CHAPTER 12

Neurophysiological Effects of Transcranial Direct Current Stimulation

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INTRODUCTION

Transcranial direct current stimulation (tDCS) is a technique of brain stimulation that has been increasingly investigated as a clinical tool for the

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treatment of neuropsychiatric disorders. The growing interest in this technique underscores the importance of elucidating its underlying neurophysiology. Here we provide a review of research on the neurophys iological effects of tDCS. Studies from electrophysiology and transcranial magnetic stimulation have shown that tDCS can modulate cortical excitability in a polarity dependent fashion. Generally, anodal stimulation increases cortical excitability, while cathodal stimulation decreases it. Furthermore, these changes in cortical excitability are dependent on cur rent density and stimulation duration. tDCS has been shown to modulate activity in both the motor and visual cortices, and more recently has been shown to directly influence excitability of the spinal cord. Anodal tDCS has been shown to increase intracortical facilitation and diminish intracor tical inhibition, while cathodal tDCS has been shown to have the reverse effect. tDCS has also been shown to modulate transcallosal inhibition and may be a promising tool for enhancing the effects of paired associative stimulation. Neuropharmacological studies suggest that the immediate effects of tDCS are due to modulation of neuronal membrane potentials at subthreshold levels, thus increasing or decreasing the rate of action potential firing. Long term effects, lasting for periods well beyond the time of stimulation, likely involve NMDA receptor dependent mechan isms. Future research should utilize alternative experimental techniques, study the neurophysiology underlying the clinical effects of tDCS, investi gate improved tDCS technology and parameters of stimulation, and examine whether the neurophysiological effects of tDCS vary in popula tions with neuropsychiatric conditions.

THE GROWING FIELD OF BRAIN STIMULATION

Applications of brain stimulation have been rapidly growing in the neuro logical sciences. Deep brain stimulation allows for the precise stimulation of deep neural structures such as thalamic, subthalamic, and pallidal nuclei. Such interventions are used clinically, for example, in the treatment of advanced Parkinson's disease, providing excellent results in controlling dystonias and tremors (Limousin & Martinez Torres, 2008) and holding some promise for the treatment of mood disorders (Mayberg et al., 2005) and obsessive–compulsive disorder (Lakhan & Callaway, 2010). At the level of the cortex, electrodes placed in the epidural area above the motor cortex are used for motor cortex stimulation, a clinical treatment shown to assuage many forms of chronic neuropathic pain (Lima & Fregni, 2008).

While these methods of brain stimulation have demonstrated remarkable progress, one limitation is the need for surgical penetration of the skull and brain, an expensive procedure that carries considerable risk.

Due to the downsides of surgical approaches, methods of neurofeed back and transcranial brain stimulation have become substantially more appealing for their capacity to safely modulate brain activity in a manner that is both more accessible and affordable. Neurofeedback is a method of endogenous neuromodulation in which the subject responds to real time measurements of brain activity such as electroencephalography (Egner & Sterman, 2006; Gevensleben et al., 2010). In recent years, two external neuromodulatory techniques have been revisited that stimulate the human brain through the intact scalp: transcranial magnetic stimulation (TMS) and low intensity transcranial electrical stimulation. Substantial research has been devoted to TMS, a method of brain stimulation that involves using a large, rapidly changing magnetic field to induce electrical stimulat ing currents in the brain. However, growing evidence suggests that transcranial electrical stimulation, which has different mechanisms of action, may also be a powerful and cost effective approach to neuromodu lation (Priori, Hallett, & Rothwell, 2009; Zaghi, Heine, & Fregni, 2009). Increased understanding of the neurophysiology underlying transcranial direct current stimulation (tDCS), a form of low intensity transcranial electrical stimulation, has further stimulated research into clinical applica tions of this technology.

Among the various techniques of brain stimulation, tDCS stands out as one of the simplest in design. tDCS involves the administration of direct current through the scalp. A battery powered current generator capable of delivering small currents (usually less than 10 mA) is attached to two sponge based electrodes. The sponge electrodes are soaked, applied over the hair to the scalp, and held in place by a non conducting rubber band affixed around the head. Current is injected through the scalp and skull to change the membrane potentials of neurons in the underlying cortex, resulting in real time neurophysiological effects (see Figure 12.1). Importantly, tDCS only modulates neuronal activity and does not actually stimulate action potentials.

tDCS has been valuable in exploring the effects of cortical modulation on various neural networks implicated in language (Floel, Rosser, Michka, Knecht, & Breitenstein, 2008), sensory perception (Boggio, Zaghi, Lopes, & Fregni, 2008), decision making (Fecteau et al., 2007), memory (Fregni, Boggio, Nitsche et al., 2005), and emotional pain (Boggio, Zaghi, &

Figure 12.1 Transcranial direct current stimulation. In tDCS, two sponge-enclosed rubber electrodes are soaked in saline and applied to the scalp. Small wires attach the electrodes to a battery-powered direct current (DC) generator. In series with the DC generator, there is an amperemeter, which allows the tDCS operator to alter the internal resistance of the device with a dial to reach a target current ranging from 0.5 mA to 2.0 mA. Stimulation diffuses through the scalp and skull, resulting in real-time neurophysiological effects.

Fregni, 2009), among other cognitive processes. tDCS has also been introduced as an effective tool to alleviate chronic pain. Preliminary small sample size studies and case reports with tDCS have shown initial positive results in modulating chronic pain in patients with terminal cancer (Silva et al., 2007), fibromyalgia (Fregni, Gimenes et al., 2006), and traumatic spinal cord injury (Fregni, Boggio, Lima et al., 2006). Recent studies suggest that tDCS may also facilitate motor and working memory rehabilitation following stroke, showing significant effects lasting two weeks (Boggio, Nunes et al., 2007; Jo et al., 2009; Nowak, Grefkes, Ameli, & Fink, 2009). Additionally, tDCS might be an interesting tool for modulating mood and other cognitive processes such as craving in substance abuse (Boggio, Bermpohl et al., 2007; Boggio, Sultani et al., 2008; Fregni et al., 2008). (For review of clinical applications of tDCS, see Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010.)

Although these recent studies show encouraging results in the clinical arena, it is critical that we understand the underlying neurophysiology of tDCS so that we can optimize the parameters of stimulation and use of this technique. The field of neurophysiology includes the study of nervous system function with a scope that ranges from effects on membranes and cells to systems and behavior. Here we provide an up to date review of

current research on the neurophysiological effects of tDCS and provide directions for future research in the field.

ELECTROPHYSIOLOGY OF tDCS

Historical Perspective

The utilization of low intensity electrical stimulation likely had its origins in the eighteenth century, with studies of galvanic (i.e., direct) current in animals and humans by Giovanni Aldini and Alexandro Volta (Goldensohn, 1998; Priori, 2003). Yet because such stimulation induced variable results, or sometimes none at all, the use of low intensity direct current was progressively abandoned in the first half of the 20th century with the introduction of neuropsychiatric drugs and other forms of brain stimulation such as electroconvulsive therapy (Priori, 2003), which involves transcranial stimulation at substantially higher intensities (>500 mA).

At the turn of the millennium, increasing interest in TMS, which was first developed in 1985 (Barker, Jalinous, & Freeston, 1985), revitalized interest in other forms of transcranial brain stimulation such as tDCS. Using TMS induced motor evoked potentials as a marker of motor cortex excitability, Nitsche and Paulus (2000) demonstrated the possibility of modulating cortical excitability with tDCS. They found that weak direct current applied to the scalp was associated with excitability changes of up to 40% that lasted several minutes to hours after the end of stimulation (Nitsche & Paulus, 2000). Importantly, in this initial seminal study, they showed that electrode montage was essential for determining the effects of tDCS. A mathematical model then showed that while around half of the tDCS current diffuses across the scalp, the current distribution penetrating the scalp and skull is indeed sufficient to modify the transmembrane neuronal potential and influence the excitability of individual neurons without actually eliciting an action potential (Miranda, Lomarev, & Hallett, 2006; Wagner, Valero Cabre, & Pascual Leone, 2007). As our understanding of the neurophysiology of tDCS has improved over the past decade, we can now in hindsight appreciate the mixed results produced in studies on the effects of tDCS that took place in the mid twentieth century (Murphy, Boggio, & Fregni, 2009).

TMS is a method of neurostimulation and neuromodulation that has been central to the investigation of the neurophysiological effects of tDCS, as it provides a measure of cortical excitability. We therefore begin our discussion of the electrophysiology of tDCS with a brief discussion of TMS.

TMS as a Tool for Measuring the Effects of tDCS

TMS was introduced about 25 years ago by Barker et al. (1985) who showed that it is possible to activate the corticospinal tract by applying a short lasting magnetic field over the intact scalp in awake human subjects (Barker et al., 1985). TMS is a technique of brain stimulation that uses the principle of electromagnetic induction to induce currents in the brain. A coil of copper wire encased in plastic is placed on the subject's scalp overlying the region of the brain to be stimulated. As current passes through the coil, a magnetic field is generated in a plane perpendicular to the coil. The current passed is strong but extremely brief, producing a magnetic field that changes rapidly in time, reaching 2 Tesla in about 50 μs and decaying back to 0 Tesla in the same amount of time. For single pulse stimulators, magnetic fields of 1 4 Tesla in strength and durations of approximately 1 millisecond are typically used. The quickly changing magnetic field penetrates the skin and skull of the subject unimpeded, without causing discomfort, and induces a secondary electrical current in the subject's brain that is strong enough to depolarize cellular membranes and induce neuronal activity (Fregni, Boggio, Valle et al., 2006; Zaghi et al., 2009) (see Figure 12.2).

When TMS is applied to the motor cortex at suprathreshold intensity, it generates electrical currents in the motor cortex, which are observed as a contraction of muscles on the contralateral side of the body. TMS does not activate corticospinal neurons directly, but instead activates interneur ons as demonstrated by research showing that TMS induces a cortico spinal volley with indirect waves rather than direct waves. It is possible then to measure the latency and amplitude of the evoked potentials in electromyographic (EMG) signal recordings from the muscles, referred to as motor evoked potentials or MEPs as a measure of general corticospinal excitability. Since MEPs measure cortical excitability at any given moment in time, valuable information about the electrophysiology of the corti cospinal tract can be acquired using this method (Ilmoniemi et al., 1997; Petersen, Pyndt, & Nielsen, 2003). Similarly, TMS can be employed to evoke the perception of visual phosphenes (sensation of light due to a stimulus other than light rays) when pulses are applied to the occipital cortex.

TMS can be used to study other aspects of motor cortex function such as intracortical facilitation and inhibition (ICF and ICI, respectively) and bihemispheric interactions via transcallosal inhibition using paired pulse

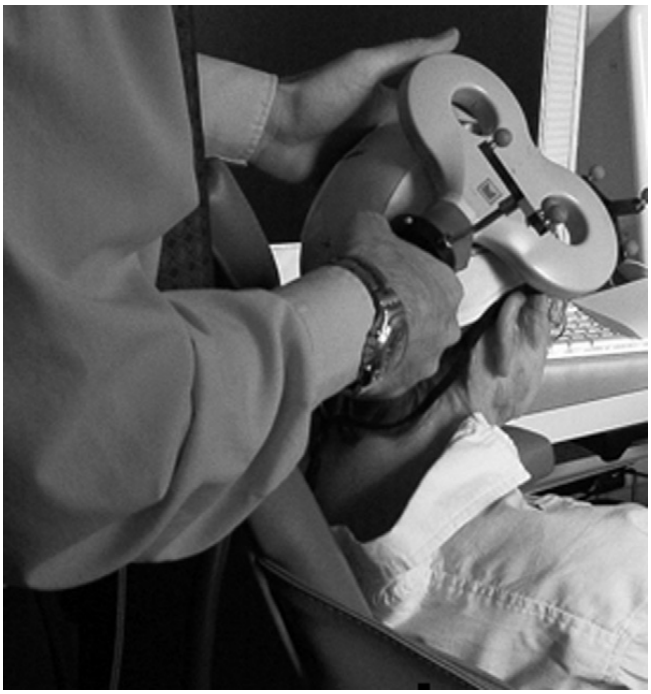

Figure 12.2 Transcranial magnetic stimulation. In TMS, a coil of copper wire encased in plastic is rested on the subject's scalp overlying the area of the brain to be stimulated. As current is delivered through the coil, a magnetic field reaching 2 Tesla is generated in a plane perpendicular to the coil. This rapidly changing magnetic field penetrates the skin and skull of the subject unimpeded and induces a secondary electrical current in the subject's brain that is strong enough to depolarize cellular membranes and induce neuronal activity.

TMS. Paired pulse stimulation involves administration of two consecutive stimuli using the same coil for ICF and ICI, or two coils for transcallosal inhibition. Additionally, when a TMS pulse is administered to the occipi tal cortex during the presentation of a visual stimulus, it is possible to record changes in the waveform and topography of visual evoked poten tials (VEP) in electroencephalography (EEG) recordings. It is also possible to measure cortical potentials induced by TMS using EEG (Miniussi & Thut, 2010). This combination of TMS and high resolution EEG pro vides a remarkably powerful tool for the assessment of corticocortical and interhemispheric functional connections (Thut, Ives, Kampmann, Pastor, & Pascual Leone, 2005). Moreover, the mapping and localization of neuronal responses to TMS stimulation of motor and visual cortices are substantially affected by baseline cortical excitability, execution of neuropsychological tasks, and medication use (Fregni, Boggio, Valle et al., 2006). Thus, TMS

can be used to study the electrophysiological properties of transcranial direct current stimulation (Fregni, Boggio, Valle et al., 2006; Thut et al., 2005).

Transcranial Delivery of Current

The first consideration in understanding the neurophysiology of tDCS is to appreciate how currents applied with tDCS might affect neuronal activity. That is, how does direct current applied at the scalp translate into modulation of neuronal excitability? The central idea is that the current applied at the scalp produces an extracellular voltage gradient at the level of the cortex that alters the potential difference across neuronal mem branes. A step by step, detailed explanation follows.

In tDCS, two (or more) relatively large anode and cathode sponge enclosed rubber electrodes are applied to the scalp. The sponge electrodes usually measure about 20–35 cm^2 in area. Small wires attach the electro des to a battery powered direct current (DC) generator. The DC genera tor can be powered with as little as two AA batteries (~3 volts) or a single 9 volt battery. In series with the DC generator, there is an ampere meter, which allows the tDCS operator to alter the internal resistance of the device with a dial to reach a target current. In tDCS, target currents usually range from 0.5 mA to 2.0 mA.

The objective of tDCS is for low amplitude direct currents to pene trate the skull and enter the brain. However, because current will flow in the path of least resistance, there is substantial shunting of current at the scalp. In this context, the current density plays an important role in deter mining the extent to which the applied current actually penetrates the skull to enter the brain.

By means of a magnetic resonance imaging (MRI) derived finite ele ment model specific to tDCS, Wagner et al. (2007) tested various elec trode montages to analyze the role that tissue heterogeneity and anatomical variations played on the final current density distribution along the scalp and at the cortex (Wagner, Fregni et al., 2007). In one modeling experiment, the electrode area was varied from 1 to 49 cm^2 while main taining fixed electrode placement (anode over the right M1 and cathode over the left supraorbital area) and non variable constant current flow of 1 mA. Although the applied current densities (i.e. current intensity/elec trode size) ranged from 10 A/m^2 (for the 1 cm^2 electrode) to 0.21 A/m^2 (for the 49 cm^2 electrodes), the shunting (i.e., the flow of current along

the scalp surface as opposed to the cortex) effects were considerably larger for the 1 cm^2 electrodes compared to the other montages. Current densi ties in the skin were as much as 86 times greater than those seen in the cortex for the 1 cm^2 electrodes compared to a factor of approximately 9 for the 49 cm^2 electrodes. In other terms, 98.8% of the current was shunted through the skin vs. the cortex with use of the small 1 cm^2, but only 89.5% of the current was shunted through the skin with use of the larger 49 cm^2 electrodes. This shows that roughly 1.2% of the 10 A/m^2 (or 0.12 A/m^2) and 10.5% of the 0.21 A/m^2 current density (or 0.021 A/m^2) does penetrate to the level of the cortex with the use of small and large electrodes, respectively. Essentially, greater shunting occurs with smaller electrode areas, although a greater final cortical current density can be achieved. According to the study, the maximum local cortical current densities in this experiment ranged from 0.081 to 0.141 A/m^2, which were distributed in a non linear fashion reflective of the relative hetero geneous anatomical and geometrical properties of the brain tissue. With varying electrode placement and constant current source (1 mA/35 cm^2 surface electrode area, or 0.29 A/m^2), the maximum local cortical current densities ranged from 0.077 to 0.20 A/m^2, with current densities of oppo site polarity underlying the cathode and anode electrodes. Scalp current densities ranged from 8.85 to 17.25 times larger in magnitude than the cortical current densities (89.8% to 94.5% shunting rate).

The above discussion underscores the fact that low amplitude current applied at the scalp can indeed penetrate to the level of the cortex. It is important to keep in mind that this current flow is reflective of an electric potential (or voltage gradient) which allows for the flow of ions between the two electrodes. On a cellular level, the voltage gradient establishes opposing polarities at either end of the neurons affected by the electric field. This creates a difference in the transmembrane potential along the neuronal membrane and so causes current to flow across the membrane and along the inside of the neuron according to the resistances presented by properties of the neuronal membrane and intracellular space (Jefferys, Deans, Bikson, & Fox, 2003). This current flow modulates the neuronal membrane potential and therefore results in changes to spontaneous neuronal activity.

Current Density

Neurons and other excitable cells produce two types of electrical poten tial. The first is a non propagated local potential called an electrotonic potential, which is due to a local change in ionic conductance (e.g.,

synaptic activity that engenders a local current). When it spreads along a stretch of membrane, the electrotonic potential decrements to become exponentially smaller. The second form of electric potential is a propagated impulse called an action potential. Electrotonic potentials represent changes to the neuron's membrane potential that do not lead directly to the generation of new current by action potentials. Neurons that are small in relation to their length (such as some neurons in the brain) have only electrotonic potentials; longer neurons utilize electrotonic potentials to trigger the action potential.

This discussion becomes important as we continue to appreciate how tDCS affects neuronal excitability. In contrast to TMS, which can both induce action potentials (neurostimulation) and modulate neuronal activity by influencing electrotonic potentials (neuromodulation) or inducing secondary synaptic changes, tDCS is strictly a neuromodulatory technique. tDCS does not induce action potentials because of limitations in cortical current density. As a reference point, cortical current density magnitudes are far lower than action potential thresholds: 0.079 to 0.20 A/m^2 induced by tDCS as compared to 22 to 275 A/m^2 required to trigger an action potential (Tehovnik, 1996). Thus, the effects of tDCS on cortical neurons are transmitted as electrotonic potentials only, which spread along the neuron, altering the likelihood with which that neuron may reach an action potential via temporal and spatial summation with other electrotonic synaptic inputs. This underscores the point that the magnitude of the current density has important implications in the neuromodulatory outcome of stimulation. Indeed, it has been shown that larger current densities result in stronger effects of tDCS (Boggio et al., 2006; Iyer et al., 2005; Nitsche & Paulus, 2000), while lower current densities (less than 0.24 A/m^2) for a few minutes do not induce any significant biological changes (Paulus, 2004).

Stimulation Duration

Interestingly, depending on the duration of stimulation, the effects of tDCS may outlast the stimulation period. In a study by Nitsche and Paulus (2000), it was shown that a stimulus duration of at least 3 minutes at 1 mA (35 cm^2 surface electrode area, 0.29 A/m^2) or an intensity of 0.6 mA (35 cm^2 surface electrode area, 0.17 A/m^2) for 5 minutes could induce measurable after effects in cortical excitability (Nitsche & Paulus, 2000). Using TMS induced MEPs as a measure of cortical excitability, Nitsche

and Paulus (2000) demonstrated a clear increase of MEP amplitude and endurance of the effect with rising stimulus duration and intensity. Indeed, the duration of stimulation plays a significant role in determining: (1) the occurrence and (2) the duration of after effects in humans and animals (Bindman, Lippold, & Redfearn, 1964; Nitsche, Nitsche et al., 2003; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). For example, whereas 5 and 7 minute tDCS results in after effects lasting for no longer than 5 minutes, 9 to 13 minute tDCS results in after effects lasting from 30 to 90 minutes, respectively (Nitsche & Paulus, 2001). Therefore, when we discuss electrophysiological effects of tDCS it is important to distinguish between: (1) immediate effects (e.g., anodal tDCS as excitatory, cathodal tDCS as inhibitory); and (2) the after effects of stimulation (e.g., facilitation vs. inhibition of activity) as they may be related to different mechanisms of action (e.g., membrane vs. synaptic mechanisms).

While the above neurophysiological studies only examined variation in duration of a single session of tDCS, behavioral evidence suggests that repeating sessions of tDCS over several consecutive days can enhance the effects of tDCS as well (Boggio, Nunes et al., 2007). Boggio et al. (2007) examined improvement of motor performance in stroke patients following four weekly sessions of tDCS and five consecutive daily sessions of tDCS. In both experimental paradigms, they found significant motor function improvement after either cathodal tDCS of the unaffected hemisphere or anodal tDCS of the affected hemisphere when compared to sham tDCS. Importantly, while they did not find a significant cumulative effect associated with weekly sessions of tDCS, consecutive daily sessions of tDCS were associated with significant improvement over time that was sustained for 2 weeks after treatment. Future neurophysiological studies should confirm whether the neuromodulatory effects of tDCS could indeed be enhanced by consecutive daily sessions.

Stimulation Polarity

Direct current appears to modulate spontaneous neuronal activity in a polarity dependent fashion. For example, anodal tDCS applied over the motor cortex increases the excitability of the underlying motor cortex, while cathodal tDCS applied over the same area decreases it (Nitsche & Paulus, 2001; Wassermann & Grafman, 2005). Similarly, anodal tDCS applied over the occipital cortex produces short lasting increases in visual cortex excitability (Antal, Kincses, Nitsche, & Paulus, 2003; Lang et al.,

2007). Purpura and McMurtry (1965) showed in an animal model that upon anodal stimulation membranes are depolarized at a subthresh old level, whereas upon cathodal stimulation they are hyperpolarized (Purpura & McMurtry, 1965). Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and while anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitabil ity, the direction of polarization depends strictly on the orientation of axons and dendrites in the induced electric field.

In vitro experiments with slices of tissue from mammalian hippocam puses show that electric fields applied to brain tissue affect cellular proper ties in a predictable fashion (Jefferys et al., 2003). Specifically, the electric fields hyperpolarize the ends of cells closest to the negative part of the field (cathode), and depolarize the ends closest to the positive part (anode). In the case of neurons, this change in excitability results from alterations in the capacitance of the neuronal membrane. Indeed, changes to the capacitance are induced by an accumulation of charges along the conducting surface of the neuronal membrane due to the presence of the applied electric field. As charge builds on the outer surface of the neuro nal membrane, charges of opposite polarity build up on the inner surface of the neuronal membrane, and the charges are separated by the insulating lipid bilayer. In this way, the neuronal membrane functions as an electric capacitor (by storing and separating charges) creating an electric field that in turn induces a directional capacitative current within the neuron. The polarity dependent storage of charges along the neuronal membrane and the resulting current are at the heart of the depolarizing and hyperpolariz ing differences between anodal and cathodal tDCS.

How these changes in transmembrane potential are distributed depends on the length, size, and geometry of the neuron, in addition to the pattern of dendritic arborization and relative orientation of axons, den drites, and soma in the applied electric field. Although such properties of the neurons vary widely across the nervous system, a recent experiment by Radman et al. (2009) in rat cortical neurons suggests that the soma of layer V pyramidal cells are individually most sensitive to polarization by opti mally oriented subthreshold fields. Moreover, Radman et al. (2009) also reveal that cortical layer V/VI neurons had the lowest absolute action potential thresholds. This suggests that while the electric field induced by tDCS likely has sensitizing effects at the dendrites of neurons in all six cor tical layers (Radman, Datta, Ramos, Brumberg, & Bikson, 2009), it is the soma of the neurons in layers V and VI that are most susceptible to the

polarizing and excitability modulating effects of tDCS (Radman, Ramos, Brumberg, & Bikson, 2009).

Importantly, anatomical changes due to pathology can significantly alter the current distribution induced by tDCS. For instance, in subjects with stroke, the affected cortical area is usually replaced by cerebrospinal fluid, which has a high conductance, and current can accumulate on the edges of cortical stroke lesions (Wagner, Fregni et al., 2007). Therefore, in cases of pathologies that affect neuroanatomy, such as stroke or traumatic brain injury, individual modeling might be recommended before tDCS application.

Stimulation Site

The location of the electrode placement in tDCS is critically important because placement of the electrodes in different areas will result in distribution of current density to those respective areas of the brain. Indeed, imaging studies confirm that the polarizing effects of tDCS are generally restricted to the area under the electrodes (Nitsche, Liebetanz et al., 2003; Nitsche, Niehaus et al., 2004). Stimulation of motor cortex (M1), occipital cortex (V1), somatosensory cortices, and dorsolateral prefrontal cortex all have been shown to deliver site specific and differential effects on a gamut of cognitive, behavioral, psychosomatic, and electrophysiological tests (Zaghi et al., 2010). (It is worth noting that the position of the reference electrode is as important as the stimulating electrode for inducing the proper amount of current under the stimulating electrode.) Additionally, some evidence suggests that tDCS can have highly focal effects. In a study examining the combined effects of tDCS and peripheral nerve stimulation, Uy and Ridding (2003) optimized (using TMS) the site of tDCS for the first dorsal interosseous muscle and observed significant excitability changes for this muscle, but not the nearby abductor digiti minimi and flexor carpi ulnaris muscles (Uy & Ridding, 2003). A recent modeling study, however, has suggested that electric current might actually have its peak between the two electrodes (Datta et al., 2009).

While the polarizing effects of tDCS are generally confined to the areas under and surrounding the electrodes, the functional effects appear to perpetuate beyond the immediate site of stimulation. That is, tDCS induces distant effects that go beyond the direct application of current, likely via the influence of a stimulated region on other neural networks. For example, anodal tDCS of premotor cortex increases the excitability of the ipsilateral

motor cortex (Boros, Poreisz, Munchau, Paulus, & Nitsche, 2008), and stimulation of the primary motor cortex has inhibitory effects on contralateral motor areas (Vines, Cerruti, & Schlaug, 2008). This supports the notion that tDCS has a functional effect not only on the underlying corticospinal excitability but also on distant neural networks (Nitsche et al., 2005). Indeed, fMRI studies reveal that although tDCS has the most activating effect on the underlying cortex (Kwon et al., 2008), the stimulation provokes sustained and widespread changes in other regions of the brain as well (Lang et al., 2005). EEG studies support these findings, showing that stimulation of a particular area (e.g., frontal cortex) induces changes to oscillatory activity that are synchronous throughout the brain (Ardolino, Bossi, Barbieri, & Priori, 2005; Marshall, Molle, Hallschmid, & Born, 2004).

Hence, this evidence suggests that the effects of DC stimulation are site specific but not site limited. That is, stimulation of one area will likely have effects on other areas, most probably via networks of interneuronal circuits (Lefaucheur, 2008). This phenomenon is not surprising given the neuroanatomic complexity of the brain, but it raises interesting questions as to: (1) how the effects are transmitted; and (2) whether the observed clinical effects (e.g., pain alleviation) are mediated primarily through the area of the cortex being stimulated or secondarily via activation or inhibition of other cortical or subcortical structures (Boggio, Zaghi, & Fregni, 2009; Boggio, Zaghi, Lopes et al., 2008). For instance, Roche et al. (2009) demonstrated that anodal tDCS of the motor cortex modifies excitability at the level of the spinal cord by showing that tDCS increases reflexive inhibition directed from the extensor carpi radialis to flexor carpi radialis, which is mediated by inhibitory interneurons located in the spinal cord (Roche, Lackmy, Achache, Bussel, & Katz, 2009). Therefore, observed clinical effects from tDCS might be explained by changes to several possible regions in the central nervous system (see Table 12.1 for a summary of the effects of varying parameters of tDCS).

Neurophysiological Effects of tDCS as Indexed by Cortical Excitability

Just as changes to motor evoked potentials and motor thresholds as measured by TMS provide insight into the excitability level of corticospinal neurons, so too changes to intracortical inhibition (ICI) and intracortical facilitation (ICF) as measured by TMS can provide helpful insight into the effects of tDCS on cortical interneurons. First we discuss the measurement of ICI and ICF, and then we describe the effect of tDCS on these

Table 12.1 Varying parameters of tDCS

Parameter	Standard range	Effect
Electrode size	20 cm^2–35 cm^2	Smaller electrode size results in greater final cortical current density, but also greater shunting to the scalp. Unipolar stimulation can be achieved through a small electrode by enlarging the area of the other electrode
Current intensity	1.0 mA–2.0 mA	A current intensity of 0.6 mA is necessary to observe after effects. Larger current intensity results in greater amplitude of effect (as measured by MEPs) and longer lasting effects
Current density on scalp surface	24 $\mu A/cm^2$–29 $\mu A/cm^2$	Larger current densities result in stronger effects of tDCS. Lower current densities (less than 24 $\mu A/cm^2$) for a few minutes do not induce any significant effects. (This is the ratio of current intensity and electrode size)
Stimulation duration	5 min–30 min	Longer duration results in longer lasting effects. Whereas 5 and 7 minute tDCS results in after effects lasting for no longer than 5 minutes, tDCS from 9 to 13 minutes result in after effects lasting from 30 to 90 minutes, respectively
Stimulation polarity	Anodal or cathodal (applied to cortical region of interest)	Effect depends strictly on the orientation of axons and dendrites in the induced electrical field. Generally, anodal tDCS increases the excitability of the underlying cortex by depolarizing neuronal membranes to subthreshold levels, while cathodal tDCS applied over the same area decreases it by hyperpolarizing neuronal membranes

(*Continued*)

Table 12.1 (Continued)

Parameter	Standard range	Effect
Stimulation site	M1, V1, somatosensory cortex, dorsolateral prefrontal cortex	Site specific and differential effects on a gamut of cognitive, behavioral, psychosomatic, and electrophysiological tests. While the polarizing effects of tDCS are generally confined to the areas under the electrodes, the functional effects appear to perpetuate beyond the immediate site of stimulation. Anodal tDCS of the premotor cortex, for instance, increases the excitability of the ipsilateral motor cortex and inhibition of the contralateral motor areas

measures. We then discuss the effects of tDCS on transcallosal inhibition, cortical silent period, and paired associative stimulation.

Intracortical Inhibition and Facilitation

Intracortical inhibition and facilitation are measured using a particular technique of TMS known as paired pulse TMS. In this technique, the TMS device is used to produce two back to back stimuli separated by a range of inter stimulus intervals (ISIs).

In the measurement of short interval intracortical inhibition (SICI), a sub threshold conditioning stimulus precedes a supra threshold stimulus by a short interval of 1 to 6 ms in time. Interestingly, the preceding condi tioning pulse suppresses the amplitude of the MEP induced by the supra threshold stimulus. In SICI, the subthreshold stimulus inhibits the effect of the supra threshold pulse by activating low threshold $GABA_A$ dependent inhibitory circuits (via inhibitory post synaptic potentials, or IPSPs). In long interval intracortical inhibition (LICI), two TMS pulses are delivered at supra threshold intensities at intervals of 50−200 ms. LICI is mediated by long lasting $GABA_B$ dependent IPSPs and activation of pre synaptic $GABA_B$ receptors on inhibitory interneurons, but this measurement is not frequently used. In intracortical facilitation, the amplitude of a test MEP can be enhanced if it is accompanied by a sub threshold conditioning pulse applied 10−25 ms earlier. Glutamatergic

interneurons at the level of M1 are likely to be involved in ICF since it is reduced by NMDA antagonists such as dextromethorphan. ICF is believed to result from the net facilitation of inhibitory and excitatory mechanisms mediated by $GABA_A$ and NMDA receptors, respectively.

Nitsche et al. (2005) used paired pulse TMS techniques to examine the effects of tDCS on ICF, SICI, and LICI (Nitsche et al., 2005). They employed a protocol that included ISIs of 2, 3, and 4 ms to examine inhibitory effects and ISIs of 10 and 15 ms to examine facilitatory effects. Using TMS induced MEPs as a measure, they tested for intra tDCS excitability changes, short lasting after effects (5−10 minutes after stimu lation) and long lasting after effects (up to 35 minutes after stimulation). With regard to intra tDCS excitability changes, they found that anodal tDCS did not induce cortical inhibition or facilitation, while cathodal tDCS reduced facilitation. For the short lasting after effects, they found that anodal tDCS reduced inhibition and enhanced facilitation, while cathodal tDCS enhanced inhibition and reduced facilitation. Finally, for the long lasting after effects anodal tDCS decreased inhibition for ISIs of 3 ms, while cathodal tDCS increased inhibition at ISIs of 2 ms and 5 ms. Though for long lasting effects the ISI of 15 ms condition did not show modified facilitation, anodal tDCS increased facilitation at ISI of 10 ms, while cathodal tDCS reduced facilitation.

These results suggest that intracortical inhibition and facilitation can be modified by tDCS. For the short lasting and long lasting effects, anodal tDCS can increase facilitation and decrease inhibition, while cath odal tDCS can produce the opposite effect. While intra tDCS facilitatory effects are not observed for anodal stimulation, they are decreased for cathodal stimulation.

Transcallosal Inhibition

In transcallosal inhibition, the two motor cortices are stimulated with a delay of 10 ms. The first pulse (the conditioning pulse) is applied over the primary motor cortex and the second pulse (the test pulse) is applied after a delay of 10 ms in the contralateral primary motor cortex. It has been shown that the second pulse is associated with a significant inhibition in the MEP characteristics.

Transcallosal inhibition induced by tDCS has been explored for clinical use in rehabilitating motor function following stroke. Following stroke, the brain compensates for motor loss by increasing activity in the unaffected hemisphere and limb. Transcallosal inhibition from this

cortical region can decrease activity in the affected hemisphere. Fregni et al. (2005) investigated whether reduction of activity in the unaffected hemisphere by cathodal tDCS would result in improved motor performance due to decreased transcallosal inhibition. Indeed, they found that cathodal stimulation of the unaffected hemisphere, as well as anodal stimulation of the affected hemisphere, significantly improved motor performance compared to sham tDCS (Fregni, Boggio, Mansur et al., 2005). In a recent study of healthy subjects, Williams, Pascual Leone, and Fregni (2010) combined bilateral motor cortex tDCS with contralateral hand restraint of the dominant hand. When comparing active stimulation to sham stimulation, they found a decrease in cortical excitability in the dominant hemisphere and a decrease in transcallosal inhibition from the dominant hemisphere to the non dominant hemisphere. The decrease in transcallosal inhibition correlated with motor performance enhancement in the non dominant hand (Williams et al., 2010).

These findings therefore suggest that tDCS not only effects the proximal area of stimulation, but can have effects on more distal areas of the brain, which may have substantial implications for clinical treatments such as rehabilitation of motor function following stroke.

Cortical Silent Period

Another common phenomenon induced by transcranial stimulation that has been used as a measure of intra cortical inhibition is known as cortical silent period (Hallett, 1995; Tergau et al., 1999). Similar to a refractory period, cortical silent period refers to an inhibitory response observed through electromyography following administration of TMS in which there is a period following the stimulation of the motor cortex during which a second stimulus would be ineffective. This period of depressed activity appears to be important for maintaining motor control as well as averting seizures. While cortical silent period has mainly been studied in TMS research, we expect that future investigation of this phenomenon following tDCS might yield comparable results due to the similar neuromodulatory effects tDCS can have when compared to TMS. Furthermore, evidence suggests that cortical silent period may also serve as a tool to index GABA activity, and may therefore be useful in confirming whether cathodal tDCS inhibits cortical excitability via a GABA dependent pathway (McDonnell, Orekhov, & Ziemann, 2006; Ziemann, Lonnecker, Steinhoff, & Paulus, 1996).

Paired-Associative Stimulation

Classic theories of associative neuroplasticity predict that coactivation of two synaptic inputs modifies synaptic strength, having strong implications for learning processes. Paired associative stimulation (PAS) has been proposed as a technique to explore the mechanisms by which this occurs (Classen et al., 2004). PAS refers to the administration of two stimuli at once or in close proximity so as to lead the subject to associate them. Wolters et al. (2003) showed that PAS increases or decreases motor cortical excitability (as measured by MEPs) when the interval between peripheral nerve stimulation and subsequent TMS pulse is 25 ms and 10 ms, respectively. This PAS induced plasticity appears to be NMDA receptor dependent and has been shown to influence motor learning (Stefan et al., 2006; Wolters et al., 2003; Ziemann, Ilic, Pauli, Meintzschel, & Ruge, 2004).

Nitsche et al. (2007) explored whether tDCS induced background network activity changes effect PAS induced plasticity. They hypothesized according to homeostatic plasticity theory that the effect of PAS would be enhanced with decreased background activity (Nitsche et al., 2007). Administering the PAS protocol to 12 healthy subjects, Nitsche et al. (2007) slowly stimulated the right ulnar nerve at the wrist at an intensity 300% above sensory threshold while a single TMS pulse was delivered over the contralateral motor cortical region representing the right abductor digiti minimi muscle. This protocol was performed alone, following anodal and cathodal tDCS, and simultaneously with anodal and cathodal tDCS. When administered simultaneously with PAS, excitability enhancing (anodal) tDCS decreased the efficacy of PAS and excitability diminishing (cathodal) tDCS increased the efficacy of PAS. This same effect was observed for prolonged administration of tDCS as well, but was not observed when tDCS was administered before PAS. This suggests, in accordance with theories of homeostatic plasticity, that tDCS has the potential to modify the efficacy of PAS by modulating background activity in the brain. For instance, decreased excitability of the cortex induced by cathodal tDCS, when applied in combination with PAS, has the potential to increase associative synaptic plasticity.

NEUROCHEMISTRY OF tDCS

As noted above, transcranial direct current results in polarity specific changes during and after application of tDCS. Whereas anodal stimulation depolarizes membrane potentials to subthreshold levels leading to increased

cortical excitability, cathodal stimulation hyperpolarizes membrane potentials leading to increases in cortical inhibition. Effects on cortical excitability can be immediate and short lasting (up to 5 minutes following stimulation) and they can also be longer lasting (up to 1 hour following stimulation). These changes in cortical excitability are associated with changes of the underlying cortical neuronal activity. But what do we know from a neurochemistry standpoint about the effects of tDCS on neuronal activity?

Ion Channel Conductance and NMDA-Receptors

Several pharmacological studies have examined the roles of various ion channels and receptors in the modulation of cortical excitability by tDCS. Liebetanz, Nitsche, Tergau, & Paulus (2002) found that administration of the sodium channel blocker carbamazepine prior to tDCS eliminated the excitatory effects of anodal stimulation. Furthermore, the N methyl D aspartate (NMDA) receptor antagonist dextromethorphan eliminated the long lasting after effects of both anodal and cathodal stimulation (Liebetanz et al., 2002), suggesting that tDCS after effects are associated with synaptic effects. In a later pharmacological study in healthy human subjects, Nitsche, Fricke et al. (2003) further examined the impact of carbamazepine, dextro methorphan, and the calcium channel blocker flunarizine on tDCS elicited motor cortical excitability changes. They found similar effects resulting from blocking sodium channels and NMDA receptors, and further demon strated that blocking calcium channels led to elimination of the excitatory effects of anodal stimulation (Nitsche, Fricke et al., 2003). Additionally, D cylcoserine, a partial NMDA agonist shown to improve cognitive func tions in humans, has also been found to prolong the cortical excitability induced by anodal tDCS (Nitsche, Jaussi et al., 2004). Extending these find ings, a recent study using mouse M1 slices demonstrated that anodal tDCS combined with repetitive low frequency synaptic activation induces long term synaptic potentiation that is NMDA receptor dependent and mediated by secretion of brain derived neurotrophic factor (BDNF) (Fritsch et al., 2010). The combined results of these studies suggest that changes in cortical excitability during tDCS depend on membrane polarization, which is determined by the conductance of sodium and calcium channels. Moreover, they suggest that NMDA dependent mechanisms are central to inducing the after effects of tDCS. The above studies also suggest avenues for prolonging the effects of tDCS on cortical excitability and plasticity through the combination of tDCS with pharmacologic interventions.

Neurotransmitters Involved: GABA, Glutamate, and Dopamine

While the above studies suggest that sodium and calcium channels are central to the effects of tDCS, the evidence for the involvement of excitatory neurotransmitters such as glutamate or inhibitory neurotransmitters such as gamma aminobutyric acid (GABA) is limited. In a magnetic resonance (MR) spectroscopy study, Stagg et al. (2009) found that anodal tDCS is related to decrease in GABA concentration and cathodal tDCS is related to decrease in both glutamate and GABA (Stagg et al., 2009). This suggests that tDCS affects activity of inhibitory interneurons, potentially explaining the mechanism by which cortical excitability increases and decreases upon stimulation. Nitsche et al. (2006) also found that dopaminergic mechanisms may be involved in NMDA induced after effects, as D2 receptor blocking by sulpiride eliminated the after effects of cathodal tDCS, while enhancement of the receptors using pergolide consolidated tDCS generated inhibition until the morning after stimulation (Nitsche et al., 2006).

Anodal tDCS has also been shown to manipulate cortical spreading depression (CSD), which is influenced by changes in the concentrations of ions and neurotransmitters that control cortical excitability like GABA and glutamate. CSD, which is thought to underlie migraine aura, is a wave of neuronal excitation followed by inhibition that spreads through the cortex (at a rate of 2–5 mm/min) as a result of alterations in cortical ion homeostasis. Using a rat model, Liebetanz et al. demonstrated that the propagation velocity of CSD increases following the administration of anodal tDCS. Cathodal and sham tDCS did not influence the CSD propagation velocity (Liebetanz et al., 2006). Since anodal tDCS is known to increase cortical excitability, this study supports the theory that CSD propagation velocity reflects cortical excitability and suggests that anodal tDCS might increase the likelihood of migraine attacks in migraine patients.

Changes to Oxyhemoglobin Concentration

Studies of tDCS induced cortical excitability have previously focused on the motor cortex and visual cortex since the effects of stimulation in these areas can be assessed by TMS motor evoked potentials and phosphene thresholds. To examine the effects of tDCS on other areas in the brain such as the prefrontal cortex, Merzagora et al. (2010) employed another technique called functional near infrared spectroscopy (fNIRS), which allows for a non invasive and portable measure of regional cerebral blood flow (rCBF) (Merzagora et al., 2010). fNIRS records cerebral concentrations of

oxyhemoglobin and deoxyhemoglobin by observing the absorption of near infrared light in particular regions of the brain and relating this to rCBF. In a sham controlled study, Merzagora et al. (2010) stimulated two prefrontal locations for 10 minutes and found that oxyhemoglobin concentration was significantly increased following anodal stimulation compared to sham stimulation, suggesting that anodal stimulation increased rCBF in the stimulated regions. fNIRS data showed that this effect lasted for 8–10 minutes following stimulation, and that cathodal stimulation only induced a negligible effect on rCBF. This study potentially supports the use of changes to oxyhemoglobin concentration via fNIRS as an additional method for monitoring the neuromodulatory effects of tDCS.

Alterations to Membrane Phospholipids

Finally, one recent study suggests that tDCS may have some effects on membrane phospholipid metabolism. Myoinositol is an essential compound for the synthesis of inositol containing phospholipids that has been found to be altered in many physiological and pathological conditions. Using proton magnetic resonance spectroscopy, Rango et al. (2008) showed that the concentration of myoinositol was increased with anodal tDCS of the right motor cortex compared to sham tDCS (the effect was not observed in a control visual cortical region) (Rango et al., 2008). This study suggests that monitoring of the brain content of myoinositol may serve to further monitor the effects of tDCS.

While much remains to be explored regarding the neurochemistry of tDCS, studies to date have supported the understanding that tDCS exerts its effects primarily by depolarizing or hyperpolarizing neuronal membrane potentials, reinforcing these effects through NMDA dependent mechanisms and increasing cerebral blood flow to the stimulated region.

SAFETY CONSIDERATIONS FOR tDCS

Numerous studies verify that low intensity transcranial stimulation is safe for use in humans and that it is linked with only rare and relatively minor adverse effects (Poreisz, Boros, Antal, & Paulus, 2007). tDCS does not elevate the serum levels of molecular markers of neuronal injury such as neuron specific enolase (Nitsche & Paulus, 2001) or N acetyl aspartate (Rango et al., 2008). Furthermore, both contrast enhanced MRI and EEG studies have found no pathological changes associated with application of tDCS (Iyezr et al., 2005; Nitsche, Niehaus et al., 2004).

Additionally, no instances of epileptic seizures caused by tDCS have been observed in humans (Poreisz et al., 2007). In fact, pulsed transcranial stimulation has been correlated with an antiepileptic effect in rats (Liebetanz et al., 2006) and a previous tDCS study in patients with refractory epilepsy did not show an increase in seizures or EEG epileptiform discharges (Fregni, Thome Souza et al., 2006). The most common side effects observed with tDCS are mild tingling (70.6%), moderate fatigue (35.3%), sensations of light itching (30.4%), slight burning (21.6%), and mild pain (15.7%) under the electrodes (Poreisz et al., 2007).

Less commonly, some subjects report headache (11.8%), trouble concentrating (10.8%), nausea (2.9%), and sleep disturbances (1.0%) (Poreisz et al., 2007). Skin lesions in the form of burns following administration of tDCS have been reported (Palm, 2008). Visual sensations associated with turning the stimulation on or off have occurred in a small number of cases, but this can be avoided by slowly changing the current level at the start and end of stimulation. tDCS delivered at a level of 2 mA and administered according to current stimulation guidelines (Nitsche, 2008) has been shown to be safe for use in both healthy volunteers (Iyer et al., 2005) and patients with neurological injury (Boggio, Nunes et al., 2007). Using a rat model, researchers investigated the safety limits of extended cathodal tDCS and found the charge density threshold to be two orders of magnitude greater than the charge currently administered in humans (Liebetanz et al., 2009). The safety of tDCS use in pregnant women and children, however, has not yet been investigated.

CONCLUSIONS AND FUTURE DIRECTIONS

There is much left to be explored in understanding the neurophysiological effects of tDCS. Studies from electrophysiology and TMS have shown that tDCS can modulate cortical excitability in a polarity dependent fashion. Generally, anodal stimulation increases cortical excitability, while cathodal stimulation decreases it. Furthermore, these effects are dependent on current density and stimulation duration. tDCS has been shown to modulate activity in both the motor and visual cortices, and more recently has been shown to directly influence excitability of the spinal cord. Anodal tDCS has been shown to increase intracortical facilitation and diminish intracortical inhibition, while cathodal tDCS has been shown to have the reverse effect. Furthermore, tDCS appears to have substantial effects on transcallosal inhibition and may be a promising tool for

enhancing the effects of PAS. While the neurochemical mechanisms underlying these effects are incompletely understood, neuropharmacology studies suggest that immediate effects are due to modulation of neuronal membrane potentials, thus increasing or decreasing the rate of action potential firing. Long term effects, lasting for minutes to hours beyond the time of stimulation, likely involve NMDA receptor dependent mechanisms. It is critical that we integrate the results from these studies as the neurophysiological effects and clinical applications of tDCS continue to be explored.

Future studies should combine other brain imaging methods such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG) before, during, and following the administration of tDCS. fMRI for instance has high spatial resolution that can assist in more precisely examining regions of the brain. PET can be utilized to monitor glucose or neurotransmitter uptake to observe the neurochemical effects of tDCS. Awake animal models combined with such imaging modalities might prove useful in probing the physiological effects of tDCS. Furthermore, additional research into the effects of tDCS on conditions such as chronic pain may shed light onto the neurophysiological mechanisms underlying these effects (see Zaghi et al., 2010, for recent review of the clinical applications of tDCS). Precise and stable positioning of the tDCS device remains one limitation of current tDCS research. Future engineering research should be targeted at improving the stability, focality, and depth of stimulation that can be administered by stimulation devices, as well as developing alternative stimulation parameters (e.g., alternating current, simultaneous administration of two tDCS devices), which would potentially enhance our ability to utilize tDCS in future research and clinical practice (Miranda et al., 2006). One interesting alternative that should be further explored is high density tDCS (HD tDCS) using ring electrodes to produce a more focal stimulation area (Datta et al., 2009). Finally, most research to date on the neurophysiological effects of tDCS has been conducted in healthy subjects, though we have reason to suspect such effects may be altered in patients with neuropsychiatric conditions who often exhibit differing baseline brain activity (Fregni, Boggio, Valle et al., 2006; Siebner et al., 2004). Future investigation should therefore examine whether the neurophysiological effects of tDCS vary in populations with neuropsychiatric conditions.

The key points from this chapter are summarized in Table 12.2.

Table 12.2 Transcranial direct current stimulation: summary of key points

Growing interest in the clinical applications of tDCS underscores the importance of elucidating the underlying neurophysiology of this brain stimulation technique
Transcranial magnetic stimulation is a method of neurostimulation and neuromodulation that has been central to the investigation of the neurophysiological effects of tDCS
Low amplitude current applied at the scalp can penetrate to the level of the cortex
Greater shunting to the scalp occurs with smaller electrode areas, although a greater final cortical current density can be achieved
Because of limitations in cortical current density, tDCS does not induce action potentials. The effects of tDCS on cortical neurons are transmitted as electrotonic potentials only, which spread along the neuron, altering the likelihood with which that neuron may reach an action potential
Larger current densities result in stronger effects of tDCS, while lower current densities for short periods of time do not induce any significant changes
Greater tDCS duration and intensity lead to greater endurance of its effects
Direct current modulates the spontaneous neuronal activity in a polarity dependent fashion
Generally, anodal tDCS increases cortical excitability of the stimulated area, while cathodal tDCS decreases cortical excitability
Soma of the neurons in layers V and VI are most susceptible to the modulating effects of tDCS
Anodal tDCS of the motor cortex modifies excitability at the level of the spinal cord
Although tDCS has the most activating effect on the underlying cortex, the stimulation provokes sustained and widespread changes in other regions of the brain as well as through intracortical inhibition and facilitation
tDCS affects transcallosal inhibition. Cathodal stimulation of the unaffected hemisphere in stroke patients decreases transcallosal inhibition and significantly improves performance of motor tasks controlled by the affected hemisphere
Transcranial magnetic stimulation can induce a short cortical silent period, or refractory period, following stimulation. Future research should examine whether tDCS produces similar effects
tDCS has the potential to modify the efficacy of paired associative stimulation by modulating background activity in the brain. For instance, decreased excitability of the cortex induced by cathodal tDCS, when applied in combination with paired associative stimulation, has the potential to increase associative synaptic plasticity
Changes to cortical excitability during tDCS depend on membrane polarization, which is determined by the conductance of sodium and calcium channels. After effects of tDCS may be additionally dependent on NMDA receptors

(*Continued*)

Table 12.2 (Continued)

Anodal stimulation is associated with decrease in GABA concentration and cathodal tDCS is associated with decrease in both glutamate and GABA
Dopaminergic mechanisms may be involved in NMDA induced after effects
Oxyhemoglobin concentration significantly increases following anodal stimulation compared to sham stimulation, suggesting that anodal stimulation increases rCBF in the stimulated regions. The concentration of myoinositol increases with anodal tDCS as well
Neurochemistry studies to date have served to reinforce the understanding that tDCS exerts its effects primarily by depolarizing or hyperpolarizing neuronal membrane potential, reinforcing these effects through NMDA dependent mechanisms and increasing cerebral blood flow to the stimulated region
Numerous studies verify that low intensity transcranial stimulation is safe for use in humans (but not pregnant women and children) and that it is linked with only rare and relatively minor adverse effects
Future studies should examine the effects of tDCS using other imaging modalities. Research should also aim to understand the mechanisms underlying observed clinical effects, develop improved tDCS technologies and alternative parameters for enhanced use in research and clinical practice, and examine whether the neurophysiological effects of tDCS vary in populations with neuropsychiatric conditions

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