction of LTP. C-fos expression is modulated during motor skill learning (Kleim et al. 1996).

Secretion of BDNF depends on a particular gene that has different variants in the population. This gene variant affects how people perform at motor tasks (Kleim et al. 2006; McHughen et al. 2010). It also affects the ability of tDCS to induce long-term potentiation in motor

cortex slices (Fritsch et al. 2010) and the ability of tDCS to improve motor learning (Fritsch et al. 2010).

Modulation of the neurotransmitter GABA is critical for motor learning and memory. GABA is decreased during motor learning (Floyer-Lea et al. 2006), and its increase reduces rates of adaptation (Donchin et al. 2002). A decrease in GABA reduces the specificity of neural firing in M1. That is, a neuron that would only fire for a specific input will start firing for various inputs after decrease in GABA concentration (Matsumura et al. 1992). In addition, a decrease in GABA concentration shortly after stroke improves motor recovery in rats (Clarkson et al. 2010). The concentration of this neurotransmitter is modulated during tDCS (Stagg et al. 2009). Both anodal and cathodal stimulation decrease GABA concentration while only cathodal tDCS also decreases glutamate concentration (Stagg et al. 2009). In addition, inter-individual differences in the sensitivity of the GABAergic system to tDCS were an excellent predictor of inter-individual skill learning performance (Stagg et al. 2011a). Adenosine, which is another neurotransmitter and is involved in LTD in cortical areas, is modulated during anodal polarization (Hattori et al. 1990) and influences the effect of cathodal polarization (Márquez-Ruiz et al. 2012).

In summary, most of the synaptic events that accompany motor learning (i.e., LTP, protein synthesis and decrease in GABA concentration) are modulated by direct current stimulation in such a way that anodal polarization should facilitate motor learning.

Methodological note

There exist many different tDCS protocols, and there is no general consensus about which parameters are optimum. There are three main degrees of freedom: current type, time of stimulation (before or during training), and electrode montage. Electrode size (Nitsche et al. 2007), current density (Galea et al. 2009; Bastani and Jaberzadeh 2012), and stimulation frequency and duration (Shekhawat et al. 2013; Bastani and Jaberzadeh 2014) can also modulate the effectiveness of the stimulation.

The impact of current type (continuous, intermittent, alternating, or random noise) on motor learning/control has not been investigated in details yet (see next section) although one study suggests that intermittent stimulation was more efficient than continuous current (Bindman et al. 1964).

The time of stimulation (before or during the training) appears critical to determine the effect of stimulation (Stagg et al. 2011b). Most of the studies on motor learning apply the stimulation during and not before or after training. The effect of tDCS on memory consolidation (stimulation after

learning) yielded very mixed results (Rosenkranz et al. 2000; Tecchio et al. 2010).

Finally, the impact of electrode montage has been largely investigated. When the stimulating electrode is place on one motor cortex, the reference electrode is usually placed on the contralateral supraorbital position (supra-orbital or unilateral montage). However, both extra-cephalic reference (ipsilateral arm/shoulder; extra-cephalic montage) and the contralateral motor cortex (bilateral montage) have been also used. The use of extra-cephalic reference reduces the effectiveness of the stimulation (Bikson et al. 2010; Moliadze et al. 2010a; DaSilva et al. 2011; Schambra et al. 2011). A new electrode montage (HD tDCS; Kuo et al. 2012) has appeared recently, but its impact on motor functions has not been tested yet. In healthy subjects, the bilateral montage might be more effective than the supra-orbital montage for augmenting motor learning (Vines et al. 2008a). However, this effect has not been demonstrated for stroke patients (Mahmoudi et al. 2011). For these patients, stimulating the ipsilesional hemisphere with anodal polarization or the contralesional hemisphere with cathodal polarization appears equally effective (Mahmoudi et al. 2011; Stagg et al. 2012). However, in some cases, the electrode montage appears critical to improve motor function in patients. For instance, bilateral montage is required to improve the symptoms of hand dystonia (Furuya et al. 2014) as a unilateral montage is not effective (Buttkus et al. 2010; Benninger et al. 2011; Furuya et al. 2014) although these results require further confirmation.

In conclusion, it appears that cephalic montages have a larger effect on motor function than extra-cephalic montage (e.g., Schambra et al. 2011). In addition, stimulating during and not before the performance of a motor task is also more effective (e.g., Stagg et al. 2011b).

Limitations of current tDCS work

1. Our three principles are directly drawn from the effect of polarization on single neurons activity. However, it is difficult to draw direct inferences from modulation of single neurons by tDCS and modulation of function at the network level. Indeed, recent works (Bikson et al. 2004; Radman et al. 2009) suggest that the direction of the dendrites is particularly important in order to decide the effect of tDCS on neuronal activity. Therefore, it seems that inferring the impact of polarization on motor function from its impact on neuronal activity is tenuous. However, this review suggests that there are impressive similarities between the effects of polarization on function and on single neurons.

2. Older studies demonstrate that the effect of DC polarization on neurons decreased with distance from the

polarizing electrode (Morrell 1961). Accordingly, behavioral studies demonstrated that anodal tDCS on the leg area of the motor cortex could selectively improve leg motor behavior but not hand motor behavior (Tanaka et al. 2009) and tDCS on the little finger area selectively increased MEPs in the little finger but not in the index finger (Nitsche et al. 2007). Finally, stimulating the motor cortex and not the posterior parietal cortex influences the generalization of force-field adaptation (Orban de Xivry et al. 2011b). These evidences for spatial specificity are confounded by most models that predict current flow from tDCS. In these models, the peak activation is often not localized beneath the electrode (see Fig. 2 of Datta et al. 2012). This feature is very surprising because the anodal tDCS is placed on the motor cortex and not posterior to it in order to obtain an increase in MEPs. Therefore, these models directly contradict data from the above-mentioned studies. There is a need to validate these models with independent data (Caparelli-Daquer et al. 2012; Edwards et al. 2013). This validation should include the direct comparison between different electrode montages (e.g., effect of conventional vs. HD tDCS on MEP size) and the effect of each of these montages on motor function.

3. Most of the studies discussed in this review focus on the modulation of the motor cortex by anodal stimulation. In contrast, the mechanisms of cathodal stimulation have received much less attention. For instance, in the most cited tDCS studies (Nitsche et al. 2003; Galea and Celnik 2009; Reis et al. 2009; Fritsch et al. 2010), cathodal stimulation does not modulate the task at hand and is not discussed further. More surprisingly, some studies reported similar effects for anodal and cathodal stimulations of the motor cortex on task modulation (Orban de Xivry et al. 2011b; Stagg et al. 2011b).

4. The reliability of the effects of tDCS on the different aspects of motor control and motor learning is currently unknown but might not be very high. For instance, many studies do not test adequately for interactions (Nieuwenhuis et al. 2011) and do not correct for multiple comparisons (Bennett et al. 2011), and the spectra of p-hacking are well present (Simmons et al. 2011; Murayama et al. 2013). The real questions are as follows: (1) How many of the current results are we able to replicate? Though it is important to bear in mind that non-replication does not equate fraud and that it can happen for any perfectly fine study (Ioannidis, 2014); and (2) How many studies did not reach statistical significance and were therefore never published? (aka the file-drawer problem; Simonsohn et al. 2014) These problems impact all fields of neuroscience, but solutions have been recently proposed (Lak-

ens and Evers 2014; Simonsohn et al. 2014). One easy and practical first solution would be to increase the size of the groups as studies with larger number of participants are more immune to some of these weaknesses (Button et al. 2013).

Open questions

This review of the literature brings new questions about the modern use of tDCS for experimental or clinical perspectives. Here is a list of a few questions that need to be addressed.

1. In this review, we postulated that the effect of tDCS on motor control and motor learning could be accounted for by a few principles. However, it is possible that the first principle (modulation of firing rate by polarization) can on its own account for all the effects reported in the studies presented in this review. Different results would argue against such a view. For instance, increase in evoked and spontaneous discharge rate by anodal polarization is present during and after tDCS, but the effect of tDCS on learning appears to be different if polarization is delivered during or before motor training (Stagg et al. 2011b). Low-frequency rTMS but not cathodal tDCS delivered on the motor cortex can relieve hand dystonia (Siebner et al. 1999; Buttkus et al. 2010; Benninger et al. 2011) while both techniques decrease evoked neural activity (Creutzfeldt et al. 1962; Aydin-Abidin et al. 2006; Allen et al. 2007). Therefore, the causal link between the modulation of firing rates by tDCS (first principles) on one hand and the strengthening of new associations and the modulation of memory (second and third principles) should be explored in the future. Looking at the effects of modulation of neural activity by other means than electrical current (e.g., optogenetics) on motor control and learning should answer this question.

2. The links between the different models of actions of tDCS should also be investigated into more details. For instance, we currently do not know whether modulation of motor cortex activity by polarization induced a modulation of GABA concentration or whether the modulation of GABA concentration by polarization is responsible for the change in neuronal activity under the electrode. In addition, high-frequency stimulation of the motor cortex, which induces LTP in the motor cortex, leads to an increase in GABA concentration and impairs skilled reaching in mice (Henderson et al. 2012). Similar links should be sought to understand the modes of action of tDCS.

3. Older studies employed different stimulation protocols. Often, the current was pulsatile, i.e., the device was only on for every other 15-s time interval. This patterned tDCS appeared to be more effective than a constant current flow (Bindman et al. 1964; Albert 1966). Such intermittent tDCS has been used on the dorsolateral prefrontal cortex to modulate working memory (Marshall et al. 2005). There is a limited view on the efficacy of different versions of DC polarization (transcranial alternating current stimulation, transcranial random noise stimulation, etc.). One study suggests that tACS and tDCS influence firing rates, but that spike timing was only affected by tACS (Reato et al. 2010). Interestingly, transcranial alternate current stimulation modulates motor cortex excitability but not motor performance at SRTT (Moliadze et al. 2010b) while transcranial random noise stimulation affected both (Terney et al. 2008). It is unclear which tDCS protocol (continuous, intermittent, alternating or random noise) is the most effective.

4. Synaptogenesis is considered a critical component of motor learning (Xu et al. 2009; Yang et al. 2009; Yu and Zuo 2010; Fu et al. 2012; Peters et al. 2014). It is known that the direction of an electric field can influence the direction of nerve growth (Fox et al. 1984; McCaig and Rajnicek 1991). However, it is unknown whether tDCS directly affects the rate of new synapses or their direction. Alternatively, tDCS could only facilitate long-term potentiation of nascent spines (Hill and Zito 2013).

5. Brazovskaya et al. (1972) demonstrated that there was an increase in the number of glial cells near pyramidal neurons after anodal polarization of the cortex. The influence of tDCS on glial cells has been postulated on the basis of theoretical arguments (Ruohonen and Karhu 2012). How glial cells modulate learning and how their function is modulated by tDCS remains unknown.

6. While the effect of tDCS on manual dexterity of stroke patients and some specific aspects of their motor function appears to be consistent across laboratory studies (Kandel et al. 2012; Butler et al. 2013; Marquez et al. 2013a, b), evidence for the ability of tDCS to improve activities of the daily living is still weak (Elsner et al. 2013), which questions the clinical relevance of tDCS for stroke rehabilitation. Clearly, large clinical trials are needed to settle this question not only for stroke but for any neurological disorders whose symptoms have been claimed to be alleviated by tDCS (PD, dystonia, etc.).

Conclusion

Electrifying the motor engram has become popular over the last decade, and its clinical applications have gained interest.

In this review, we highlighted the similarities between the effects of brain polarization on neuronal activity and its effects on motor performance and learning. In addition, we detailed the neural substrate of the motor engram and showed that many of the mechanisms that are implicated in the formation of this engram are modulated by brain polarization. While these mechanisms are also likely responsible for the clinical benefits of tDCS demonstrated in several studies, further research is needed to demonstrate the clinical relevance of the tDCS technique. Further success of the tDCS technique will depend on the ability of scientists to provide reliable studies on the effects of tDCS on motor function in health and disease and to deepen our understanding of the mechanisms of tDCS on the motor engram.

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