Physiological Basis of Transcranial Direct Current Stimulation

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Abstract

Since the rediscovery of transcranial direct current stimulation (tDCS) about 10 years ago, interest in tDCS has grown exponentially. A noninvasive stimulation technique that induces robust excitability changes within the stimulated cortex, tDCS is increasingly being used in proof-of-principle and stage IIa clinical trials in a wide range of neurological and psychiatric disorders. Alongside these clinical studies, detailed work has been performed to elucidate the mechanisms underlying the observed effects. In this review, the authors bring together the results from these pharmacological, neurophysiological, and imaging studies to describe their current knowledge of the physiological effects of tDCS. In addition, the theoretical framework for how tDCS affects motor learning is proposed.

Keywords

transcranial direct current stimulation, synaptic plasticity, neocortex, physiology, motor learning

Background

Transcranial stimulation paradigms have been receiving increased interest in recent years as tools for modulating cortical excitability and behavior in a range of clinical settings and experimental conditions. Transcranial direct current stimulation (tDCS) is a stimulation paradigm that holds particular promise in both of these settings as it is noninvasive, painless, and well-tolerated.

To date, tDCS has been shown to have beneficial effects in a wide range of diseases, for example, neurological conditions such as stroke (Fregni and others 2005; Hummel and others 2005) and refractory epilepsy (Fregni, Thome-Souza, and others 2006), psychiatric indications such as chronic depression (Boggio, Rigonatti, and others 2007) and drug cravings (Fregni and others 2008), and pain conditions such as fibromyalgia (Fregni, Boggio, and others 2006) and traumatic spinal cord injury (Fregni, Boggio, and others 2006).

However, to date, the behavioral effects of single sessions of tDCS are relatively short lived, lasting for a maximum of a few tens of minutes. Recently, early evidence is emerging that multiple, spaced sessions may increase the duration of these behavioral effects to several weeks both in healthy controls (Reis and others 2009) and in patients (Boggio, Nunes, and others 2007; Boggio and others 2008), but the mechanisms underlying these changes has not been explored.

For a therapeutic intervention to have the potential to induce long-lasting changes in behavior, either in healthy controls or patients, it must first be demonstrated to be able to induce long-lasting functional changes within the cortex. In terms of the underlying physiology, the only mechanism by which long-lasting functional changes are known to occur in the cortex is via modulation of the strength of the underlying synaptic connections (i.e., by synaptic plasticity).

In this review, we aim to draw together evidence from pharmacological, neurophysiological, and magnetic resonance spectroscopy (MRS) studies to summarize what is known about the physiological effects of tDCS, how these might interact with synaptic plasticity in motor learning, and what questions remain to be answered. The major pharmacological agents used are listed in Table 1, and an overview of transcranial magnetic stimulation (TMS) protocols is presented in Table 2 (for a full review, see Ziemann 2008).

The vast majority of evidence has been gained from stimulation of the primary motor cortex (M1), and therefore, we concentrate on these studies. It is not clear to

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Table 1. Common Pharmacological Agents

Name	Abbreviation	Role	Notes
Nonsynaptic mechanisms			
Flumazenil	FLU	$Ca2^+$ channel blocker	
Carbamazepine	CBZ	Na^+ channel blocker	Also increases acetylcholine (ACh) release (Mizuono and others 2002) and raises DA levels (Okada and others 1997)
Lamotrigine	LG	$Ca2^+$ and Na^+ channel blocker	
Neurotransmitters			
Dextrometorphan	DMO	NMDA receptor antagonist	Also blocks Na^+, K^+, and $Ca2^+$ channels at higher concentrations (Netzer and others 1993)
D-cycloserine	CYC	Partial NMDA receptor agonist	Binds to the glycine-binding site, leading to upregulation of NMDA receptor function (Thomas and others 1988)
Lorazepam	LOR	$GABA_A$ receptor agonist	
Neuromodulators			
Propranolol	PROP	β receptor antagonist	
Amphetamine	AMP	Nonspecific NA and DA agonist	Also decreases extracellular GABA concentration (Bourdelais and Kalivas 1990) and stimulates the glutamatergic system (Karler and others 1995; Kelley and Throne 1992)
Pergolide	PGL	DA agonist	Shows much higher affinity for D2 than D1 receptors (Fici and others 1997; Kvernmo and others 2006)
L-DOPA		DA agonist	Shows higher affinity for D2 than D1 receptors but is less specific to D2 than PGL
Ropinerole	RP	D2 agonist	
Rivistigmine		ACh esterase inhibitor	Increases ACh by reducing the rate of its catabolism
Citalopram	CIT	Selective serotonin reuptake inhibitor	

A number of the most common pharmacological agents used to study the effects of transcranial direct current stimulation. The table is divided into drugs with a primary mode of action on nonsynaptic mechanisms, those that modulate the major neurotransmitters, and those that act to modulate the neuromodulators. Few of the drugs are specific.

what extent these findings are transferable to other areas of the cortex, although it is likely that the mechanisms are similar. In addition, we concentrate on the effects within the healthy motor cortex, as the context of wider damage adds an additional layer of complexity to the interpretation of results.

Synaptic Plasticity within the Neocortex

In his seminal work of 1949, Hebb proposed a mechanism for plasticity within the brain: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one of both cells, such that A's efficiency, as one of the cells firing B, is increased" (Hebb 1949). Since this time, many mechanisms for modulation of synaptic strength have been discovered. One of these, long-term potentiation (LTP), is of particular interest as it allows for modulation of synaptic strength that stabilizes for days, months, or even years and has therefore been postulated as a likely candidate for memory formation in the brain (Anderson and Lomo 1966; Bliss and Lomo 1973). LTP and its antithesis long-term depression (LTD) have been studied extensively in the hippocampus and refer to highly specific processes (for a review, see Bliss and others 2003). Synaptic plasticity with very similar properties has been demonstrated in the neocortex and is therefore commonly referred to as LTP-like plasticity.

The plasticity associated with motor learning and that associated with rehabilitation from an experimentally induced lesion in rats occurs in the horizontal connections within the primary motor cortex (Hess and Donoghue 1994; Huntley 1997; Jacobs and Donoghue 1991; Rioult-Pedotti and others 1998). LTP- and LTD-like plasticity are difficult to elicit in these neuronal pools, requiring multiple spaced sessions of stimulation (Trepel and Racine 1998). The evidence from animal studies of neocortical

Table 2. Common Transcranial Magnetic Stimulation (TMS) Protocols

TMS Measure	Abbreviation	Protocol	Neurons Stimulated	Notes
Motor threshold	MT	Single pulse	Corticospinal tract (CST) neurons and closely associated intracortical neurons	No clear involvement for glutamate or GABA (Ziemann 2008)
Input/output curves	I/O curves	Single pulse, multiple intensities	CST neurons and intracortical neurons over a wider area than MT	Glutamatergic involvement (Boroojerdi and others 2001) and some GABAergic involvement at higher intensities (Boroojerdi and others 2001; Schonle and others 1989)
Short interval intracortical inhibition	SICI	Paired pulse, subthreshold, then suprathreshold pulse, ISI 1–5 ms (Kujirai and others 1993)	$GABA_A$ergic interneurons (Di Lazzaro and others 2000, 2005; Ilić and others 2002; Ziemann, Lönnecker, and others 1996)	Also increased by glutamate antagonists (Schwenkreis and others 2000; Schwenkreis and others 1999; Ziemann, Chen, and others 1998); increased by DA (Korchounov and others 2007; Ziemann, Bruns, and others 1996), decreased by NA (Korchounov and others 2003) and ACh (Korchounov and others 2005)
Intracortical facilitation	ICF	Paired pulse, subthreshold, then suprathreshold pulse, ISI 7–20 ms (Kujirai and others 1993; Ziemann, Rothwell, and others 1996)	Primarily glutamatergic interneurons, with some GABAergic effects.	Modulated by GABA (Inghilleri and others 1996; Ziemann, Lönnecker, and others 1996)

A number of the transcranial magnetic stimulation protocols have been used to investigate the mechanisms underlying transcranial direct current stimulation.

LTP- and LTD-like mechanisms can be confusing; often the results from in vitro and in vivo preparations differ, and it is not clear how to interpret these.

Induction of Hebbian processes within the neocortex, as elsewhere within the brain, depends critically on changes within NMDA receptor–dependent glutamatergic interneurons (Aroniadou and Keller 1995; Castro-Alamancos and others 1995; Hess and others 1996). Compared with LTP- and LTD-like effects elsewhere in the brain, neocortical LTP is also dependent on GABAergic interneurons (Trepel and Racine 1998, 2000). LTP in neocortical slice preparations can only robustly be induced by reducing the local GABAergic tone (Castro-Alamancos and others 1995; Hess and Donoghue 1996), and administration of the GABA agonist lorazepam (LOR) prior to stimulation in the intact rat abolished LTP induction (Trepel and Racine 2000).

LTD can be induced in the neocortex via a number of mechanisms, and generalizing across synapses may be misleading (Malenka and Bear 2004). However, in the main, LTD induced in vitro in the agranular cortex is dependent on NMDA receptor activity (Castro-Alamancos and others 1995), although it is independent of NMDA receptors in the sensorimotor cortex of freely moving rats (Froc and Racine 2004). The involvement of GABA in LTD is not clear, although it has been postulated that changes in GABAergic transmission may also underlie both LTD and alterations in movement representations within the horizontal interneurons (Campbell Teskey and others 2007; Kourrich and Chapman 2003).

Neuromodulators

Neocortical LTP-like plasticity is modulated by a number of other neurochemicals known as neuromodulators. These are a heterogenous and poorly defined group of chemicals that induce little or no change in basal neuronal activity within the neocortex but potentiate or attenuate responses evoked by another transmitter substance (Table 3; Barchas and others 1978).

The role of the neuromodulators in long-term synaptic changes is critically dependent on the receptor subtypes, the concentration and phasic activity of the modulators, and their site of action. As few studies have investigated the role of the neuromodulators in the agranular M1, the results from slice preparations outside this area are discussed here, although these must be interpreted with caution.

The distribution of noradrenaline (NA) receptors in the cortex varies significantly between cortical areas and has not been studied in detail in the agranular cortex. Elsewhere, in vitro, NA has been shown to facilitate synaptic plasticity (both LTP and LTD) by enhancing the NMDA receptor–dependent component (Brocher and others 1992; Kirkwood and others 1999).

The dopaminergic input to primate motor cortex is concentrated via D_1 receptors in layers I to III_A (Lidow and

Table 3. Neurotransmitters and Neuromodulators

Family	Name	Abbreviation	Source	Notes
Neurotransmitters				
Amino acids	Glutamate	GLU	Throughout brain	GABA is synthesized from glutamate by glutamic acid decarboxylase, a synthetic enzyme restricted to GABAergic neurons
	γ-amino butyric acid	GABA	Throughout brain	
Neuromodulators				
Catecholamines (monoamines)	Noradrenaline (norepinephrine)	NA	Locus coeruleus	NA is synthesized from DA by dopamine β-hydrolase, a synthetic enzyme restricted to catcholamine-synthesizing cells; pharmacological interventions are rarely specific to one catecholamine
	Dopamine	DA	Ventral tegmental area	
	Acetylcholine	ACh	Nucleus basalis of Meynert	
	Serotonin (5-hydroxytryptamine)	5-HT	Raphe nuclei	

A number of neurotransmitters and neuromodulators are implicated in synaptic plasticity mechanisms within the primary motor cortex.

others 1990). No effect of dopamine (DA) on neuroplasticity has yet been demonstrated in the agranular cortex, although in vitro studies of the prefrontal cortex suggest that dopamine facilitates both LTP- and LTD-like plasticity in rats (Blond and others 2002; Gurden and others 2000; Jay and others 1996; Otani and others 1998). There is evidence that dopamine may modulate cortical excitability via changes in both ion channels and synaptic plasticity, and its effects on synaptic plasticity may be specific to the different cortical layers or on different types of input (see Seamans and Yang 2004 for a review). In the prefrontal cortex, studies have reported interactions between DA and both NMDA and GABAergic neurons. There is an inverted U-shape dose-response curve to DA, such that physiological doses of DA, presumed to be acting via the D_1 receptor subtype, led to an increase in NMDA-mediated responses in cortical neurons (Wang and O'Donnell 2001) but decreased responses at high doses of DA, when coactivation of the D_2 receptor subtype is thought to occur (Zheng and others 1999). This inverted U-shaped response is also seen in memory tasks when performance is worsened by nonphysiological low or high levels of DA (Floresco and Phillips 2001).

Acetylcholine (ACh) receptors are found in the highest density in layer I of the neocortex (Gu 2002; Yasuda and others 1993). Activation of the nicotinic ACh receptor subtype modulated both LTP and LTD in the hippocampus (Ge and Dani 2005; Ji and others 2001). In the rat motor cortex, blockade of the muscarinic ACh receptor subtype prevented the development of LTP but facilitated the development of LTD (Hess and Donoghue 1999).

The distribution of serotonergic (5-HT) neurons in the cortex varies between cortical areas, and serotonergic neurons synapse both directly onto pyramidal neurons and GABAergic interneurons (DeFelipe and others 1991; Papadopoulos and others 1987; Takeuchi and Sano 1984). In vitro studies showed that serotonin modulated both LTP- and LTD-like plasticity bidirectionally, depending on subreceptor specificity, location, and frequency of applied stimulation. Although serotonin facilitated the induction of both LTP and LTD in the developing visual cortex of the kitten (Kojic and others 1997), serotonin agonists suppressed LTP-like plasticity in the adult rat visual cortex (Edagawa and others 1998a, 1998b, 1999). However, serotonin appears to have no effect on plasticity within the rat barrel cortex (Turlejski and others 1997), and application of a selective serotonin reuptake inhibitor (SSRI) led to an augmentation of LTP-like plasticity in the rat hippocampo-medial frontal cortex pathway (Ohashi and others 2002).

Electrical Stimulation Techniques

Early Studies of Polarizing Currents

Historical perspective. Strong electrical currents have been delivered to patients for the relief of headache and epilepsy for approximately two millennia. Scribonius Largus, Pliny the Elder, and Galen all used torpedo electric fish to elicit a sudden, transient stupor (Kellaway 1946). The effects of electrical stimulation were subsequently studied using modern scientific methods by many scientists, notably Galvani and Volta (Priori 2003). In 1804, Aldini, Galvani's nephew, was the first scientist in the modern era to report the use of electrical stimulation in the treatment of mental disorders, thus pioneering the field of

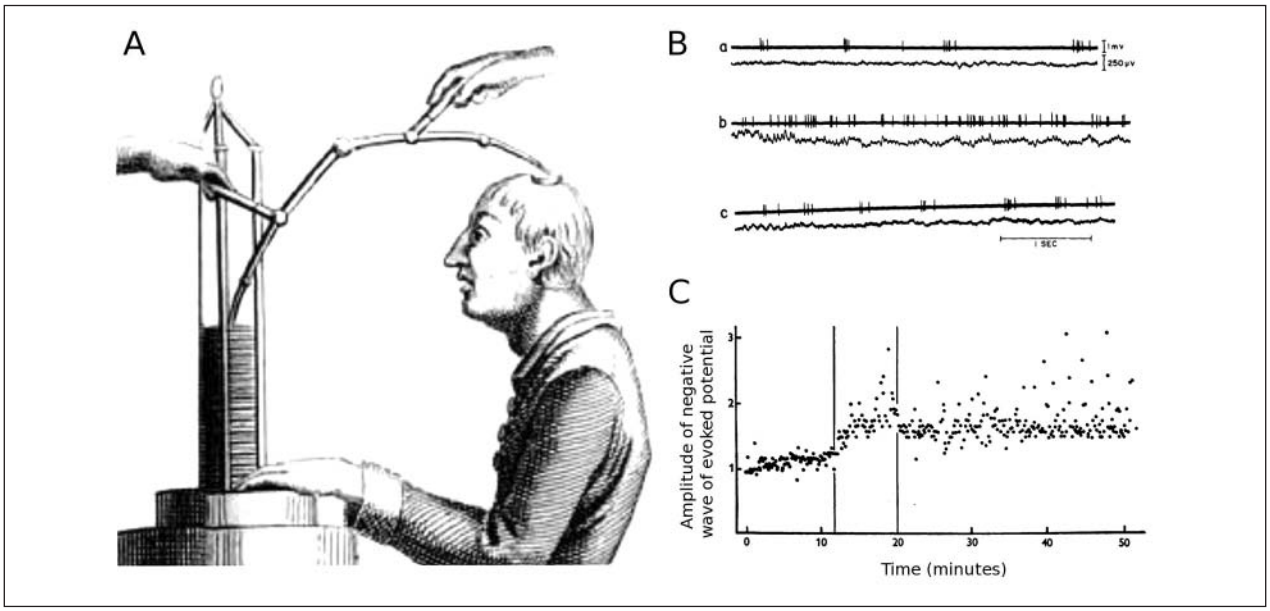

Figure 1. (A) Details from plate V in Aldini J, *Essai théorique et experimental sur le galvanisme.* It illustrates the treatment of Luigi Lanzarini with galvanism applied to the head (figure from Parent 2004). (B) The effect of transcortical DC current on spontaneous activity (top line) and EEG (lower line) in the motor cortex. (a) Control condition. (b) During 1000 μA anodal current. (c) Control condition, 20 seconds after (b). A clear increase in neuronal firing can be seen in (b) during anodal stimulation (adapted from Fig. 1; Creutzfeldt and others 1962). (C) The aftereffects of anodal stimulation on the peak amplitude (mV) of the evoked potential. Between the 12th and 20th minute, a current of 25 μA was passed (figure 4, Bindman and others 1964).

electrotherapy (Fig. 1A; Parent 2004). However, subsequent studies using low-level DC current showed variable results, and after the discovery of electroconvulsive therapy in the 1930s, fewer studies focused on weak DC currents. We discuss these here, before moving on to discuss the modern technique of tDCS in depth.

Neurophysiological effects during current application. The effects of weak polarizing currents appear to be critically dependent on both the strength of the current applied and the duration of that application. DC stimulation is often described in terms of the charge density (C/cm^2), where 1 coulomb (C) is the amount of electric charge transported in 1 second by a steady current of 1 ampere.

Early studies in animals using direct cortical stimulation with a stimulus of 0.00013 to 0.3 C/cm^2 showed that if the anode was placed above or within the cortex, spontaneous neuronal activity was increased, whereas cathodal polarity resulted in reduced spontaneous unit discharges (Fig. 1B; Bindman and others 1964; Creutzfeldt and others 1962; Purpura and McMurtry 1965), due to subthreshold changes in membrane polarization (Purpura and McMurtry 1965; Scholfield 1990). However, neurons throughout the cortex were not modulated in a homogenous manner. Neurons in deep cortical layers were often deactivated by anodal and activated by cathodal stimulation (Purpura and McMurtry 1965). This would suggest that the orientation of neurons relative to the electrical field is of vital importance to their response to stimulation. In addition, the different subpopulations of neurons appear to have different thresholds for modulation. Nonpyramidal tract neurons were stimulated at lower total charges than pyramidal tract neurons, the activity of which was modulated only at charge densities greater than 0.008 $\mu C/cm^2$ (Purpura and McMurtry 1965). These findings are important for human studies, as they suggest that tDCS will stimulate both pyramidal tract neurons and interneurons.

Neurophysiological effects after current application. Modulation of neuronal firing occurs after the current was switched off, and indeed, the maximum effects may be seen a few minutes after the current had ceased. In the rat, a 25-μA anodal current passed through the cortex for 8 minutes led to an increase in neuronal excitability for at least 50 minutes (Fig. 1C). A cathodal current led to a decrease in neuronal excitability of a similar duration, provided it was applied for more than 5 minutes (Bindman and others 1964). The aftereffects of current application are dependent on the strength of the current: A 25 μA surface-positive current led to an increase in firing, whereas a 200 μA surface-positive current applied for 2 seconds led to an abolition of all neuronal activity, which only slowly recovered over the next 30 minutes, presumably due to a depolarization block (Bindman and others 1964).

The aftereffects of current application depend on the duration of the current applied over and above the total charge applied. For example, a total charge density of 0.06 C/cm^2 applied over 40 seconds in the cat induced aftereffects of only a few seconds (Purpura and McMurtry 1965), whereas 0.03 C/cm^2 applied over 20 minutes or more in the rat led to a change in firing rates for tens of minutes (Bindman and others 1964).

These long-term effects are not just an electrical phenomenon but also depend on protein synthesis (Gartside 1968a, 1968b). More recent work has suggested that anodal stimulation increases intracellular calcium levels as well as early gene expression. These effects were shown to be NMDA receptor dependent (Islam, Aftabuddin, and others 1995; Islam, Moriwaki, and others 1995), although the 30 minutes of stimulation applied in these experiments is greater than that used in standard tDCS experiments. This difference in stimulation duration may be important, as 0.068 C/cm2 decreased cAMP, whereas the same current applied for 10 times longer increased cAMP (Hattori and others 1990).

Early human studies. It is important to note that in the animal studies discussed, the electric current was applied directly to the cortex. In all of the human studies we will discuss, the current is applied transcranially, adding complexity within the path of the current from the electrode to the cortex. Many early studies of polarizing currents in humans used current densities that were insufficient to modulate cortical excitability to any great degree. Anodal stimulation of the M1 with event-related DC stimulation led to an improvement in performance in a choice reaction time task (Elbert and others 1981; Jaeger and others 1987). In the visual cortex, relatively strong anodal stimulation (3.06 C/cm^2) worsened visual perception (Korsakov and Matveeva 1982).

However, although modulating behavior is the ultimate aim of stimulation, behavior is an indirect and nonspecific measure of cortical excitability changes. Apart from an early EEG study (Pfurtscheller 1970), the first modern study to investigate cortical excitability per se investigated the effects of up to 0.5 mA currents applied using an M1-chin montage on motor evoked potential size (Priori and others 1998). This demonstrated a significant decrease in cortical excitability when a 0.3 mA anodal current was applied prior to a cathodal current and then alternated for 7 seconds each, with 90 seconds between each application. However, no effect of either anodal or cathodal stimulation in isolation was observed. It is not clear why no effect was demonstrated in this study, but it may be due to the short stimulation periods used or that this electrode placement induces a suboptimal current path through the cortex.

Overall, the results from these early studies are difficult to interpret and give no overall clear impression of the effects of weak polarizing currents. The first study to use the standard modern current and electrode parameters was published 10 years ago (Nitsche and Paulus 2000). For the purposes of this review, we will concentrate on studies of tDCS broadly using the parameters determined in this study.

Overview of Modern tDCS

For motor cortical stimulation, the stimulating electrode is most commonly placed over the motor cortex (M1) and the reference electrode over the contralateral supraorbital ridge (Fig. 2A). For stimulation of the hand representation within M1, the M1 electrode is centered over the hand-knob area using TMS assessment of the TMS-located motor "hot spot" (Nitsche and Paulus 2000, 2001) or in accordance with anatomical localization (Stagg and others 2009).

Most studies use two surface conductive rubber electrodes sized between 25 cm^2 and 35 cm^2. Using these electrodes, current intensities vary between 1 mA and 2 mA and are commonly applied for between 10 and 20 minutes. More recently, small electrodes have been used to focus the effects of tDCS on the M1 (Nitsche and others 2007). In this study, currents of 0.1 mA were used in combination with an electrode size of 3.5 cm^2, thereby maintaining the current density of 0.01 mA but applied to a smaller region of the cortex.

Safety considerations. More than 100 studies have been performed using tDCS in healthy controls and in patient populations, and no serious side effects have occurred (for a review, see Nitsche and others 2008). Slight itching under the electrode, headache, fatigue, and nausea have been described in a minority of cases in a series of more than 550 subjects (Poreisz and others 2007). Detailed studies have been performed to assess the safety of tDCS. These have shown that there was no evidence of neuronal damage as assessed by serum neuron-specific enolase after application of a 1 mA anodal current for 13 minutes (Nitsche and Paulus 2001; Nitsche, Nitsche, and others 2003) or MRI measures of edema using contrast-enhanced and diffusion-weighted MRI measures after application of a 1 mA current for 13 minutes (anodal) or 9 minutes (cathodal; Nitsche, Niehaus, and others 2004). No pathological waveforms were seen on EEG, and no worsening of neuropsychological measures was observed after frontal lobe stimulation with current intensities of up to 2 mA for 20 minutes (Iyer and others 2005). No heating occurred under the electrode during 20 minutes of 2 mA stimulation, even within the bore of a 7T MRI scanner (Stagg and others 2009).

Although a number of safety limits were defined for direct electrical stimulation of the cortex in humans (Agnew and McCreery 1987), it is not clear how these relate to tDCS, which does not involve direct contact between the electrodes and the cortex. In a study using direct cortical stimulation, tissue damage has been detected at a total charge

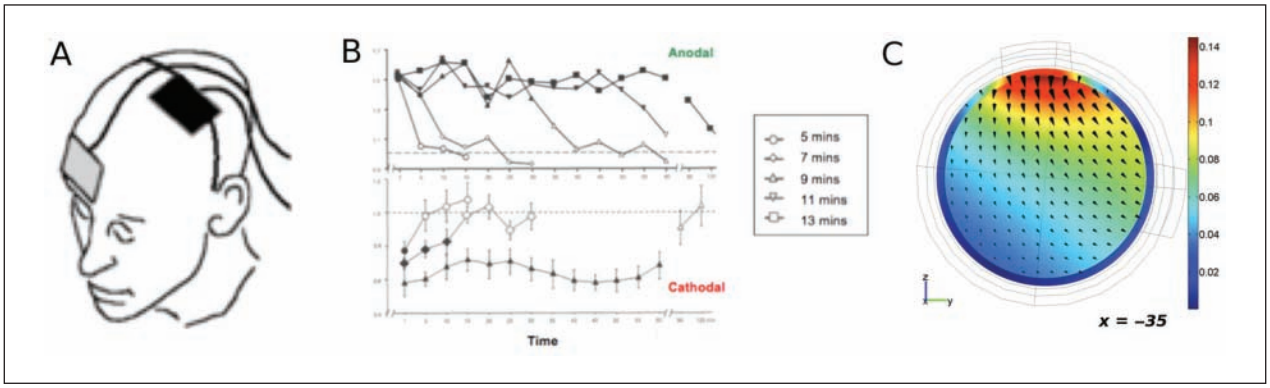

Figure 2. (A) Schematic representation of the location of the stimulating electrodes used for transcranial direct current stimulation (tDCS). The stimulating electrode (black) is placed over the primary motor cortex; the reference electrode (gray) is placed over the contralateral supraorbital ridge. (B) The aftereffects of 1 mA of anodal (upper part) and cathodal (lower part) tDCS applied to the motor cortex. Increasing the length of stimulation increases the duration of the aftereffects (shown as a ratio to baseline; colored points demonstrate a significant difference from 1; adapted from figure 1, Nitsche, Liebetanz, and others 2003). (C) Plot of the magnitude (color bar) and direction (arrows) of the current density in the brain for a 2-mA current applied via a small anode placed over M1 and a small reference electrode over the contralateral supraorbital ridge. The arrows have a significant latero-mesial component (out of the paper) throughout the plane of the figure (Miranda and others 2006).

of 216 C/cm^2 (Yuen and others 1981), whereas tDCS applied even at 2 mA and 20 minutes results in a total charge of only 0.09 C/cm^2.

In addition, a recent study was performed in rats using an epicranial electrode montage designed to be similar to that used in tDCS (Liebetanz and others 2009). This demonstrated that brain lesions occurred only at current densities greater than 1429 mA/cm^2 applied for durations longer than 10 minutes. In standard tDCS protocols in humans, a current density of approximately 0.05 mA/cm^2 is produced.

Effects on cortical excitability. The direction of the effects of tDCS on cortical excitability is polarity specific. Anodal stimulation increases cortical excitability both during and after stimulation, provided the stimulation period is of sufficient duration, and cathodal stimulation leads to a decrease in excitability within the cortex (Fig. 2B).

The effects of tDCS are in the majority intracortical (Nitsche and Paulus 2000, 2001; Nitsche, Nitsche, and others 2003). One study has demonstrated effects on cortico-spinal tract excitability (Ardolino 2005), although this was not seen at lower current intensities (Nitsche and Paulus 2001). Models of current flow suggest that a significant current density is seen only relatively local to the stimulated cortex (Miranda and others 2006; Wagner and others 2007; Fig. 2C). These findings are in line with those from the animal literature, as discussed above.

Effects of stimulation duration on cortical excitability. The mechanisms underlying cortical excitability changes induced by tDCS differ between those effects seen during stimulation and those induced after stimulation has ceased, despite similar neurophysiological effects. For that reason, effects during stimulation and those seen after stimulation are discussed separately in this review.

Delineating the path of the stimulating current. Accurately measuring the path of current flow through the head of human subjects poses clear difficulties, and therefore, our knowledge of the path of current flow and the density of current within a distinct area of cortex is based on indirect observation in the human and animal studies and mathematical models.

In 1975, Dymond and colleagues investigated the intracortical current flow between pairs of small scalp electrodes: two placed over the frontal poles and two over the mastoids. These results suggest that approximately 45% of the current applied passed through the brain. These results are close to those predicted by Rush and Discroll (1968) using an electrolytic tank model consisting of a half human skull suspended in fluid. Results from this model were very similar to those derived from a more theoretic model using three concentric spheres (Rush and Driscoll 1968), a model that has subsequently been used for modeling the effects of tDCS with the modern parameters (Miranda and others 2006). This latter study suggests that only about 10% of a scalp current of 2 mA reaches the cortex (Fig. 2C).

Effects of tDCS on Neurons during Stimulation

The effects of anodal tDCS during stimulation appear to be solely dependent on changes in membrane potential. The calcium channel blocker flunarizine (FLU) reduced and the sodium channel blocker carbamezipine (CBZ)

abolished the effects of anodal stimulation (Nitsche, Fricke, and others 2003).

Neither dextromethorphane (DMO), an NMDA receptor antagonist (Nitsche, Fricke, and others 2003) nor LOR, a $GABA_A$ receptor agonist (Nitsche, Grundey, and others 2004) had a modulatory effect on the intrastimulation response. Anodal tDCS did not alter TMS measures of either glutamatergic interneurons (intracortical facilitation [ICF]) or GABAergic interneurons (short-interval cortical inhibition [SICI]; Table 2), suggesting that no significant modulation of the GABAergic or glutamatergic interneuronal pools occurred (Nitsche and others 2005).

Likewise, the excitability changes during cathodal stimulation are also probably due to membrane potential modulation. Unlike anodal stimulation, neither blockade of voltage-dependent Ca^{2+} nor Na^+ channels had any effect on excitability shifts (Nitsche, Fricke, and others 2003). This is in accordance with tDCS-generated hyperpolarization of the neuron leading to inactivation of the relevant voltage-gated channels and therefore negation of any drug effect.

In addition, neither NMDA nor GABA blockade modulated the effects of intrastimulation cathodal tDCS (Nitsche, Fricke, and others 2003; Nitsche, Liebetanz, and others 2004). However, although the overall changes in cortical excitability induced by cathodal tDCS were not modulated significantly by DMO, tDCS did lead to a decrease in ICF.

The motor threshold (MT), a measure of pyramidal neuron excitability (Table 2), was not altered by either anodal or cathodal stimulation, suggesting that tDCS predominantly modulates interneurons (Nitsche and others 2005). In addition, the input/output (I/O) curve was modulated by cathodal tDCS (Nitsche and others 2005). I/O curves are thought to reflect the excitability within a wider area of cortical neurons than the MT and may be influenced by excitability within the interneuronal pool to a greater extent than the MT. In light of the pharmacological evidence, it would appear that the change in ICF and I/O curve during cathodal tDCS is due to direct modulation in resting membrane potential of the glutamatergic interneurons rather than synaptic modulation.

In summary, therefore, both anodal and cathodal tDCS primarily affect resting membrane potential during stimulation, with no significant effects on synaptic plasticity.

Aftereffects of tDCS

Anodal. Induction of the aftereffects of anodal tDCS, at least, is dependent on membrane depolarization. The addition of the either the Ca^{2+} channel blocker FLU or the Na^+ channel blocker CBZ resulted in the abolition of the aftereffects of tDCS (Nitsche, Fricke, and others 2003). In addition, anodal stimulation increased the slope of the I/O curve but did not modulate the MT, suggesting a more widespread effect on the intracortical neurons (Nitsche and others 2005).

The aftereffects of anodal tDCS do appear to be dependent on synaptic modulation. Anodal stimulation increased ICF, and DMO blocked the increase of excitability seen after tDCS (Liebetanz and others 2002; Nitsche, Fricke, and others 2003). Application of d-cycloserine (CYC), a specific NMDA receptor agonist, increased the duration but not the magnitude of the aftereffects (Nitsche, Jaussi, and others 2004).

In addition, $GABA_A$ergic interneurons play a role. TMS studies demonstrated a reduction in SICI and an increase in I-wave facilitation after tDCS, both measures of GABAergic interneuronal activity (Table 2; Nitsche and others 2005). LOR attenuated the tDCS-induced excitability increase for the first 10 minutes, after which an increased excitability was seen (Fig. 3A; Nitsche, Liebetanz, and others 2004). The mechanism for this increase is not clear; it may be that these effects are due to an increase in the tonic GABAergic inhibition in sites distant to the stimulated M1 or may reflect recovery of the tDCS-induced increase in corticospinal tract excitability. However, the study suggests the importance of GABA in modulating intracortical excitability after anodal tDCS, a finding in agreement with an MRS study that showed a decrease in GABA concentration within the stimulated cortex after 10 minutes of anodal tDCS (Stagg and others 2009; Fig. 4).

Neuromodulators. The aftereffects of anodal tDCS are enhanced by the addition of amphetamine (AMP), but only in the absence of DMO, suggesting that the catecholaminergic system is specifically modulating NMDA-dependent LTP-like plasticity (Nitsche, Grundey, and others 2004). In addition, the aftereffects of anodal tDCS were considerably shortened by the addition of popranolol (PROP), a β-receptor antagonist (Nitsche, Grundey, and others 2004).

Increasing dopaminergic tone using L-DOPA reversed the increased excitability after anodal tDCS to a reduction in excitability, resulting in changes of the same direction and magnitude as cathodal tDCS (Fig. 3B; Kuo, Paulus, and others 2008). Selectively blocking D_2 receptors led to an abolition of the aftereffects of anodal tDCS (Nitsche and others 2006), demonstrating the importance of D2 receptors for this kind of plasticity. The conversion of the aftereffects of anodal tDCS, however, cannot be attributed solely to the effect of D_2 or D_1 receptors, since selective enhancement of both did not result in a similar effect (Monte-Silva and others 2009; Nitsche, Kuo, Grosch, and others 2009). Therefore, it appears that the ratio of D_1 to D_2 activity is important. In addition, however, these effects are complicated by a U-shaped dose-response curve, where

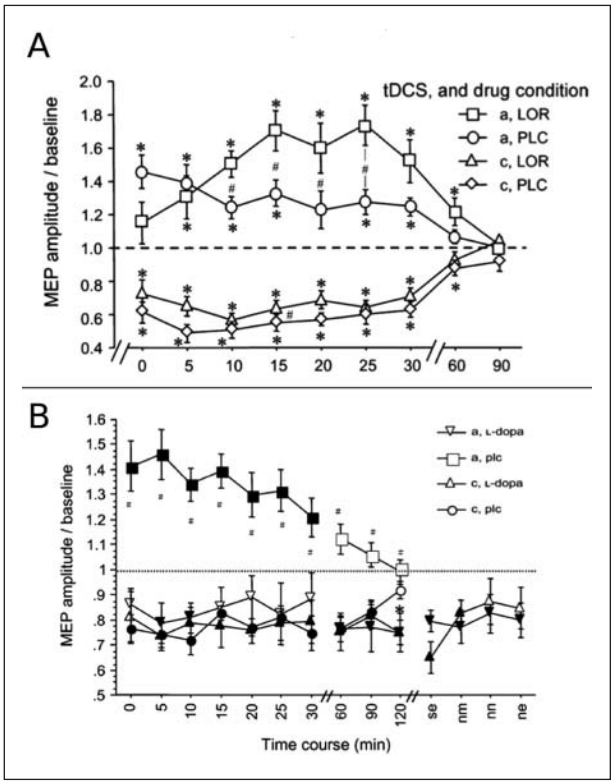

Figure 3. (A) Changes in motor evoked potential (MEP) amplitude induced by transcranial direct current stimulation (tDCS) in the presence of the GABA agonist lorazepam (LOR) or placebo (PLC). LOR led to a significant initial decrease in the cortical excitability after anodal tDCS, followed by a significant increase in magnitude, but not duration, of the effects compared with placebo. There is no significant modulation of the aftereffects of cathodal tDCS. Values given as a ratio to the baseline MEP size (mean ± SE). *Significant deviation from baseline; #significant difference between the placebo and drug condition (figure 2, Nitsche, Liebetanz, and others 2004). (B) Changes in MEP size induced by tDCS in the presence of the dopamine agonist L-DOPA or placebo (PLC). L-DOPA reversed the increase in excitability induced by anodal tDCS into a decrease and increased the duration but not the magnitude of the aftereffects of cathodal tDCS. Filled symbols indicate a significant deviation from baseline. *Significant difference between the placebo and drug condition (figure 1, Kuo, Paulus, and others 2008).

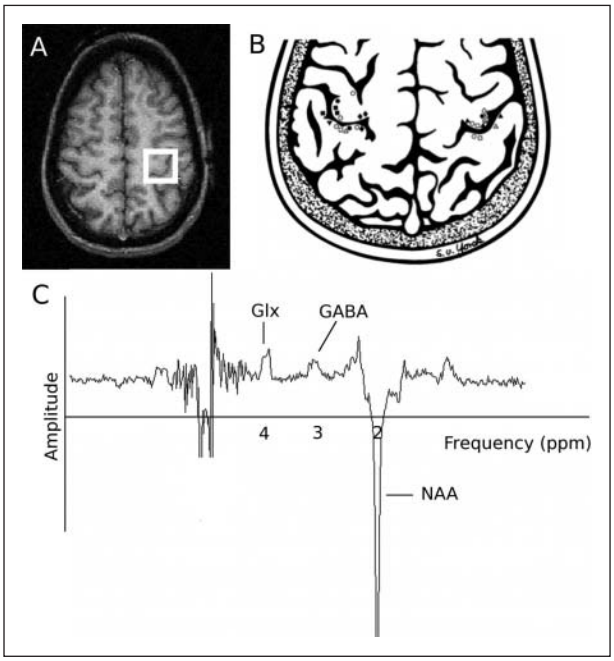

Figure 4. Single-voxel magnetic resonance spectroscopy is a noninvasive technique that allows accurate quantification of a given neurochemical within a defined volume of interest. (A) An axial slice demonstrating the location of the volume of interest within the left primary motor cortex. Spectra are acquired solely from this area. (B) A schematic drawing illustrating the motor hand activations, as determined by fMRI, in 10 healthy controls (figure 2, Yousry and others 1997). The location of the voxel of interest was centered on these areas. (C) A representative GABA-optimized spectrum from this voxel of interest. Individual neurochemicals are represented within the spectrum at characteristic frequencies (given as the dimensionless constant of parts per million [ppm]). GABA is seen at 3 ppm. The concentration of the neurochemicals is proportional to the area under the peak and is given as a ratio to a reference peak, for example (N-acetylaspartate).

low and high doses of the D_2 agonist Ropinerol (RP) abolished the aftereffects of anodal tDCS, although intermediate doses preserved them (Monte-Silva and others 2009).

Increase of cholinergic tone with administration of rivistigmine abolished the effects of anodal tDCS (Kuo and others 2007). In addition, there is a significant serotonergic modulation on the aftereffects of anodal tDCS, as citalopram (CIT), an SSRI, increased both the magnitude and duration of the aftereffects of anodal tDCS (Nitsche, Kuo, Karrasch, and others 2009).

In summary, the aftereffects of anodal tDCS are dependent on modulation of both GABAergic and glutamatergic synapses. The change in both SICI and ICF suggests that these changes occur in the intracortical interneurons within the cortex. The aftereffects of anodal tDCS are modulated by the catecholamines acetylcholine and serotonin.

Cathodal. It is difficult to know to what degree the aftereffects of cathodal tDCS are dependent on membrane polarization changes. Neither FLU nor CBZ modulate the effects of cathodal tDCS, although this may be for technical reasons, as discussed above (Nitsche, Fricke, and others 2003). MT was not altered by cathodal tDCS, although the I/O curve was, possibly suggesting a more widespread effect on the intracortical neurons (Nitsche and others 2005).

The aftereffects of cathodal tDCS are dependent on modulation of glutamatergic synapses: They were abolished by DMO (Nitsche, Fricke, and others 2003), cathodal stimulation led to a significant decrease in ICF (Nitsche and others 2005), and the concentration of glutamate was significantly decreased within the stimulated cortex, as measured by MRS (Stagg and others 2009). However, d-cycloserine (CYC), a specific NMDA agonist, does not modulate the aftereffects of tDCS (Nitsche, Jaussi, and others 2004), possibly due to hyperpolarization of the postsynaptic cell modification of the CYC binding site.

The evidence for modulation of GABAergic interneurons by cathodal tDCS is less clear. SICI was enhanced after stimulation (Nitsche and others 2005), but administration of LOR had no effect on the tDCS-induced aftereffects (Nitsche, Liebetanz, and others 2004). A decrease in GABA concentration was observed within the stimulated cortex after cathodal tDCS using MRS, although this may be explained by the close biochemical relationship between GABA and glutamate. The sole synthetic pathway for GABA in the human is from glutamate, via the enzyme glutamic acid decarboxylase. A significant reduction in the availability of the substrate, as seen here, would therefore lead to a highly correlated decrease in GABA (Stagg and others 2009).

Neuromodulators. The magnitude of LTD-like plasticity induced by cathodal tDCS is not modulated by NA to any significant degree: AMP did not alter either the magnitude or the duration of the aftereffects of cathodal tDCS, although the duration of effects was decreased by PROP (Nitsche, Grundey, and others 2004).

Application of L-DOPA had no effect on the magnitude of the inhibition induced by tDCS but significantly increased its duration up until the next evening (Fig. 3B; Kuo, Paulus, and others 2008). Blockade of the D_2 receptor subtype abolished the aftereffects of cathodal tDCS (Nitsche and others 2006). Conversely, the D_2 agonists PGL and medium-dose RP led to an increase in the duration, though not the magnitude, of the stimulation-induced inhibition (Monte-Silva and others 2009; Nitsche and others 2006). Therefore, the D_2 receptor appears to be of primary importance for tDCS-induced inhibitory plasticity. The relationship between D_2 receptor activation and inhibitory plasticity is not linear, however. An inverted U-shaped dose-response curve to increasing D_2 activity has been demonstrated, such that low and high doses of RP led to an abolition of the aftereffects of cathodal tDCS, whereas an intermediate dose led to lengthening of the cortical inhibition seen (Monte-Silva and others 2009).

Increasing cholinergic tone leads to an increase in the duration, but not the magnitude, of the aftereffects of cathodal tDCS (Kuo and others 2007). Moreover, increasing serotoninergic tone with CIT reversed the inhibition seen after cathodal tDCS to a facilitation (Nitsche, Kuo, Karrasch, and others 2009).

In summary, the aftereffects of cathodal tDCS are dependent on the modulation of the glutamatergic synapses. The change in ICF suggests that this involves the intracortical interneurons. The aftereffects of cathodal stimulation are modulated by dopamine, acetylcholine, and serotonin.

Interactions between tDCS and Motor Learning

Anodal tDCS applied over M1 during task performance leads to an improvement in motor learning in a number of tasks (Table 4). Here, we propose a theoretical framework for the cellular mechanisms by which this improvement might be expected to occur.

As discussed above, in the context of animal studies from within the neocortex, the aftereffects of anodal tDCS are presumably driven by activation of the NMDA receptors in the context of a decreased GABAergic tone. Activation of NMDA receptors will result in an increase in intracellular Ca^{2+} in the postsynaptic neuron. Differing levels of activation of the NMDA receptors result in different degrees of a rise in Ca^{2+} and have different effects on subsequent synaptic modulation. A small increase in postsynaptic Ca^{2+} leads to LTD, a moderate increase induces no synaptic modulation, and a greater increase induces LTP-like changes (Lisman 2001). The points at which the response of the postsynaptic cell changes are known as modification thresholds (θ_m; Fig. 5A).

Motor learning within M1 is also presumed to occur via LTP-like mechanisms dependent on the modulation of NMDA receptors. The improvement seen in behavioral measures of learning with synchronous application of anodal tDCS might be hypothesized to occur via an additive effect on postsynaptic Ca^{2+} levels, especially as anodal tDCS also opens voltage-gates Ca^{2+} channels, therefore leading to a greater synaptic modification over the time scales used for these experiments. The animal literature would suggest that sufficient modulation of NMDA receptors to allow sufficient increases in calcium to induce LTP is possible only in the presence of a decreased inhibitory tone from the GABAergic interneurons and can be modulated by the catecholamines ACh and 5-HT, hence explaining the pattern of dependence on neuromodulators.

Modification thresholds are altered by prior experience. Homeostatic or metaplasticity mechanisms have been proposed to operate to maintain neural activity within a useful dynamic range (Bienenstock and others 1982; Sejnowski 1977). The Bienenstock-Cooper Munroe theory assumes that the value of the modification threshold is not fixed but varies as a function of the previous activity of the

Table 4. Behavioral Studies

Study	Task	Active Electrode	Reference Electrode	Effect of Anodal tDCS	Effect of Cathodal tDCS
Online					
Rosenkranz and others (2000)	TMS practice-induced plasticity	M1	Contralateral orbit	↓	↓
Nitsche, Schauenburg and others (2003)	Implicit sequence learning	M1	Contralateral orbit	↑	↔
		Premotor	**Contralateral orbit**	↔	↔
		Prefrontal	**Contralateral orbit**	↔	↔
Lang and others (2003)	Consolidation of motor learning	M1	Contralateral orbit	↓	↔
Boggio and others (2006)	Jebson Taylor Task	Nondominant M1	Contralateral orbit	↑	NS
Vines and others 2008	Explicit sequence learning	M1	Contralateral orbit	↔	NS
		M1	M1	↑	NS
Reis and others (2009)	Visuomotor tracking	M1	Contralateral orbit	↑	↔
Galea and Celnik (2009)	Practice-dependent plasticity	M1	Contralateral orbit	↑	↔
Hunter and others (2009)	Internal Model Formation	M1	Contralateral orbit	↑	NS
Offline					
Antal and others (2008)	Visuomotor tracking task	M1	Contralateral orbit	↑	↑
		Cz	**Contralateral orbit**	↔	↔
Kuo, Unger and others (2008)	Implicit sequence learning	M1	Contralateral orbit	↓[a]	↔

Summary of behavioral studies investigating the effects of transcranial direct current stimulation (tDCS) to M1. Control experiments are entered in bold. An improvement in behavioral measures was seen in the majority of studies with online anodal tDCS. The study by Rosenkranz and others (2000) differs from the other studies described as it used a task involving practice-dependent plasticity. Lang and colleagues (2003) used an explicit sequence learning task and described a trend toward an improvement in task performance during tDCS but a significant increase in errors during recall of the sequence. The differences in methodology between these two studies and the others in the table may explain the worsening of learning with anodal tDCS observed in these two reports. No consistent effect of cathodal tDCS on learning has been observed. "Online" refers to studies in which the tDCS and task performance are synchronous; "offline" where tDCS is applied prior to performance of the task. TMS = transcranial magnetic stimulation; NS = not studied.

a. Only in the presence of d-cycloserine; no change was seen without pharmacological intervention.

postsynaptic neurons (Fig. 5B) and has been demonstrated experimentally in the visual cortex of the rat (Kirkwood and others 1996). Similarly, the effects of a train of TMS pulses normally insufficient to induce excitability changes become inhibitory if applied after anodal tDCS and excitatory if applied after cathodal tDCS (Lang and others 2004; Fig. 5C).

Prior application of anodal tDCS has been shown to suppress subsequent learning of an implicit learning paradigm, although only in conjunction with application of the partial NMDA receptor agonist CYC (Kuo, Unger, and others 2008). CYC increases the duration of the effects of anodal tDCS, thereby potentially modulating the modification threshold sufficiently to mean that the calcium shift induced by motor learning was no longer sufficient to induce LTP.

NMDA-dependent LTD can be induced by low-frequency activity in the presynaptic neuron with hyperpolarization of the postsynaptic neuron (Debanne and others 1995; Fregnac and others 1994), a plausible mechanism underlying the aftereffects of cathodal tDCS. The lack of an interaction between cathodal tDCS and motor learning may be explained in a number of ways: It may be that our behavioral measures are relatively insensitive to small changes induced by tDCS or that the LTP-like synaptic modulation that occurs during learning is of sufficiently greater strength to be able to overcome the effects of hyperpolarization.

Differences between Techniques

Although the aftereffects of tDCS may share common features with other forms of LTP-like plasticity in the neocortex, there may also be important differences. Plasticity induced by paradigms such as motor learning will be induced only in the minority of synapses that are directly involved in a specific task. The depolarization induced by tDCS is likely to affect many of the synapses within the stimulated cortex, although these effects are not uniform across the cortex, as discussed earlier, but depend on the orientation, type, and depth of the neuron in question.

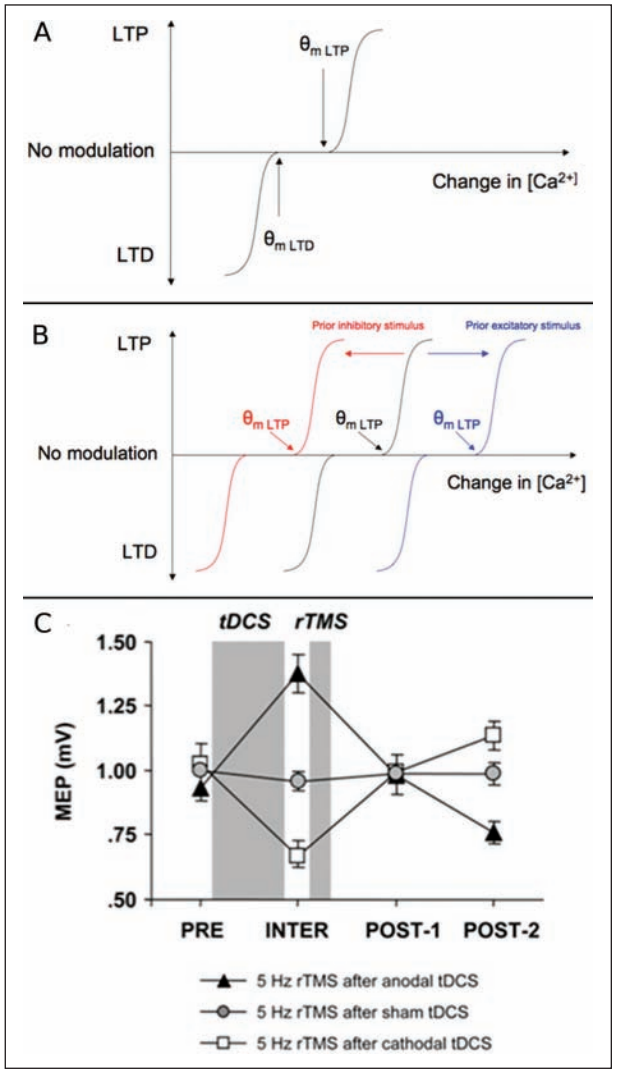

Figure 5. (A) The change in Ca^{2+} in the postsynaptic neuron modulates the response of that synapse in three distinct ways. Small rises in Ca^{2+} lead to induction of long-term depression (LTD), intermediate rises lead to no synaptic modification, and large increases lead to induction of long-term potentiation (LTP). The points at which these responses change are known as the modification thresholds (θ_m). (B) The modification thresholds are modulated by prior activation of the neuron. Prior inhibitory stimulation will shift the θ_m sufficiently that a Ca^{2+} increase that previously would have led to LTD induction will now lead to LTP induction. Prior excitatory stimulation shifts the θ_m in the other direction, meaning that LTD is now more likely than LTP. This has been proposed as the basis for homeostatic mechanisms within the cortex. (C) Experimental evidence for homeostatic mechanisms. Five-Hertz repetitive transcranial magnetic stimulation (rTMS) alone does not modulate cortical excitability, as assessed by a change in the amplitude of motor evoked potentials (MEPs). However, when preceded by anodal transcranial direct current stimulation (tDCS; triangles), the same rTMS protocol led to decrease in MEP size. Preconditioning with cathodal tDCS (squares) led to a subsequent increase in MEP size after rTMS (figure 1, Lang and others 2004).

In addition, induction of classical LTP-like plasticity requires, as Hebb stated, both the presynaptic and postsynaptic cell to repeatedly fire in synchrony. However, tDCS is a subthreshold technique that does not induce presynaptic or postsynaptic cell firing directly. In addition, classical LTP-like induction protocols involve short, phasic bursts of activity, unlike the tonic changes in membrane polarization induced by minutes of tDCS application. It may be, therefore, that the changes induced in cortical neurons by tDCS are not identical to those induced by other protocols, but the evidence we have currently for the effects of tDCS at a cellular level is limited.

It is not easy to model the exact tDCS stimulation parameters in animal models, and as discussed above, much early work was performed with higher current intensities than are used in tDCS, and via cortical electrodes, meaning caution must be exercised when interpreting findings from tDCS in light of these results. Recent studies have been performed using a specially designed rat model of tDCS, which is designed to model the effects of tDCS in the humans (Liebetanz and others 2006, 2009; Nitsche and others 2006), and this model may provide useful insights into the cortical effects of tDCS. In particular, it may allow detailed investigation into the hypothetical framework for the interaction between tDCS and motor learning as detailed above.

Conclusion

This review aimed to examine the evidence for the physiological basis of tDCS and in particular the evidence that tDCS modulates synaptic strength within the motor cortex. To this end, we have summarized the evidence from animal and human studies using low-level direct currents to modulate cortical plasticity.

Animal studies established that polarization of the cortex is capable of modulating cortical excitability and neuronal firing rates and that these effects can outlast the stimulation period for several hours, as long as critical stimulation parameters are met. Studies in the human suggest that tDCS modulates cortical excitability during stimulation by nonsynaptic changes of the cells, but there is increasing evidence that the aftereffects of tDCS are driven by synaptic modification.

These findings taken together suggest that tDCS does indeed modulate synaptic strength within the cortex, and evidence points to the involvement of intracortical neurons. The similarities between these changes and those involved in the induction of LTP-like plasticity in the M1 strongly suggest that synaptic plasticity is occurring and that it may therefore be possible, if the correct stimulation parameters are determined, to induce long-lasting excitability changes.

Within this context, we have proposed a framework by which tDCS may modulate motor learning. Although grounded in literature, this is a hypothetical framework that

appears to provide the best account for the effects of tDCS. However, it has not been tested directly. The difficulty of modeling tDCS in preparations that would allow detailed study at a cellular level means that much of the evidence discussed in this review is indirect. Further work using recently developed rat models of tDCS should allow for a more detailed understanding of the intracortical effects to be reached. A more thorough understanding of the cellular changes underlying the effects of tDCS is essential as tDCS begins to realize its promise as a clinical tool.

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