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Brain Stimulation
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Chapter 27

Transcranial electric and magnetic stimulation: technique and paradigms

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INTRODUCTION

Neural activity in the brain can be induced or modulated by an exogenous electric field and associated electric current density in the brain (see Chapters 1 and 29). The electric field can be generated noninvasively by passing electric current through electrodes or placing an induction coil over the scalp. These approaches are known, respectively, as transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS). As illustrated in Figure 27.1, TES and TMS devices consist of a waveform generator producing electric current that is delivered to scalp electrodes (for TES) or coil (for TMS).

The electric field can be characterized by a temporal waveform and a spatial distribution. The temporal waveform is controlled chiefly by the waveform generator parameters, whereas the spatial distribution is controlled chiefly by the electrode/coil configuration. Thus the stimulation current waveform and electrode/coil configuration parameters constitute the dose of TES and TMS (Peterchev et al., 2012). Depending on the specific stimulation parameters, various TES and TMS paradigms have been differentiated including, but not limited to, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), electroconvulsive therapy (ECT), repetitive TMS (rTMS), low-field magnetic stimulation (LFMS), and magnetic seizure therapy (MST). Some examples of stimulus waveforms and electric field spatial distributions for various TES and TMS paradigms are shown in Figure 27.2 and Figure 27.3, respectively.

The chief drawback of TES is that it is painful when delivered at current intensities sufficient to induce action potentials in cerebral neurons. This is due to the low electric conductivity of the skull, which requires high electric field strength in the scalp in order to generate sufficient current in the brain to activate neurons. In contrast, the magnetic field in TMS is not impeded by the scalp, resulting in a largely painless technique that is well tolerated by most subjects and patients. Another advantage of TMS is that the induced electric field is less sensitive to anatomical differences among subjects than TES (Deng et al., 2009).

The chief disadvantage of TMS over TES techniques is the need for very high coil voltages and currents to produce neural activation in the brain. Threshold-level TMS requires electric current 10 000 times stronger than TES. This results in bulky, high-power TMS equipment and coil heating issues. Finally, TMS can produce only a pulsed electric field, since a static magnetic field does not induce an electric field. There is therefore no TMS analog to direct current techniques such as tDCS.

As a result of these relative advantages and disadvantages, TES techniques are used mostly at subthreshold level (e.g., tDCS, tACS, tRNS) or under anesthesia (e.g., suprathreshold TES, ECT). Nevertheless, threshold-level TES is sometimes used in awake subjects because of the distinct neural stimulation properties of TES compared with TMS (e.g., activation of pyramidal fibers versus interneurons). In contrast, TMS is typically applied at intensities around the neural activation threshold, although techniques at subthreshold intensities (e.g., LFMS) or under anesthesia (e.g., MST) are also being developed.

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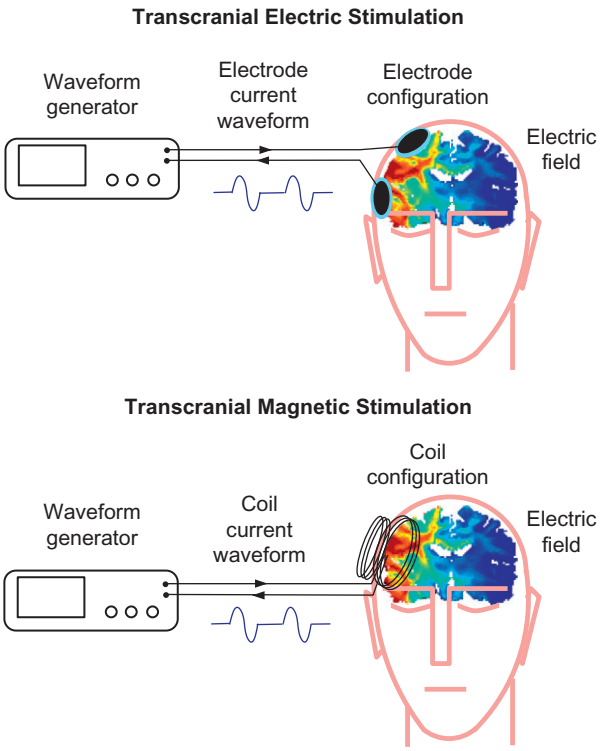

Fig. 27.1. Basic diagram of transcranial electric stimulation (top) and transcranial magnetic stimulation (bottom). A waveform generator sends current to electrodes or a coil placed on the subject's head. The electrodes inject current in the head that generates an electric field in the brain. The coil magnetically induces an electric field in the brain.

TRANSCRANIAL ELECTRIC STIMULATION

Technology

TES involves the application of current to two or more surface electrodes, with at least one of them placed on the scalp, as illustrated in Figures 27.1 and 27.3A–B. The electrode typically consists of a backing made of a solid conductor (metal or conductive rubber) attached with wires to the waveform generator, and an electrolyte fluid or gel that is placed between the skin and the solid conductor (Merrill et al., 2005). The fluid electrolyte may be suspended in a sponge (typically for large electrodes), whereas the gel may be contained inside a hollow holder (typically for smaller electrodes) (Minhas et al., 2010). The electrodes are usually fixed on the subject's head with an elastic band or cap, or held by a clinician.

The electric field waveform generated in the brain is directly proportional to the current injected in the electrodes (see Chapter 29). Therefore, most modern transcranial electric stimulators control the electrode current to follow the desired electric field waveform. The majority of stimulators generate rectangular current waveforms. Representative electrode current and voltage waveforms from a tDCS device and a pulsed TES device are shown in Figure 27.2A–D.

Near-threshold paradigms

Near-threshold transcranial electric stimulation

The first method of transcranial activation of cerebral neurons in awake subjects involved the delivery of brief current pulses through scalp electrodes (Merton and Morton, 1980). This near-threshold form of TES has been largely superseded by TMS, which is more tolerable. Nevertheless, TES is commonly used for nerve conduction monitoring in anesthetized patients during surgery. TES is also used in some experimental paradigms in awake subjects because it preferentially recruits neural populations distinct from those activated by TMS. Specifically, TES directly activates pyramidal axons in the white matter below the cerebral cortex, whereas TMS preferentially activates cortical interneurons (Di Lazzaro et al., 1998, 2004). Therefore, the contrast between TES and TMS activation can be used to characterize effects associated with these distinct neural populations and their synaptic connections (Ardolino et al., 2005; Oliviero et al., 2011). TES of the motor cortex at high intensities can access corticospinal neurons at the pyramidal decussation, and stimulation of the brainstem and the spinal cord preferentially accesses corticospinal axons (Rothwell et al., 1994).

Subthreshold paradigms

Subthreshold TES is commonly defined as stimulation of motor or sensory areas, especially the visual cortex, without eliciting a motor evoked potential (MEP) or a phosphene, respectively. In terms of cellular physiology, threshold can be defined by eliciting an action potential in the resting state and a modification of firing rate in spontaneously firing cells. In human subjects, the latter is more difficult to quantify when compared to MEP induction at rest. As shown 50 years ago (Creutzfeldt et al., 1962; Bindman et al., 1964), direct current stimulation for 10 minutes may increase or decrease firing rates for hours. Depending on the resting membrane potential, requisite intensities influencing firing rates will vary; further, distinct cell types have different thresholds (Radman et al., 2009).

Almost infinite electric stimulation possibilities exist, if all combinations of frequency, intensity, duration, and other parameters are taken into account. The simplest approach is tDCS, representing the low end of the frequency spectrum, whereas the explored upper end at present is around 200 kHz (Kirson et al., 2007).

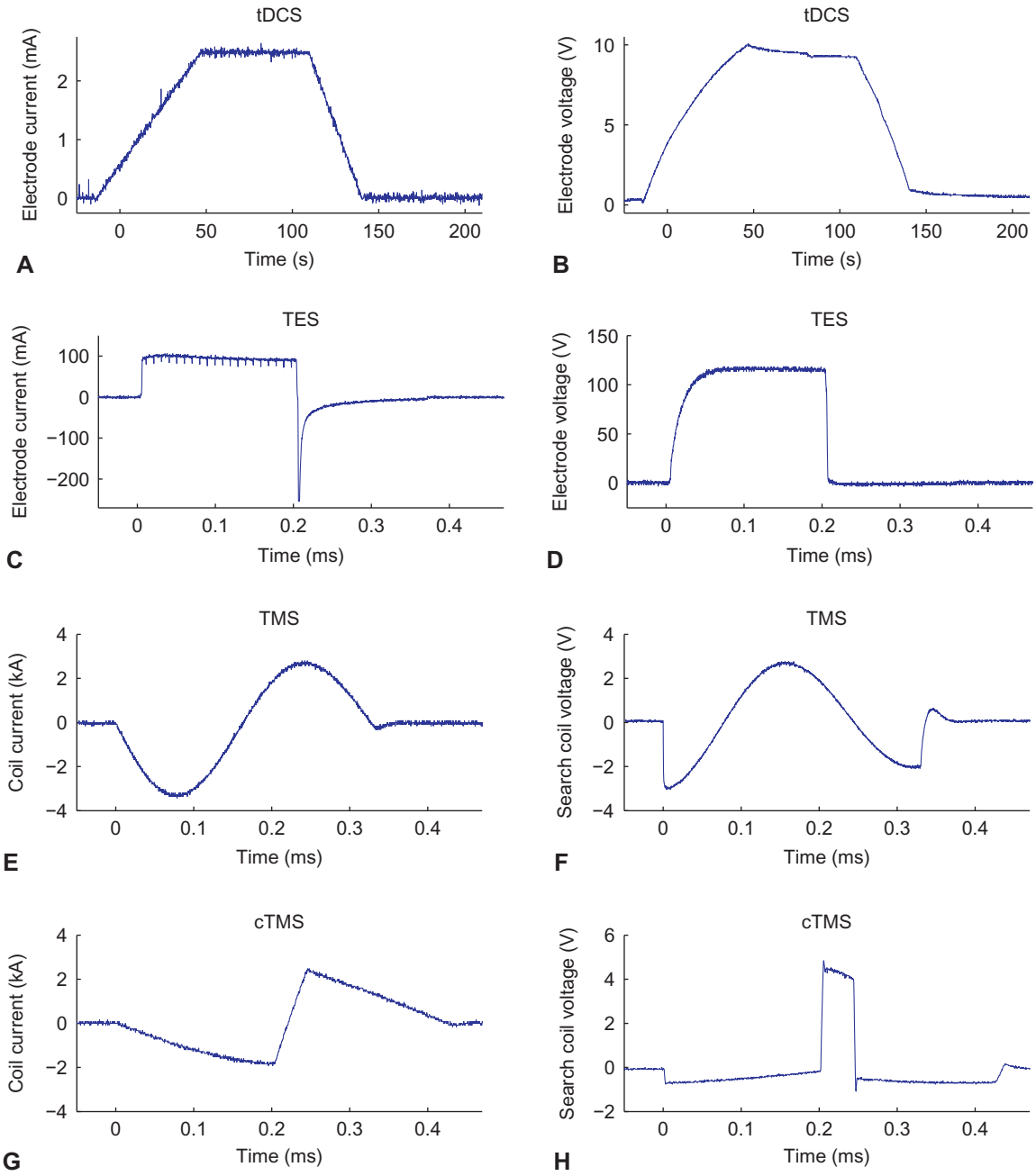

Fig. 27.2. Representative transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS) waveforms. Electrode current and voltage waveforms from a transcranial direct current stimulation (tDCS) device (**A,B**), set for 2 minutes of 2.5-mA stimulation, and a TES device (**C,D**) generating 86-mA, 0.2-ms rectangular pulses. Coil current and search coil voltage of a conventional biphasic TMS pulse (**E,F**) and a controllable TMS (cTMS) pulse (**G,H**) (Peterchev et al., 2011). The search coil voltage is proportional to the induced electric field waveform. (Modified from Peterchev et al., 2012.)

Transcranial direct current stimulation

The history of tDCS dates back to 1800. The invention of the voltaic pile allowed for the first time generation of constant direct current; soon afterwards first clinical investigations in patients were performed, claiming both positive and negative results (Hellwag and Jacobi, 1802). A revival of this method occurred in the 1960s, documenting, for example, improvement in motor response speed (Elbert et al., 1981) or successes in the treatment of depression. A systematic analysis of the relationship between physical stimulation parameters such as intensity and duration and biological effects started after

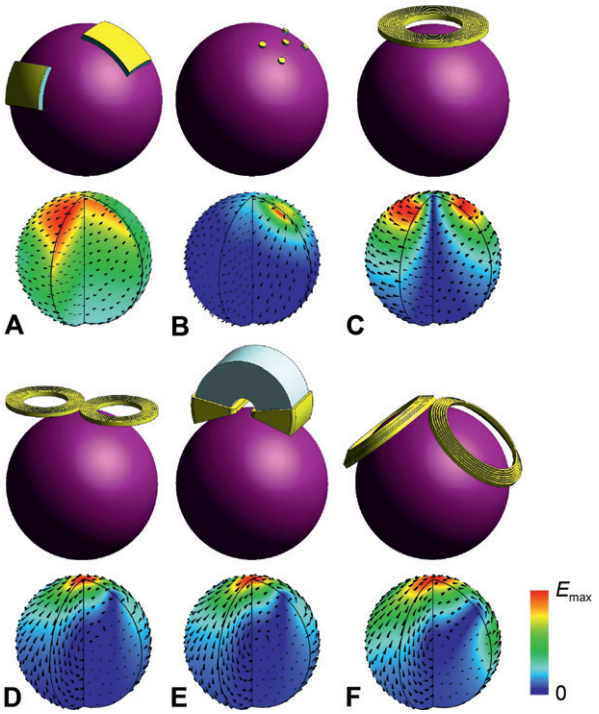

Fig. 27.3. Examples of electrode and coil configurations for transcranial electric (TES) and magnetic (TMS) stimulation, respectively. Underneath is shown the associated electric field generated in the brain in a spherical head model. The color scale depicts the electric field strength relative to the maximum value in the brain, E_{max}. The arrows indicate the electric field direction. A segment is cut out of the brain sphere to reveal the electric field distribution in depth. (**A**) Conventional transcranial direct current stimulation (tDCS) configuration with two 70×50-mm sponge electrodes. (**B**) A focal tDCS 8-mm diameter electrode configuration consisting of an "active" center electrode with four return electrodes (Datta et al., 2009). (**C**) A 90-mm winding diameter circular TMS coil. (**D**) A 70-mm winding diameter figure-8 TMS coil. (**E**) Figure-8 type TMS coil with a C-shaped ferromagnetic core (Epstein and Davey, 2002). (**F**) Double-cone coil with two 110-mm concave windings fixed at an angle of 100°. (Courtesy of Dr Zhi-De Deng.)

tDCS effects were quantified by TMS, first during a few seconds of stimulation (Priori et al., 1998) and then evaluating plastic after-effects with longer stimulation durations (Nitsche and Paulus, 2000, 2001).

Most likely, tDCS leads to a polarization of neuronal membranes. A direct current electric field that is too weak to trigger action potentials may nevertheless coherently polarize a network of neurons and thus modulate the simultaneous processing of afferent synaptic inputs, as well as the resulting changes in synaptic plasticity (Bikson et al., 2006). In present understanding, a surface anode (positive electrode) will hyperpolarize the superficial layers and depolarize layer 5, thereby increasing pyramidal tract neuronal firing rate, and vice versa with cathodal (negative electrode) stimulation (Bindman et al., 1964). Due to asymmetrical electric properties within the dendritic arborization, the membrane potential of even rather symmetrical cell types will be modulated (Radman et al., 2009). Thus, in general, *at rest* anodal stimulation leads to excitation measured most commonly in terms of MEP increase after tDCS compared with baseline, whereas cathodal stimulation induces inhibition (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). Some exceptions from this rule, however, need to be taken into account. As soon as the resting muscle is either voluntarily activated, or if attentional processes are enforced, anodal excitatory effects are converted into inhibition. Attentional reinforcement may both reduce and reverse after-effects (Antal et al., 2007). Another exception seems to be the involvement of signal-to-noise related tasks. Cathodal stimulation will likely reduce the firing rates of most cells beneath the electrode, whereas anodal stimulation will increase firing. In paradigms in which a larger signal is partially occluded by smaller noise, concomitant reduction of both will increase the signal-to-noise ratio; performance may then – seemingly paradoxically – increase with cathodal stimulation (Antal et al., 2004). Further exceptions exist with the coapplication of drugs; 100 mg L-dopa will reverse cathodal inhibition into excitation and prolong after-effects into the 36 hours range (Kuo et al., 2008). The reverse situation can be induced by application of citalopram, a serotonin reuptake inhibitor: only excitation is induced even with cathodal stimulation (Nitsche et al., 2009). There is some evidence that anodal stimulation at the leg area is more efficient than cathodal stimulation (Jeffery et al., 2007).

Stimulation intensity

At present there is good understanding of the stimulus intensity necessary for effective tDCS. Electrode current density is the decisive parameter in conventional tDCS paradigms, although in general the current intensity and electrode dimensions have distinct roles in affecting the electric field (Miranda et al., 2009). In most published studies the average electrode current density is usually between 0.029 and 0.08 mA/cm^2. As current density depends on the electrode size, it has to be referred to the electrodes used (for a more detailed description see Paulus, 2011a). An electrode size of 35 cm^2, as introduced by Nitsche and Paulus (2000), has been used frequently since then, and a commonly used intensity is 1 mA in relation to this size. tDCS intensities below 0.4 mA do not appear to have an after-effect, although this threshold has not been investigated systematically (Nitsche and Paulus, 2000). A more thorough investigation is

needed, because variation of intensity would probably shift the intracortical transition zone between excitation and inhibition, playing a decisive role likely in layers III–V. Current intensities at or above 3 mA are typically too painful for routine application (Furubayashi et al., 2008).

Stimulation duration

Taking MEPs as the criterion, the minimal duration of tDCS for induction of after-effects was demonstrated to be 3 minutes (Nitsche and Paulus, 2000). Longer stimulation duration appears to induce longer after-effects (Nitsche and Paulus, 2001; Nitsche et al., 2003). This seems, however, to be a nonlinear relationship that works up to a stimulation duration of about 20 minutes. In line with the reversal of the sign of theta burst after-effects with doubling duration (Gamboa et al., 2010), similar evidence exists that doubling the duration of 13 minutes of anodal stimulation to 26 minutes (Monte-Silva et al., 2013) reverses anodal stimulation into inhibition. For cathodal stimulation, doubling stimulation duration from 9 to 18 minutes is still inhibitory; however, with a prolongation from 60 to 90 minutes this effect is much less than would be expected. Longer stimulation durations need to be explored in order to clarify a possible reversal into excitation. At present, a more promising way to prolong after-effects seems to be the introduction of stimulation intervals. Stimulation intervals of 3 and 20 minutes, as well as 24 hours between two 9-minute session, were able to prolong excitatory aftereffects into the 24 hours range (Monte-Silva et al., 2013). A buildup of after-effects over 3 days when stimulating at a 24-hour interval had already been demonstrated (Reis et al., 2009).

An interesting aspect, so far not systematically investigated in humans, is whether intensity and duration of stimulation are interchangeable. Specifically, as charge accumulation over time is expected with tDCS, it would be interesting to know whether increasing stimulation time could lead to lower current density to induce the same after-effects as shorter stimulation with higher current density. Some evidence for this was found in an animal epilepsy model (Liebetanz et al., 2006). The roles of current intensity and time are, however, biophysically distinct. The two may be interchangeable within a limited range of parameters (as in strength–duration curves for electric stimulation), but not in general. As an example, doubling cathodal stimulation intensity to 2 mA reverses inhibition into excitation (Batsikadze et al., 2013).

Stimulation electrodes

A conventional montage includes two equally sized electrodes. For motor cortex studies one electrode is placed over the motor strip and the return electrode is on the forehead (Nitsche and Paulus, 2000) (see Fig. 27.3A). This arrangement can be refined by reducing the size of the target electrode for more focal stimulation, e.g., down to 3.5 cm^2, which allows selectively influencing plasticity of thenar and hypothenar muscles (Nitsche et al., 2007). Unwanted effects at the return electrode could be avoided by increasing the return electrode size (Nitsche et al., 2007). High-definition approaches with multiple small return electrodes increase the spatial focality (Minhas et al., 2010) and may be more effective than using a single large return electrode (Faria et al., 2011). Individual models based on magnetic resonance imaging (MRI) allow targeted electrode applications and current selection (Datta et al., 2011; Dmochowski et al., 2011). As the electric field is usually strongest between two conventional electrodes (25–35 cm^2) (see Fig. 27.3A), it has been suggested that one of the electrodes should be placed just "behind" the target relative to the other electrode, for maximum current density at the target.

Transcranial alternating current stimulation and transcranial random noise stimulation

tACS (Antal et al., 2008) and tRNS (Terney et al., 2008) use precisely defined physical stimuli such as sinusoidal and white noise stimulation, respectively, in order to get a better understanding of the relation between stimulus characteristics and biological effects. Other approaches, such as Limoge's current and several others (overview in Zaghi et al., 2010), are at present difficult to incorporate into a conceptual framework due to rather complex stimulus patterns lacking comparable biomarker studies. In the lower frequency range, between about 10 and 40 Hz, alternating current stimulation is contaminated by the induction of retinal phosphenes which can be induced with intensities of around 250 μA, depending on the electrode distance to the eye. Visual phosphenes induced with electrodes at the visual cortex (Kanai et al., 2008) are probably also due to remote retinal stimulation (Schutter and Hortensius, 2010). Facilitation of motor learning has been shown with 10 Hz tACS (Antal et al., 2008), slowing of movements with 20 Hz (Pogosyan et al., 2009), and MEP size increases after stimulation with 140 Hz and to a lesser extent with 250 Hz (Moliadze et al., 2010) and 1, 2, and 5 kHz (Chaieb et al., 2011). tRNS with spectrum between 100 and 640 Hz induces similar MEP increases (Terney et al., 2008) and improves visual learning (Fertonani et al., 2011). Both tACS at 140 Hz and tRNS induce excitation at an intensity of 1 mA, whereas at an intensity of 0.4 mA inhibition is induced (Moliadze et al., 2012).

Convulsive paradigms

Electroconvulsive therapy

ECT involves the application of high-intensity TES pulse trains to induce a therapeutic seizure in anesthetized patients (Peterchev et al., 2010). Because of its robust efficacy in major depression and other psychiatric and neurological disorders, ECT has been in continuous use since its inception in 1938 (Fink, 2001; Abrams, 2002; Lisanby, 2007). Early versions of ECT were prone to producing significant cognitive side-effects, especially amnesia, but refinement of the stimulus parameters using more focal electrode configurations (Sackeim et al., 2000) and briefer pulses (Weiner et al., 1986; Sackeim et al., 2008) have led to a dramatic reduction of side-effects with preserved efficacy.

TRANSCRANIAL MAGNETIC STIMULATION

Technology

TMS involves passing of current through one or more coils positioned on the head to generate a magnetic field that in turn induces an electric field and associated current density in the brain. The induced electric field is proportional to the rate of change of the coil current. In conventional magnetic stimulation devices, the coil voltage pulse, and hence the electric field waveform, has a damped cosine shape (Jalinous, 2002; Ruohonen and Ilmoniemi, 2002). Commercial devices offer a selection of biphasic and monophasic sinusoidal pulses with limited control over the pulse shape and width (Sommer et al., 2006; Rothkegel et al., 2010). A new generation of controllable pulse parameter TMS (cTMS) devices is capable of generating nearly rectangular electric field pulses with adjustable pulse width, number of phases, and directionality parameters (Peterchev et al., 2008, 2011). Figure 27.2E–H shows representative coil current and induced electric field waveforms for a conventional TMS device and for a cTMS device.

The stimulation coil size, geometry, and placement, and the head anatomy determine the electric field distribution induced in the brain. A variety of TMS coils are available commercially or have been proposed for special applications (Deng et al., 2013). The two most common coil geometries are circular (see Fig. 27.3C) and figure-8 (Fig. 27.3D–F). As illustrated in Figure 27.3, circular coils induce a broad circular electric field peak under the coil perimeter, whereas figure-8 type coils produce a focused electric field peak under the coil center where the loops meet. Larger coils such as the double-cone coil (Fig. 27.3F) produce deeper penetrating but less focal electric field than smaller coils (Fig. 27.3D–E). The inclusion of a ferromagnetic core in the figure-8 coil (Fig. 27.3E) substantially reduces the coil power consumption and heating, enabling long stimulation sessions without forced cooling of the coil (Epstein and Davey, 2002).

A family of coil designs called Hesed (H) coils has been proposed to achieve effective stimulation of deep brain structures (Roth et al., 2002, 2007; Zangen et al., 2005). The H coils have complex winding patterns and larger dimensions compared with conventional TMS coils, and consequently have slower electric field attenuation with depth, at the expense of reduced focality (Roth et al., 2007; Deng et al., 2013). The comparative advantage of H coils over conventional 70-mm figure-8 coils with regard to depth of stimulation has been disputed (Fadini et al., 2009, 2010; Roth et al., 2010).

The position of the TMS coil is typically maintained by a researcher or clinician holding the coil, or is fixed with a mechanical coil holder. To prevent movement of the subject's head relative to the coil, the head is typically partially immobilized in a padded head rest or chin rest. The position of the coil relative to brain structures can be tracked accurately in real time using frameless stereotactic systems (Danner et al., 2008; Saisanen et al., 2008). Robotic positioners enable the coil to track movements of the head dynamically, obviating the need to immobilize the subject's head during the stimulation session, which can improve the subject's comfort and reduce variability in the coil position over the duration of the session (Matthaus, 2008).

Near-threshold paradigms

Near-threshold TMS requires large, but brief, electric currents to be passed through the coil held over the scalp. The magnetic field is typically 1–2.5 Tesla, has a rise time of approximately 50–200 μs, and decays rapidly over distance (Rossini et al., 1994; Thielscher and Kammer, 2004; Deng et al., 2013). This rapid decay of the electric field makes TMS effective for stimulation only of relatively superficial elements including the cortex and the very superficial subcortical white matter (Salvador et al., 2011). The site of action of the stimulus is likely to be axons and not cell bodies (Nowak and Bullier, 1998a, b). The activation of cortical elements is influenced by the orientation and strength of the induced currents and the local anatomy (Balslev et al., 2007).

By placing a focal coil on the scalp over the cortical region of interest it is possible to target various cortical areas. Often the coil position is individualized based on a "hotspot," defined as the optimal site of the coil for maximum measured response. Targeting of the appropriate cortical region is relatively straightforward in the case of the primary motor cortex as there is a clearly observable and recordable response (muscle twitch and associated MEP). For this region, the coil is moved over the scalp

until a motor response is seen in the target muscle. This allows the hotspot for activation to be identified reliably. There is an open debate as to whether the old M1 at the gyral crown or the new M1 in the sulcus is preferentially stimulated. Owing to differences in neuronal orientation and cortical folding, a strong tangential electric field may theoretically stimulate horizontally oriented neurons in the crown of a gyrus or pyramidal neurons in the sulcal walls (most recent overview is given in Salvador et al., 2011). For nonmotor areas, targeting presents more of a problem. Some studies have employed standardized measurements on the scalp to target nonprimary motor areas (e.g., premotor cortex and supplementary motor cortex; Civardi et al., 2001; Baumer et al., 2009). However, it is known that there is considerable variability in interindividual cortical anatomy (Steinmetz et al., 1990), rendering this approach susceptible to inaccurate targeting. Perhaps the best approach for targeting nonprimary motor cortex is to use a stereotactic coil positioning system and either structural or functional imaging data. This allows precise targeting of cortical zones as well as accurate coil placement between trials. Studies using this approach have revealed significant problems with standardized measurement targeting of cortical regions (Herwig et al., 2001; Fitzgerald et al., 2009).

TMS can activate both excitatory and inhibitory elements within the cortex, and by changing pulse shape and amplitude it is possible preferentially to target excitatory or inhibitory neurons. It should be noted that the effect of stimulation is unlikely to be reflective of normal physiological activation. Most of what we know about TMS has arisen from studies of the motor system following stimulation of the motor cortex. This is partly because there are clear effects of stimulation, at least when suprathreshold, in the form of muscle responses. These responses can be recorded as MEPs. Many other cortical regions have also been targeted, but usually there are no obvious effects apart from stimulation of the visual cortex that can result in basic visual phenomena in the form of phosphenes (Meyer et al., 1991).

How focal is TMS? This is influenced to a great extent by the shape and size of the stimulating coil and by the coil current waveform and amplitude. It is difficult to estimate the cortical territory influenced by TMS in a real brain, as this would require detailed information on the spatial distribution of the induced electric field within the head, the local anatomy, and the interaction between the induced field and the neural tissue (Miranda et al., 2003). However, using a spherical head model and a standard figure-8 coil, it has been estimated that an area of approximately 2–3 cm^2 is stimulated at around threshold intensities (Thielscher and Kammer, 2004). More realistic computational models have shown complex local electric field maxima resulting from the brain tissue geometry and conductivity, heterogeneity, and anisotropy (Opitz et al., 2011; Thielscher et al., 2011). The properties of the neurons in these regions further affect the stimulation focality. Therefore, the area of activation cannot be simplified to a 2–3-cm^2 oval under the center of the coil. An idea of the focality achievable in practice can be gained by examining the motor responses evoked by TMS applied to the motor cortex. For example, just suprathreshold stimuli can preferentially activate small hand muscles with little activation of forearm musculature. Smaller figure-8 coils allow more focal stimulation and are of use in studies with children and some animal models.

Modification of stimulus parameters including intensity, number of stimuli, and frequency of stimulation has allowed the development of many TMS approaches. Basically, TMS can be used in several different modes to: (1) test the excitability of the corticospinal system; (2) test the excitability of intracortical inhibitory and excitatory elements; and (3) induce neuroplastic change. The use of TMS techniques has become widespread, and the employment of the different paradigms has provided novel insights into cortical function in conscious human subjects.

Single-pulse transcranial magnetic stimulation

A number of different measures can be obtained with single-pulse TMS that provide information on various aspects of corticospinal and intracortical excitability. Resting motor threshold (RMT) is commonly defined as being the minimum stimulus intensity required to evoke MEPs of at least 50 μV in 50% of trials in a series (usually 10). RMT is influenced by a number of technical factors including stimulus waveform, coil orientation, and distance of coil from cortex (Kozel et al., 2000). RMT is dependent upon the intrinsic excitability of intracortical elements in the circuit responsible for MEP generation, as well as the excitability of the excitatory synaptic inputs to the corticospinal cells. Evidence to support this has come from pharmacological studies showing that drugs that block voltage-gated sodium channels increase RMT (Ziemann et al., 1996), whereas indirect AMPA receptor (important for excitatory synaptic transmission) agonists decrease RMT (Di Lazzaro et al., 2003).

MEP amplitude provides a measure of corticospinal excitability (can be influenced by spinal excitability changes). Therefore, MEPs are useful for providing a marker of neuroplastic change within the corticospinal system. Often test MEPs evoked by set stimulus intensity (120% RMT), or of a given amplitude (1 mV), are used to establish baseline excitability prior to an intervention. Evidence of induced neuroplastic change is then provided by a change in test MEP amplitude. MEP

amplitude increases with stimulus intensity in a sigmoidal fashion (Ridding and Rothwell, 1997). Therefore, it is sometimes useful to construct stimulus response curves to characterize more fully changes in corticospinal excitability (Ridding and Rothwell, 1997).

MEPs depend on excitatory synaptic transmission and, as such, are influenced by both inhibitory and excitatory neurotransmitters. For example, $GABA_A$ receptor agonists decrease MEP amplitude (Inghilleri et al., 1996) and AMPA receptor agonists increase MEP amplitude (Di Lazzaro et al., 2003). As MEPs are dependent largely upon synaptic transmission within the cortex, they provide a useful marker of changes in synaptic efficacy. Therefore, they have proved to be a popular marker of neuroplastic change (evidenced as a change in excitability) within M1 following training or experimental paradigms (e.g., rTMS, tDCS) designed to induce neuroplastic change.

Single-pulse TMS can also be used to study the function of cortical inhibitory networks by examining the cortical silent period (CSP). The CSP is the interruption of voluntary electromyographic activity in the target muscle seen following TMS. It usually follows an MEP, although it can be seen in the absence of an MEP at low stimulus intensities. CSP increases in duration with stimulus intensity and can last for up to 200–300 ms (Cantello et al., 1992). There is evidence that this form of inhibition reflects $GABA_B$-mediated inhibition, but at certain intensities there may be a contribution from $GABA_A$-dependent inhibition (Paulus et al., 2008).

Paired-pulse transcranial magnetic stimulation

It is possible to test connectivity within and between cortical regions by employing paired-pulse TMS paradigms. Kujirai and colleagues (1993) initially developed this approach and demonstrated that a subthreshold conditioning stimulus applied at short interstimulus interval (1–5 ms) through the same coil as a second, test, stimulus could inhibit the response to the test stimulus. This inhibition is known as short-interval intracortical inhibition (SICI) and is likely due to activity in local $GABA_A$-ergic inhibitory interneurons. A facilitatory effect (intracortical facilitation; ICF) is seen at longer interstimulus interval (7–20 ms). With paired suprathreshold stimuli and long intervals (100–200 ms), a strong inhibition can be seen (Valls-Sole et al., 1992). This inhibition, known as long-interval intracortical inhibition (LICI), is dependent upon a $GABA_B$-ergic intracortical network (McDonnell et al., 2006).

Using a similar approach, but with modifications in the intensity of the paired TMS pulses, it is possible to examine intracortical facilitatory networks (short-interval intracortical facilitation; SICF). Paired stimuli at just threshold intensities (Tokimura et al., 1996), or a suprathreshold stimulus followed by subthreshold stimulus (Ziemann et al., 1998c), result in marked facilitation at specific interstimulus intervals. Usually three peaks of facilitation are seen at approximately 1.3, 2.5, and 4.3 ms.

Using a modification of these approaches and two coils, it is possible to probe the connectivity between cortical regions. Usually these studies involve application of a test stimulus to the primary motor cortex and a conditioning stimulus to a remote cortical region. Using this technique, connectivity between premotor cortex and M1 (Civardi et al., 2001), supplementary motor cortex and M1 (Civardi et al., 2001), and parietal cortex and M1 (Koch et al., 2007) has been examined. Additionally, interhemispheric connectivity between various regions, including M1 to M1 (Ferbert et al., 1992) and premotor cortex to M1 (Mochizuki et al., 2004), can be explored using twin-coil approaches.

Conventional repetitive transcranial magnetic stimulation

By applying TMS in the form of extended trains of stimuli, it is possible to induce lasting changes in the cortex. Conventional rTMS refers to the original protocols developed that employ simple trains of evenly spaced pulses. This form of stimulation usually consists of trains of stimuli applied at either low (1–2 Hz) or high (5–20 Hz) frequency. The influence of these protocols depends on a complex interaction between stimulus train frequency, intensity, and duration. However, in general, low-frequency stimulation (<2 Hz) reduces cortical excitability, and higher frequency (>5 Hz) protocols increase excitability. For example, 1500 stimuli applied at 1 Hz reduce M1 excitability for approximately 30 minutes (Touge et al., 2001). In general, these inhibitory paradigms require the application of large numbers of stimuli in order to produce lasting effects on cortical excitability. It has proved to be more difficult to develop protocols that induce lasting increases in excitability. This is partly due to safety concerns arising from the potential for higher frequency rTMS to induce seizures (Rossi et al., 2009). However, short trains of 5-Hz rTMS can increase cortical excitability.

Importantly, there is evidence that the changes induced by such induction paradigms involve functionally relevant networks in the cortex as they influence voluntary behavior. For example, Schlaghecken and colleagues (2003) reported that 1-Hz subthreshold rTMS applied to the motor cortex for 20 minutes slowed reaction time in a task performed with the hand contralateral to the stimulated hemisphere. It has also been shown that rTMS paradigms can positively influence function in neurologically impaired patients (Khedr et al., 2005), although at this stage the effects are relatively modest.

It is currently not possible to obtain direct evidence in humans for the mechanisms responsible for the

after-effects of rTMS. However, indirect evidence suggests that such changes reflect alterations in synaptic efficacy and are largely due to mechanisms similar to long-term potentiation (LTP) and long-term depression (LTD). For example, the time course, reversibility, and frequency dependence and dependence on NMDA receptors (Stefan et al., 2002; Huang et al., 2007) are consistent with LTP/LTD-like mechanisms. Additionally, in animal models the induction of LTP/LTD is facilitated by a reduction in GABA-ergic inhibition. Similarly, a paradigm known to reduce GABA-ergic inhibition in human subjects has been shown to facilitate plasticity induction following a low-frequency rTMS paradigm (Ziemann et al., 1998b).

The response to many rTMS paradigms is generally small, relatively short-lasting, and highly variable. In particular, there is a large degree of intrasubject and intersubject variability in the response (Sale et al., 2007). There is likely to be a large number of factors responsible for this variability. For example, the history of synaptic activity of the targeted region, genetic profile, and age have all been shown to influence the response to rTMS paradigms (Ridding and Ziemann, 2010).

Theta burst stimulation

More recently several new rTMS paradigms have been developed that have several advantages over conventional paradigms. These new paradigms use repeated high-frequency (50 Hz) bursts of pulses applied at theta frequency (5 Hz) and are known as theta burst stimulation (TBS). By varying the train duration and temporal spacing of the bursts it is possible to induce lasting decreases (continuous TBS; cTBS) or increases (intermittent TBS; iTBS) in cortical excitability (Huang et al., 2005). Advantages of these techniques over conventional approaches include shorter application times, lower intensities, and a more consistent response pattern. Again, there is good evidence that the changes induced by these techniques are due to LTD/LTP-like mechanisms (Huang et al., 2007).

Quadripulse stimulation

In a different experimental paradigm, repeated trains of four TMS pulses (quadripulse stimulation; QPS) separated by interstimulus intervals of 1.5–1250 ms produced a range of after-effects (Hamada et al., 2008). Hamada et al. found that QPS at short intervals facilitated MEPs for more than 75 minutes, whereas QPS at long intervals suppressed MEPs for more than 75 minutes. These effects were mainly due to effects on excitatory but not inhibitory circuits of the primary motor cortex.

Paired associative stimulation

When repetitively combining TMS with peripheral nerve stimulation at fixed time intervals, outlasting cortical excitability increases or decreases can be accomplished, depending on the time interval (Stefan et al., 2000). If the sensory stimulus is applied 10 ms before the TMS pulse, inhibition is induced; at a 25-ms interval there is excitation (Wolters et al., 2003). Repetition rate for paired associative stimulation (PAS) is effective at stimulation rates of 0.1 Hz, which is regarded as ineffective to modulate MEP after-effects by rTMS. Exceptions for rTMS have been achieved, for example by decreasing GABA-ergic inhibition by forearm ischemia (Ziemann et al., 1998a). Although regarded as ineffective at 0.1 Hz, rTMS may, however, occlude subsequently induced PAS effects (Delvendahl et al., 2010). PAS may also be applied in rapid sequences; 2 minutes of 5-Hz rPAS at and ISI of 25 ms produces a long-lasting and somatotopically specific increase in corticospinal excitability, presumably by sensorimotor disinhibition (Quartarone et al., 2006).

PAS-induced after-effects are regarded as synapse-specific in contrast to synapse nonspecific plasticity induced by tDCS. This was reflected in a pharmacological study that employed the comparative application of 100 mg L-dopa before either PAS or tDCS. This drug converted anodal excitatory after-effects into inhibitory after-effects, and prolonged both anodal and cathodal tDCS after-effects from about 1 hour to 36 hours. In contrast, it facilitated excitatory PAS after-effects by a similar factor (Kuo et al., 2008), supporting a focusing role of dopamine in enhancing synapse-specific plasticity and suppressing nonspecific plasticity.

Subthreshold paradigms

Low-field magnetic stimulation

Relatively weak pulsed magnetic fields such as the gradient fields in MRI scanners produce reduction of glucose metabolism, which is a marker of brain function (Volkow et al., 2010). The glucose metabolism reduction correlated with the estimated strength of the induced electric field. MRI gradient fields have been reported to produce antidepressant effects in humans (Rohan et al., 2004) and rats (Carlezon et al., 2005), suggesting potential clinical utility of subthreshold low-field magnetic stimulation (LFMS) paradigms.

Transcranial static magnetic field stimulation

Transcranial static magnetic field stimulation (tSMS) of motor cortex in the range of 0.1 Tesla for 10 min results in reduction of MEP amplitude by 25% for about 6 minutes after the end of stimulation in humans (Oliviero et al., 2011; Paulus, 2011b). In that experiment,

the magnetic field was produced by a neodymium–iron–boron permanent magnet, rather than by an induction coil, because the field is not pulsed. The mechanisms of neuromodulation with static fields of this magnitude are not understood, but they must be fundamentally different from those of TMS and TES, because the static magnetic field does not induce an electric field in the brain.

Convulsive paradigms

Magnetic seizure therapy

Analogously to ECT, high-intensity rTMS can be used to induce a therapeutic seizure in anesthetized patients. The resulting convulsive technique, MST, is under active study (Lisanby et al., 2001; Kosel et al., 2003; Lisanby et al., 2003; Kayser et al., 2010). Potential advantages of MST are the more focused and less variable electric field compared with conventional ECT, which could result in fewer side-effects and interindividual variability of outcome (Sackeim, 1994). Drawbacks of the technique include the need for high-power rTMS devices to generate stimulus trains of sufficient intensity to induce a seizure under anesthesia and the associated coil heating.

CONCLUSIONS AND FUTURE DIRECTIONS

TES and TMS involve numerous parameters that control the spatial and temporal characteristics of the generated electric and magnetic fields. Consequently, the search for optimal stimulation paradigms for various applications is particularly challenging. Even with the recent development of theta burst techniques, there is still considerable intrasubject and intersubject variability in the response to rTMS paradigms. In addition, the induced changes are transient and easily disrupted, limiting potential behavioral and therapeutic usefulness. Further development of stimulation paradigms is necessary to enhance the usefulness of these techniques. For example, there are some preliminary data to suggest that spaced (by tens of minutes) application of rTMS protocols might lead to the induction of more lasting neuroplastic change (Nyffeler et al., 2006; Goldsworthy et al., 2012), similar to tDCS (Monte-Silva et al., 2013). There is also evidence that monophasic TMS pulses may produce stronger and more selective neuromodulation than biphasic pulses (Antal et al., 2002; Sommer et al., 2002; Arai et al., 2005, 2007; Tings et al., 2005; Taylor and Loo, 2007; Hosono et al., 2008). Given the complexity of optimizing electric and magnetic stimulation paradigms, studies at various levels of exploration – *in vitro*, animal model, healthy human, clinical, computational model, and device development – should be deployed to address this challenge.

References

Abrams R (2002). Electroconvulsive Therapy. 4th edn. Oxford University Press, New York.

Antal A, Kincses TZ, Nitsche MA et al. (2002). Pulse configuration-dependent effects of repetitive transcranial magnetic stimulation on visual perception. Neuroreport 13: 2229–2233.

Antal A, Nitsche MA, Kruse W et al. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 16: 521–527.

Antal A, Terney D, Poreisz C et al. (2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci 26: 2687–2691.

Antal A, Boros K, Poreisz C et al. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul 1: 97–105.

Arai N, Okabe S, Furubayashi T et al. (2005). Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. Clin Neurophysiol 116: 605–613.

Arai N, Okabe S, Furubayashi T et al. (2007). Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. Clin Neurophysiol 118: 2227–2233.

Ardolino G, Bossi B, Barbieri S et al. (2005). Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol 568: 653–663.

Balslev D, Braet W, McAllister C et al. (2007). Inter-individual variability in optimal current direction for transcranial magnetic stimulation of the motor cortex. J Neurosci Methods 162: 309–313.

Baumer T, Schippling S, Kroeger J et al. (2009). Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest – a bifocal TMS study. Clin Neurophysiol 120: 1724–1731.

Batsikadze G, Moliadze V, Paulus W et al. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 591: 1987–2000.

Bikson M, Radman T, Datta A (2006). Rational modulation of neuronal processing with applied electric fields. Conf Proc IEEE Eng Med Biol Soc 1: 1616–1619.

Bindman LJ, Lippold OC, Redfearn JW (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol 172: 369–382.

Cantello R, Gianelli M, Civardi C et al. (1992). Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42: 1951–1959.

Carlezon WA Jr, Rohan ML, Mague SD et al. (2005). Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats. Biol Psychiatry 57: 571–576.

Chaieb L, Antal A, Paulus W (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor Neurol Neurosci 29: 167–175.

Civardi C, Cantello R, Asselman P et al. (2001). Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 14: 1444–1453.

Creutzfeldt OD, Fromm GH, Kapp H (1962). Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol 5: 436–452.

Danner N, Julkunen P, Kononen M et al. (2008). Navigated transcranial magnetic stimulation and computed electric field strength reduce stimulator-dependent differences in the motor threshold. J Neurosci Methods 174: 116–122.

Datta A, Bansal V, Diaz J et al. (2009). Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimulat 2: 201–207.

Datta A, Baker JM, Bikson M et al. (2011). Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimul 4: 169–174.

Delvendahl I, Jung NH, Mainberger F et al. (2010). Occlusion of bidirectional plasticity by preceding low-frequency stimulation in the human motor cortex. Clin Neurophysiol 121: 594–602.

Deng Z-D, Lisanby SH, Peterchev AV (2009). Effect of anatomical variability on neural stimulation strength and focality in electroconvulsive therapy (ECT) and magnetic seizure therapy (MST). Conf Proc IEEE Eng Med Biol Soc 2009: 682–688.

Deng Z-D, Lisanby SH, Peterchev AV (2013). Electric field depth–focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul 6: 1–13.

Di Lazzaro V, Oliviero A, Profice P et al. (1998). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalogr Clin Neurophysiol 109: 397–401.

Di Lazzaro V, Oliviero A, Profice P et al. (2003). Ketamine increases human motor cortex excitability to transcranial magnetic stimulation. J Physiol 547: 485–496.

Di Lazzaro V, Oliviero A, Pilato F et al. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol 115: 255–266.

Dmochowski JP, Datta A, Bikson M et al. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng 8: 046011.

Elbert T, Lutzenberger W, Rockstroh B et al. (1981). The influence of low-level transcortical DC-currents on response speed in humans. Int J Neurosci 14: 101–114.

Epstein CM, Davey KR (2002). Iron-core coils for transcranial magnetic stimulation. J Clin Neurophysiol 19: 376–381.

Fadini T, Matthaus L, Rothkegel H et al. (2009). H-coil: induced electric field properties and input/output curves on healthy volunteers, comparison with a standard figure-of-eight coil. Clin Neurophysiol 120: 1174–1182.

Fadini T, Matthäus L, Rothkegel H et al. (2010). Reply to "Motor evoked potential latency, motor threshold and electric field measurements as indices of transcranial magnetic stimulation depth". Clin Neurophysiol 121: 258–259.

Faria P, Hallett M, Miranda PC (2011). A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. J Neural Eng 8: 066017.

Ferbert A, Priori A, Rothwell JC et al. (1992). Interhemispheric inhibition of the human motor cortex. J Physiol 453: 525–546.

Fertonani A, Pirulli C, Miniussi C (2011). Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 31: 15416–15423.

Fink M (2001). Convulsive therapy: a review of the first 55 years. J Affect Disord 63: 1–15.

Fitzgerald PB, Maller JJ, Hoy KE et al. (2009). Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul 2: 234–237.

Furubayashi T, Terao Y, Arai N et al. (2008). Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. Exp Brain Res 185: 279–286.

Gamboa OL, Antal A, Moliadze V et al. (2010). Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204: 181–187.

Goldsworthy MR, Pitcher JB, Ridding MC (2012). The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci 35: 125–134.

Hamada M, Terao Y, Hanajima R et al. (2008). Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 586: 3927–3947.

Hellwag CF, Jacobi M (1802). Erfahrungen über die Heilkräfte des Galvanismus und Betrachtungen über desselben chemische und physiologische Wirkungen. Friedrich Perthes, Hamburg.

Herwig U, Padberg F, Unger J et al. (2001). Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 50: 58–61.

Hosono Y, Urushihara R, Harada M et al. (2008). Comparison of monophasic versus biphasic stimulation in rTMS over premotor cortex: SEP and SPECT studies. Clin Neurophysiol 119: 2538–2545.

Huang YZ, Edwards MJ, Rounis E et al. (2005). Theta burst stimulation of the human motor cortex. Neuron 45: 201–206.

Huang YZ, Chen RS, Rothwell JC et al. (2007). The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin Neurophysiol 118: 1028–1032.

Inghilleri M, Berardelli A, Marchetti P et al. (1996). Effects of diazepam, baclofen and thiopental on the silent period evoked by transcranial magnetic stimulation in humans. Exp Brain Res 109: 467–472.

Jalinous R (2002). Principles of magnetic stimulator design. In: A Pascual-Leone, NJ Davey, J Rothwell et al. (Eds.),

Handbook of Transcranial Magnetic Stimulation. Arnold, London, pp. 30–38.
Jeffery DT, Norton JA, Roy FD et al. (2007). Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. Exp Brain Res 182: 281–287.
Kanai R, Chaieb L, Antal A et al. (2008). Frequency-dependent electrical stimulation of the visual cortex. Curr Biol 18: 1839–1843.
Kayser S, Bewernick BH, Grubert C et al. (2010). Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. J Psychiatr Res 45: 569–576.
Khedr EM, Ahmed MA, Fathy N et al. (2005). Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 65: 466–468.
Kirson ED, Dbaly V, Tovarys F et al. (2007). Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 104: 10152–10157.
Koch G, Fernandez Del Olmo M, Cheeran B et al. (2007). Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27: 6815–6822.
Kosel M, Frick C, Lisanby SH et al. (2003). Magnetic seizure therapy improves mood in refractory major depression. Neuropsychopharmacology 28: 2045–2048.
Kozel FA, Nahas Z, deBrux C et al. (2000). How coil–cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 12: 376–384.
Kujirai T, Caramia MD, Rothwell JC et al. (1993). Corticocortical inhibition in human motor cortex. J Physiol 471: 501–519.
Kuo MF, Paulus W, Nitsche MA (2008). Boosting focally-induced brain plasticity by dopamine. Cereb Cortex 18: 648–651.
Liebetanz D, Klinker F, Hering D et al. (2006). Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. Epilepsia 47: 1216–1224.
Lisanby SH (2007). Electroconvulsive therapy for depression. N Engl J Med 357: 1939–1945.
Lisanby SH, Schlaepfer TE, Fisch HU et al. (2001). Magnetic seizure therapy of major depression. Arch Gen Psychiatry 58: 303–305.
Lisanby SH, Luber B, Schlaepfer TE et al. (2003). Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. Neuropsychopharmacology 28: 1852–1865.
Matthaus L (2008). A Robotic Assistance System for Transcranial Magnetic Stimulation and its Application to Motor Cortex Mapping. Institute for Robotics and Cognitive Systems University of Lübeck, Lübeck, Germany.
McDonnell MN, Orekhov Y, Ziemann U (2006). The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. Exp Brain Res 173: 86–93.
Merrill DR, Bikson M, Jefferys JG (2005). Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods 141: 171–198.
Merton PA, Morton HB (1980). Stimulation of the cerebral cortex in the intact human subject. Nature 285: 227.
Meyer BU, Diehl R, Steinmetz H et al. (1991). Magnetic stimuli applied over motor and visual cortex: influence of coil position and field polarity on motor responses, phosphenes, and eye movements. Electroencephalogr Clin Neurophysiol Suppl 43: 121–134.
Minhas P, Bansal V, Patel J et al. (2010). Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. J Neurosci Methods 190: 188–197.
Miranda PC, Hallett M, Basser PJ (2003). The electric field induced in the brain by magnetic stimulation: a 3-D finite-element analysis of the effect of tissue heterogeneity and anisotropy. IEEE Trans Biomed Eng 50: 1074–1085.
Miranda PC, Faria P, Hallett M (2009). What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? Clin Neurophysiol 120: 1183–1187.
Mochizuki H, Huang YZ, Rothwell JC (2004). Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561: 331–338.
Moliadze V, Antal A, Paulus W (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. J Physiol 588: 4891–4904.
Moliadze V, Atalay D, Antal A et al. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul 5: 505–511.
Monte-Silva K, Hessenthaler S, Kuo MF et al. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 6: 424–432.
Nitsche MA, Paulus W (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527: 633–639.
Nitsche MA, Paulus W (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57: 1899–1901.
Nitsche MA, Nitsche MS, Klein CC et al. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 114: 600–604.
Nitsche MA, Doemkes S, Karakose T et al. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 97: 3109–3117.
Nitsche MA, Kuo MF, Karrasch R et al. (2009). Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatry 66: 503–508.
Nowak LG, Bullier J (1998a). Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter I. Evidence from chronaxie measurements. Exp Brain Res 118: 477–488.
Nowak LG, Bullier J (1998b). Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter II.

Evidence from selective inactivation of cell bodies and axon initial segments. Exp Brain Res 118: 489–500.
Nyffeler T, Wurtz P, Luscher HR et al. (2006). Extending lifetime of plastic changes in the human brain. Eur J Neurosci 24: 2961–2966.
Oliviero A, Mordillo-Mateos L, Arias P et al. (2011). Transcranial static magnetic field stimulation of the human motor cortex. J Physiol 589: 4949–4958.
Opitz A, Windhoff M, Heidemann RM et al. (2011). How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. Neuroimage 58: 849–859.
Paulus W (2011a). Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods. Neuropsychol Rehabil 21: 602–617.
Paulus W (2011b). Transcranial static magnetic field stimulation in man: making things as simple as possible? J Physiol 589: 5917–5918.
Paulus W, Classen J, Cohen LG et al. (2008). State of the art: pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul 1: 151–163.
Peterchev AV, Jalinous R, Lisanby SH (2008). A transcranial magnetic stimulator inducing near-rectangular pulses with controllable pulse width (cTMS). IEEE Trans Biomed Eng 55: 257–266.
Peterchev AV, Rosa MA, Deng Z-D et al. (2010). Electroconvulsive therapy stimulus parameters: rethinking dosage. J ECT 26: 159–174.
Peterchev AV, Murphy DL, Lisanby SH (2011). A repetitive transcranial magnetic stimulator with controllable pulse parameters. J Neural Eng 8: 036016.
Peterchev AV, Wagner TA, Miranda PC et al. (2012). Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul 5: 435–453.
Pogosyan A, Gaynor LD, Eusebio A et al. (2009). Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 19: 1637–1641.
Priori A, Berardelli A, Rona S et al. (1998). Polarization of the human motor cortex through the scalp. NeuroReport 9: 2257–2260.
Quartarone A, Rizzo V, Bagnato S et al. (2006). Rapid-rate paired associative stimulation of the median nerve and motor cortex can produce long-lasting changes in motor cortical excitability in humans. J Physiol 575: 657–670.
Radman T, Ramos RL, Brumberg JC et al. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul 2: 215–228, 228.e1–228.e3.
Reis J, Schambra HM, Cohen LG et al. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106: 1590–1595.
Ridding MC, Rothwell JC (1997). Stimulus/response curves as a method of measuring motor cortical excitability in man. Electroencephalogr Clin Neurophysiol 105: 340–344.
Ridding MC, Ziemann U (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 588: 2291–2304.
Rohan M, Parow A, Stoll AL et al. (2004). Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. Am J Psychiatry 161: 93–98.
Rossi S, Hallett M, Rossini PM et al. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120: 2008–2039.
Rossini PM, Barker AT, Berardelli A et al. (1994). Noninvasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91: 79–92.
Roth Y, Zangen A, Hallett M (2002). A coil design for transcranial magnetic stimulation of deep brain regions. J Clin Neurophysiol 19: 361–370.
Roth Y, Amir A, Levkovitz Y et al. (2007). Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. J Clin Neurophysiol 24: 31–38.
Roth Y, Pell GS, Zangen A (2010). Motor evoked potential latency, motor threshold and electric field measurements as indices of transcranial magnetic stimulation depth. Clin Neurophysiol 121: 255–258.
Rothkegel H, Sommer M, Paulus W et al. (2010). Impact of pulse duration in single pulse TMS. Clin Neurophysiol 121: 1915–1921.
Rothwell J, Burke D, Hicks R et al. (1994). Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. J Physiol 481: 243–250.
Ruohonen J, Ilmoniemi RJ (2002). Physical principles for transcranial magnetic stimulation. In: A Pascual-Leone, NJ Davey, J Rothwell et al. (Eds.), Handbook of Transcranial Magnetic Stimulation. Arnold, London, pp. 18–29.
Sackeim H (1994). Magnetic stimulation therapy and ECT. Convuls Ther 10: 255–258.
Sackeim HA, Prudic J, Devanand DP et al. (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 57: 425–434.
Sackeim HA, Prudic J, Nobler MS et al. (2008). Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 1: 71–83.
Saisanen L, Julkunen P, Niskanen E et al. (2008). Motor potentials evoked by navigated transcranial magnetic stimulation in healthy subjects. J Clin Neurophysiol 25: 367–372.
Sale MV, Ridding MC, Nordstrom MA (2007). Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. Exp Brain Res 181: 615–626.
Salvador R, Silva S, Basser PJ et al. (2011). Determining which mechanisms lead to activation in the motor cortex:

a modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry. Clin Neurophysiol 122: 748–758.

Schlaghecken F, Munchau A, Bloem BR et al. (2003). Slow frequency repetitive transcranial magnetic stimulation affects reaction times, but not priming effects, in a masked prime task. Clin Neurophysiol 114: 1272–1277.

Schutter DJ, Hortensius R (2010). Retinal origin of phosphenes to transcranial alternating current stimulation. Clin Neurophysiol 121: 1080–1084.

Sommer M, Lang N, Tergau F et al. (2002). Neuronal tissue polarization induced by repetitive transcranial magnetic stimulation? NeuroReport 13: 809–811.

Sommer M, Alfaro A, Rummel M et al. (2006). Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. Clin Neurophysiol 117: 838–844.

Stefan K, Kunesch E, Cohen LG et al. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123: 572–584.

Stefan K, Kunesch E, Benecke R et al. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 543: 699–708.

Steinmetz H, Furst G, Freund HJ (1990). Variation of perisylvian and calcarine anatomic landmarks within stereotaxic proportional coordinates. AJNR Am J Neuroradiol 11: 1123–1130.

Taylor JL, Loo CK (2007). Stimulus waveform influences the efficacy of repetitive transcranial magnetic stimulation. J Affect Disord 97: 271–276.

Terney D, Chaieb L, Moliadze V et al. (2008). Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 28: 14147–14155.

Thielscher A, Kammer T (2004). Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency. Clin Neurophysiol 115: 1697–1708.

Thielscher A, Opitz A, Windhoff M (2011). Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. Neuroimage 54: 234–243.

Tings T, Lang N, Tergau F et al. (2005). Orientation-specific fast rTMS maximizes corticospinal inhibition and facilitation. Exp Brain Res 164: 323–333.

Tokimura H, Ridding MC, Tokimura Y et al. (1996). Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol 101: 263–272.

Touge T, Gerschlager W, Brown P et al. (2001). Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses? Clin Neurophysiol 112: 2138–2145.

Valls-Sole J, Pascual-Leone A, Wassermann EM et al. (1992). Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol 85: 355–364.

Volkow ND, Tomasi D, Wang GJ et al. (2010). Effects of low-field magnetic stimulation on brain glucose metabolism. Neuroimage 51: 623–628.

Weiner RD, Rogers HJ, Davidson JR et al. (1986). Effects of stimulus parameters on cognitive side effects. Ann N Y Acad Sci 462: 315–325.

Wolters A, Sandbrink F, Schlottmann A et al. (2003). A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. J Neurophysiol 89: 2339–2345.

Zaghi S, Acar M, Hultgren B et al. (2010). Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation. Neuroscientist 16: 285–307.

Zangen A, Roth Y, Voller B et al. (2005). Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin Neurophysiol 116: 775–779.

Ziemann U, Lönnecker S, Steinhoff BJ et al. (1996). Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40: 367–378.

Ziemann U, Corwell B, Cohen LG (1998a). Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 18: 1115–1123.

Ziemann U, Hallett M, Cohen LG (1998b). Mechanisms of deafferentation-induced plasticity in human motor cortex. J Neurosci 18: 7000–7007.

Ziemann U, Tergau F, Wassermann EM et al. (1998c). Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol 511: 181–190.