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Chapter 37

Transcranial magnetic stimulation

JEAN-PASCAL LEFAUCHEUR[1,2]*

[1]*Excitabilité Nerveuse et Thérapeutique, Faculté de Médecine de Créteil, Créteil, France*

[2]*Service de Physiologie—Explorations Fonctionnelles, Hôpital Henri Mondor, Créteil, France*

Abstract

This review presents the neurophysiologic principles and clinical applications of transcranial magnetic stimulation (TMS) and other related techniques of noninvasive cortical stimulation. TMS can serve various purposes for diagnosis or treatment. Regarding diagnosis, TMS is mainly dedicated to the recording of motor evoked potentials (MEPs). MEP recording allows investigation of corticospinal conduction time and cortical motor control in clinical practice. Especially when using image-guided neuronavigation methods, MEP recording is a reliable method to perform functional mapping of muscle representation within the motor cortex. Using various types of paired-pulse paradigms, TMS allows the assessment of brain circuit excitability or plastic changes affecting these circuits. In particular, paired-pulse TMS paradigms are able to appraise the intracortical balance between inhibitory controls mediated by GABAergic neurotransmission and excitatory controls mediated by glutamatergic neurotransmission. Finally, TMS delivered as repetitive trains of stimulation (rTMS) may activate, inhibit, or otherwise interfere with the activity of neuronal cortical networks, depending on stimulus frequency and intensity, and brain-induced electric field configuration. Therefore by modifying brain functions, with after-effects lasting beyond the time of stimulation, rTMS opens exciting perspectives for therapeutic applications, especially in the domain of depression and chronic pain syndromes.

INTRODUCTION: HIGH-VOLTAGE TRANSCRANIAL ELECTRICAL STIMULATION

Noninvasive brain stimulation is an increasingly growing domain of research and development for clinical neurophysiology, covering various applications, such as disease diagnosis, pathophysiologic investigation of cortical excitability changes, mapping of cortical function (e.g., before brain surgery), and therapeutics. A variety of techniques for transcranial brain stimulation has been proposed, using either electric or magnetic shocks delivered over the scalp.

In clinical neurophysiology practice, the initial objective of noninvasive cortical stimulation was to stimulate the motor cortex to study corticospinal conduction time, i.e., to record motor evoked potentials (MEPs). For this purpose, high-voltage electrical stimulators (transcranial electrical stimulation, or TES) were first used (Merton and Morton, 1980). They delivered brief high-voltage single electrical shocks through the scalp by means of a couple of electrodes, one anode and one cathode (bipolar montage). High voltage is required to cross the electric resistance of the skull and to produce efficacious currents into the motor cortex. The pyramidal tract axons are directly stimulated by high-voltage TES (at least under the anodal electrode), as shown by spinal recording of short-latency D-waves as descending volleys (Di Lazzaro et al., 1998). At high intensities, TES also activates intracortical interneurons, leading to an indirect activation of pyramidal neurons (multiple long-latency I-waves).

However, due to the high pain level that is generated at scalp level by high-voltage shocks and the development

*Correspondence to: Pr. Jean-Pascal Lefaucheur, M.D., Ph.D., Service de Physiologie—Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique—Hôpitaux de Paris, 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil, France. Tel: +33-1-49-81-26-90, Fax: +33-1-49-81-46-60, E-mail: jean-pascal.lefaucheur@aphp.fr

of better tolerated techniques of magnetic cortical stimulation, the clinical use of high-voltage TES has been restricted to the monitoring of motor pathways under general anesthesia, e.g., for spinal cord or aortic surgery (Macdonald, 2006; Deletis and Sala, 2008). In all other applications, TES has been replaced by transcranial magnetic stimulation (TMS), which was introduced by Barker et al. (1985) as a much less painful technique than TES to activate the motor cortex.

PRINCIPLES OF TRANSCRANIAL MAGNETIC STIMULATION

TMS is based on the scientific principle of electromagnetic induction discovered by Faraday in 1831. It consists of the passage of a brief current of very high intensity (several thousand amps) in a copper wire coil, which in turn produces a magnetic field that can reach up to about 2 T and lasts for about 100 µs. The magnetic field pulse delivered by a stimulating coil applied on the scalp is able to pass through skull bone without being attenuated and to generate an electric field when entering the brain (Fig. 37.1). The intensity of the induced current is sufficient to produce action potentials and to activate brain networks safely and painlessly. The first TMS machines for clinical use were built in the mid-1980s (Barker et al., 1985).

Various parameters modulate the geometry of the induced electric field and thereby the nature of the neural structures activated by TMS. These parameters include the orientation and type of TMS coil, which can be unique (circular) or double (double-cone, figure-of-eight), and the waveform of the magnetic pulse, which is usually monophasic or biphasic.

Regarding coil design, large circular coils with winding diameter of about 110–130 mm (number of windings: 14) were first used. With this coil, the area of cortical stimulation is relatively large. Therefore, double coils with smaller diameters were designed to produce more focal activation of the brain, such as the figure-of-eight coil (winding diameter: 75–87 mm (×2); number of windings: 9–10 (×2)), e.g., for brain mapping or therapeutic application of TMS. However, coils with smaller diameter heat up more rapidly in the case of repetitive stimulation, leading to the development of static- or active-liquid or air-cooling systems. At present, a variety of coils are available for different purposes (Fig. 37.2), including magnetic seizure therapy (Cretaz et al., 2015), which are distinguished by the different geometries of induced brain activation (Deng et al., 2014).

The type of coil determines the area of stimulation, while the pulse waveform (monophasic or biphasic) determines the nature of the cortical circuits that are activated in this area. When applied to the motor cortex (at least hand representation in the motor hand knob), a monophasic pulse delivered by a figure-of-eight coil with lateromedial orientation generates mostly a direct activation of corticospinal axons, as shown by recording

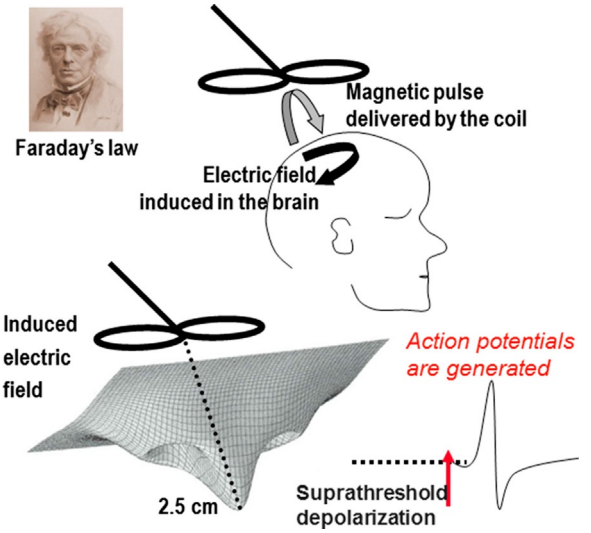

Fig. 37.1. Principle of electromagnetic induction (Faraday's law), geometry of the electric field induced into the brain, and excitatory effects of transcranial magnetic stimulation delivered by a figure-of-eight coil.

Fig. 37.2. Examples of coils usable for transcranial magnetic stimulation or magnetic seizure therapy (MST).

descending volleys as D-waves. In contrast, a figure-of-eight coil with posteroanterior orientation elicits only I-waves (Kaneko et al., 1996; Nakamura et al., 1996) and even later I-waves with an anteroposterior orientation (Di Lazzaro et al., 2001). The production of I-waves suggests a tangential stimulation of horizontal fibers at the surface of the precentral gyrus, leading to an indirect, transsynaptic activation of pyramidal cells. These observations may be relevant for stimulation applied outside the motor cortex, at least in the neocortex (Amassian and Stewart, 2003).

Biphasic stimulations are thought to be more powerful than monophasic stimulations, in particular to produce MEPs in response to the stimulation of the motor cortex (Kammer et al., 2001). Biphasic stimulation is even the standard pulse waveform used for applications of TMS delivered as repetitive trains of stimulation (rTMS), because of lower energy requirements (Sommer et al., 2006). The most effective current induced in the brain corresponds to the second phase of a biphasic stimulus (Di Lazzaro et al., 2001). However, comparing studies may be confusing since the direction of the pulse waveform can be reversed depending on the type of magnetic stimulator and the manufacturer (Kammer et al., 2001). Biphasic pulses generate a more complex pattern of neural activation and activate a less uniform population of neurons as compared to monophasic pulses. Therefore, monophasic pulses could be more effective than biphasic pulses to produce sustained after-effects when applied repetitively in the rTMS protocol (Sommer et al., 2002; Arai et al., 2005). For example, monophasic pulses produce more marked and prolonged MEP size reduction following 1-Hz rTMS delivered to the motor cortex (Taylor and Loo, 2007) and MEP enhancement following 10-Hz rTMS (Arai et al., 2007). However, at present it is not technically possible to deliver prolonged rTMS protocols including several trains using monophasic magnetic stimuli. Modulating the magnetic pulse waveform surely represents a way of optimizing future therapeutic applications of rTMS.

The intensity of stimulation also frankly impacts on TMS effects (Lang et al., 2006; Todd et al., 2006). Actually, the depth of penetration of the TMS pulse into the brain is relatively low when using a standard figure-of-eight or even a circular coil. The intensity of the induced current rapidly falls with the squared distance to the site of stimulation (Mills et al., 1987). However, the induced electric field goes deeper into the brain if stimulation intensity increases and is able to recruit additional neural networks. For example, when the motor cortex is stimulated at high intensity using a figure-of-eight coil, D-waves arising from the axon hillock of pyramidal cells can be elicited in addition to I-waves, even if the coil has a posteroanterior orientation (Di Di Lazzaro et al., 1998). To reach much deeper brain structures, specific coils have been designed, such as double-cone coils (combination of two large circular coils with an angle of 120 degrees) or "H-coils" (Zangen et al., 2005) (Fig. 37.2).

Both TES and TMS stimulate axons rather than cell bodies of neurons since the latter have longer electrical time constant and higher threshold. However, the currents induced in the brain by TES and TMS have an important directional component: axons are best stimulated by a current that flows in parallel with their grand axis. With respect to TMS, this means that stimulation often occurs at the point where the axon bends out of the field and the change in electric field is the greatest (Maccabee et al., 1993). Because TMS acts by activating circuits, the biological changes provoked by TMS may occur at a distance from the site of axonal activation, as demonstrated, for example, for the analgesic effects of precentral gyrus stimulation (Lefaucheur, 2016).

MOTOR EVOKED POTENTIALS

The main use of TMS in clinical neurophysiology is to assess the conduction of the descending corticospinal (or corticonuclear) pyramidal tract by recording MEPs. The MEPs are recorded over target muscles with surface electrodes and bipolar belly-tendon montage. The placement of the electrodes, as well as band-pass and amplification settings, are identical to those used for recording compound muscle action potentials (CMAPs) to distal electrical stimulation of a peripheral motor nerve. In practice, MEPs are recorded to nonfocal stimulation of the motor cortex and spinal roots (or the facial motor nerve for the face). To stimulate the cortical representation of upper limb or facial muscles over the lateral aspect of precentral gyrus convexity, a large circular coil is classically used. To reach the cortical representation of lower limb, torso, or pelvic floor muscles in the more medial and deeper interhemispheric aspect of precentral gyrus, it is better to use a double-cone coil.

When magnetic stimulation is delivered over the spine, it preferentially acts on nerve roots at the level of intervertebral foramina. Except in a few special cases (Tomberg, 1995), the magnetic pulse cannot directly stimulate the spinal cord itself within the vertebral canal because of the excitability properties of neural structures. As intraforaminal nerve roots, the facial nerve is particularly excitable at the stylomastoid foramen. Therefore, using TMS for recording MEPs, the total motor conduction time (TMCT) from the motor cortex to the target muscles can be divided into: (i) a "central" motor conduction time (CMCT), including conduction along the pyramidal tract from the cortical (upper) motor neurons to the lower motor neurons and the proximal part of the peripheral nerve (to intervertebral or stylomastoid

foramina), and (ii) a purely "peripheral" motor conduction time (PMCT), but assessing the peripheral nerve at a distance of the lower motor neuron cell body. In particular, for lower limb or pelvic floor muscle recordings, the relatively long pathways of lumbar and sacral spinal roots within the spinal canal (cauda equina) are taken into account in the CMCT.

It must also be emphasized that with TMS (monophasic pulses delivered by a circular coil), cortical (upper) motor neurons are usually excited transsynaptically via intracortical interneurons, in contrast to high-voltage TES that directly activates the corticospinal tract within the motor cortex. Therefore, the CMCT is longer when using TMS than TES, and is influenced by the level of excitability of cortical neurons. The CMCT decreases over the years in children, in parallel with central nervous system maturation until adolescence. In adults, CMCT has significant correlation not with age or gender but with body height, at least for lower limb MEPs. In practice, the CMCT is calculated by subtracting the PMCT from the TMCT (Fig. 37.3) and is very symmetrical. Therefore, the observation of between-side CMCT differences may be clinically meaningful.

Two remarks should be made about the PMCT. First, root stimulation can be performed using TMS (placing the coil over the spine), but also using electrical stimulation, e.g., with a high-voltage TES device (placing the cathode over the relevant root exit zone with the anode over the spine, some centimeters more rostrally). Nerve roots can also be stimulated invasively using monopolar needle electrodes inserted in their vicinity as a stimulating cathode. Second, there is an alternative method to root stimulation for measuring the PMCT, which is based on F-wave recordings. When recorded for the target muscle to distal electrical nerve stimulation, the F-wave latency (FWL) measures antidromic conduction time along the motor axons to the lower motor neuron cell bodies in the anterior horn of the spine, plus the reexcitation of the motor neuron pool (about 1 ms), and then the orthodromic conduction time from the anterior horns to the muscle. Accordingly, the PMCT can be estimated by taking half of the sum of FWL and the terminal motor latency (TML) to nerve stimulation and subtracting 1 ms, i.e., (FWL + TML − 1)/2 (Rossini et al., 1987). The PMCT measured with the F-wave technique is slightly longer than the PMCT to direct root stimulation because it includes the conduction time of the radicular pathways within the spinal canal from the anterior horns to the intervertebral foramina. Therefore, it is theoretically valuable to compare the PMCT (or CMCT) estimated with the methods based on root stimulation or F-wave recordings to assess these intracanal radicular pathways, e.g., corresponding to the cauda equina for lumbar and sacral spinal roots. However, the major limitation of the

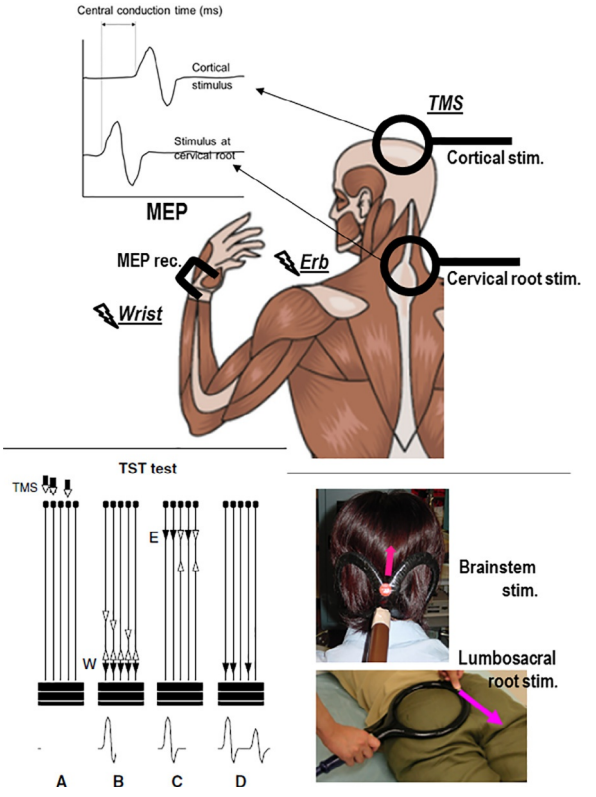

Fig. 37.3. *Upper panel*: classic method of motor evoked potential (MEP) recording at the hand in response to cortical and cervical root stimulation using a circular coil, with calculation of central motor conduction time. *Lower panel*, left: triple stimulation technique (TST) combining transcranial magnetic stimulation (TMS) of the motor cortex and peripheral nerve electrical stimulation at proximal (Erb's point, E) and distal (wrist, W) sites. (A)–(D) MEPs resulting from the TST test protocol, according to consecutive collision phenomena. Lower panel, right: techniques of brainstem and lumbosacral root stimulation, using a double-cone coil and a large 20-cm diameter circular coil, respectively. Partially adapted from Chen R, Cros D, Curra A et al. (2008). The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 119: 504–532 and Matsumoto H, Hanajima R, Terao Y et al. (2013). Magnetic-motor-root stimulation: review. Clin Neurophysiol 124: 1055–1067.

F-wave method is that F-waves may be difficult to reliably obtain in proximal muscles, which are targeted for MEPs. In addition, the FWLs, even if they are satisfactorily measurable, provide a measure of conduction for the fastest motor axons, which may be not those recruited by cortical or spinal TMS.

For spinal root or motor nerve TMS, the targeted muscles must be at rest, but for cortical TMS and CMCT measurement, the targeted muscles can be voluntarily contracted. Voluntary contraction increases the size and shortens the latency of the MEPs because it "preactivates" the spinal motoneuronal pools and puts

them closer to their firing thresholds. However, voluntary contraction also increases temporal dispersion of the MEPs and may create difficulties in distinguishing between normal and abnormal recordings in patients.

However, in practice, MEPs are usually recorded after asking the patient/subject to preactivate the target muscle at 10%–20% of maximum strength. For each muscle site, four to six consecutive MEPs should be recorded during slight tonic contraction and only the MEP with the largest amplitude should be considered. In patients with an inability to contract the target muscle (for instance, due to severe paresis), voluntary activation of the homologous muscle of the other side or motor imagery of target muscle contraction may facilitate MEPs, but to a lesser extent than the specific contraction of the target muscle.

MEP amplitude is not a reliable index and, in particular, no normative data can be reliably used in clinical practice. A frank asymmetry in MEP size (>50%) or MEP morphology is more relevant for diagnosis. In contrast, robust normative data can be established for MEP latency and conduction time variables. For example, in response to cortical stimulation, MEP latency should be less than 12 ms for trapezius and deltoid muscles, 15 ms for biceps and triceps brachii muscles, 19 ms for forearm muscles, 24 ms for hand muscles (abductor pollicic brevis (APB) or adductor digiti minimi (ADM) muscles), 25 ms for perineal muscles, 27 ms for the quadriceps, 32 ms for the tibialis anterior muscle, and 45 ms for foot muscles (abductor hallucis muscle). The CMCT ranges between 10 and 18 ms for hand and leg muscles, respectively.

Facial muscles can also be examined, but facial MEP recording is biased by the current spread and direct activation of the facial nerve induced by the scalp stimulation. Therefore facial MEPs are more difficult to perform reliably than limb MEPs in clinical routine.

MEPs can be applied for the diagnosis of central motor disorders, as well as peripheral motor disorders. For example, root stimulation can be used to show conduction block in proximal peripheral nerves. Regarding central motor disorders, prolonged CMCT can be observed in various types of myelopathies or in multiple sclerosis, for example (review in Chen et al., 2008).

TRIPLE STIMULATION TECHNIQUE

The MEPs obtained in response to cortical stimulation have a larger trial-to-trial variability than the peripherally evoked CMAPs. This is due to intrinsic and brain state-dependent fluctuations of corticomotor excitability or cortico-muscular coherence between the power and phases of EEG and EMG activities (Keil et al., 2014). In addition, MEPs to cortical stimulation, even performed at maximal stimulator output and recorded in a voluntarily contracted muscle, are always smaller than CMAPs to supramaximal peripheral electrical stimulation (Rossini et al., 1987; Day et al., 1989). This is not due to the fact that TMS is not sufficiently powerful to recruit all cortical motor neurons, but to a process of phase cancellation of motor unit potentials (Rossini et al., 1995; Magistris et al., 1998). Phase cancellation results from the length of neural pathways between stimulation and recording sites on one hand, and from differences in diameter and then conduction velocity between corticospinal axons on the other hand. This results in cortically evoked MEPs significantly less synchronized and of lower amplitude than CMAPs to distal nerve stimulation. The impact of conduction velocity differences between axons in the peripheral nerve segment is less critical regarding temporal dispersion of MEPs in healthy subjects (Groppa et al., 2012).

However, in pathological conditions a “peripheral” damage (denervation of the targeted muscles) may frankly increase the temporal dispersion of the MEPs, whether the stimulation is performed at spinal or cortical level. In this case, it may be difficult to ascertain the existence of a “central” lesion (affecting the upper motor neurons or the corticospinal tracts) in addition to an underlying “peripheral” lesion. This is a particularly important practical problem in interpreting MEP recordings for the diagnosis of amyotrophic lateral sclerosis (ALS). To address this difficulty, a specific technique, called the triple stimulation technique (TST), has been developed.

The TST is a collision method introduced by Magistris et al. (1998) to “resynchronize” corticomotor excitation at a “peripheral” level and to avoid the impact of phase cancellation. The TST can be implemented as a valuable technique of clinical neurophysiology to estimate the number of cortical motor neurons and then to give evidence of upper motor neuron loss, e.g., in ALS.

In brief, three consecutive stimuli are delivered: the first one over the motor cortex using TMS and the next two on the peripheral nerve supplying the target muscle by means of supramaximal electrical stimulation, first distally (close to the muscle) and then proximally (as proximally as possible) (Fig. 37.3). This leads to evoking of two successive MEPs of the same amplitude (or area) in the absence of cortical motor lesion. Two collisions occur: first, between the descending volley from the cortical TMS pulse and the ascending antidromic volley from the distal nerve stimulation and, then, between the descending volley from the proximal electrical stimulation and the ascending antidromic volley from the distal nerve stimulation. Proximal electrical stimulation will produce a MEP only for the spinal motor neurons

that have been initially excited by the cortical TMS pulse (Fig. 37.3). If some cortical neurons are not activated by the initial TMS pulse, collision does not occur in response to distal nerve stimulation but to proximal nerve stimulation in some axons, reducing the amplitude of the second MEP. Thus, comparing to a control curve obtained by a triple stimulation performed only on the peripheral nerve, the reduction in MEP amplitude produced by TST reliably measures the loss of recruitable cortical (upper) motor neurons.

OTHER SPECIFIC MEP CONDUCTION TECHNIQUES

Using specific coils, neural structures such as the brainstem or the cauda equina and conus medullaris can be investigated. First, a double-cone coil can be placed over the inion or the midpoint between the inion and the ipsilateral mastoid process to induce upward current into the brainstem (Fig. 37.3) to activate the corticospinal tracts at the pyramidal decussation within the foramen magnum (Ugawa et al., 1994). Brainstem stimulation can be used to calculate a cortical–brainstem conduction time and a brainstem–spinal root conduction time and make the diagnosis of corticospinal tract lesion above or below the pyramidal decussation level (Ugawa et al., 1996). For cauda equina and conus medullaris stimulation, a 20-cm diameter circular coil has been developed to produce Magnetic Augmented Translumbosacral Stimulation (MATS) (Fig. 37.3), in order to distinguish between cortico-conus and cauda equina motor conduction times with MEP recordings in leg muscles (Matsumoto et al., 2009). This method could be very useful to identify lesions affecting the cauda equina within the spinal canal, but unfortunately is not widely available in routine practice.

MOTOR CORTICAL MAPPING

TMS can be used to map functional cortical representations of muscles, based on MEP recordings. Stimulation is delivered with a figure-of-eight coil at various scalp sites and a fixed intensity above the rest motor threshold (cf. "Motor Threshold" section). The amplitudes of the MEPs evoked in muscles contralateral to the stimulation are measured. Then, a map of the scalp sites from which responses are obtained can be delineated for each muscle of interest. TMS cortical mapping can provide several variables, such as the area and position of the motor map (to compare to normal values), the motor hotspot location (scalp site from which MEP amplitude has a maximum value), and the center of gravity (CoG) of the map (scalp site corresponding to the mean location of the weighted relative distribution of MEP size over the map area). The CoG provides a weighted center of the motor function, which may be more representative than the hotspot.

TMS maps are rather accurate, as highlighted, for instance, by the nonoverlapping representation of the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles (the APB representation being more lateral than the ADM one). In addition, motor maps are quite symmetrical and any asymmetry can reveal monohemispheric lesion or plasticity changes (e.g., poststroke adaptive plasticity) affecting the motor system. Finally, TMS mapping of cortical motor function can be used for presurgical assessment and has been validated for this purpose in patients with brain tumors in the rolandic region (Lefaucheur and Picht, 2016). However, these maps can be modified by various technical factors, such as changing coil orientation or stimulation intensity, for example. It is also important to keep in mind that any change in spinal cord excitability may also have an impact, as for any technique based on MEP recordings.

In practice, motor mapping can be performed using a grid drawn on a Lycra swim cap placed on the scalp (Thickbroom et al., 1999) or a navigation system with dedicated software, integrating individual brain imaging data (Fig. 37.4).

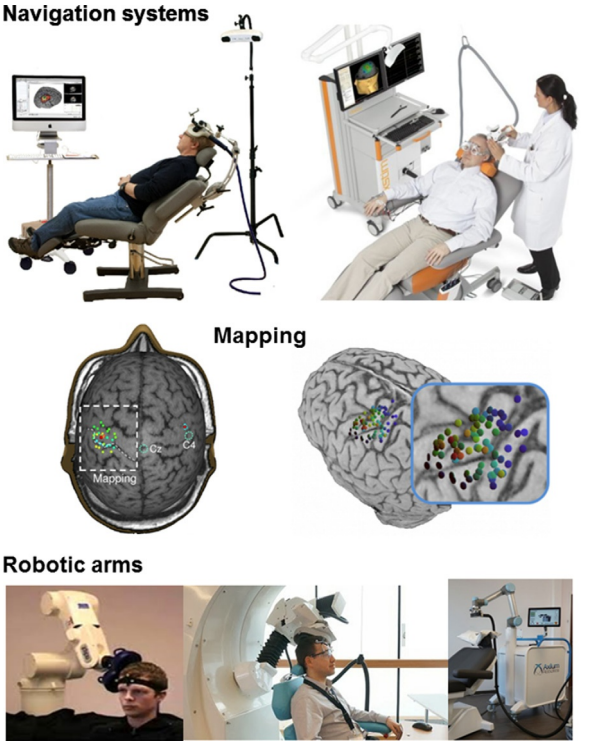

Fig. 37.4. Examples of image-guided navigation systems, cortical mapping using neuronavigated transcranial magnetic stimulation (TMS) technique, and robotic arms for TMS practice.

PRINCIPLES OF NEURONAVIGATION

A common method to identify a brain area relates to the effects produced by its stimulation. Examples of cortical functional localization include the production of movements following precentral gyrus stimulation, speech arrest following left frontal stimulation (Pascual-Leone et al., 1991), or phosphenes following occipital cortex stimulation (Amassian et al., 1998). Another strategy is to use the depicted correlations between scalp locations and underlying brain structures according to the International 10–20 system of EEG electrode placement. However, this technique does not take into account inter- and intraindividual variability of cortical anatomy.

Therefore, for mapping procedures or when the same target brain area has to be stimulated in follow-up sessions, an accurate localization of specific brain areas to stimulate requires a precise online matching system between the orientation of the coil on the scalp and the site of stimulation. Introduced some years ago, dedicated navigation systems integrating individual brain imaging data serve these objectives (Lefaucheur, 2010): (i) to determine the exact cortical location of a TMS target; (ii) to ensure the reproducibility of TMS targeting during repeated sessions or follow-up studies; (iii) to improve the accuracy of TMS motor mapping methods; (iv) to determine the functional involvement of a cortical region (in motor ability or speech, as examples), especially in the context of presurgical mapping.

The frameless stereotaxic neuronavigation system combines magnetic resonance imaging (MRI) data with TMS, guiding the coil to regions selected on the MR images (Herwig et al., 2001b, 2002). Stereotaxic neuronavigation is usually based on individual structural (anatomical) or functional MRI but can also be performed on averaged neuroimaging data or brain model taken from the literature or dedicated databases. The subject's head and the MRI slices are coregistered in a common reference space using a set of anatomical landmarks (such as the nasion or ear tragi), allowing a virtual linkage between MRI reconstruction and real anatomy for a three-dimensional (3D) interactive visual navigation. An optical-tracking system uses a camera to determine in real-time the spatial locations of specific trackers on the coil and subject's head (Fig. 37.4). Therefore, this system allows monitoring of coil position and subject's head movements for maintaining the accuracy of cortical targeting during a TMS session. Navigation ensures targeting accuracy on the order of a few millimeters, compared with some centimeters for a nonnavigated technique (Sparing et al., 2008). Moreover, the trial-to-trial coil replacement variability is reduced to close to zero. Such systems are particularly useful to target cortical regions other than the motor cortical region (for which MEP recording provides a reliable marker for targeting), such as the dorsolateral prefrontal cortex (Herwig et al., 2001a; Ahdab et al., 2010; Mylius et al., 2013). In combination with navigation systems, robotic arms dedicated to the practice of rTMS can be used (Fig. 37.4). Robotized rTMS allows further increase in the reliability and repeatability of the procedure in the context of long-term treatment based on multiple sessions (Quesada et al., 2018).

MOTOR THRESHOLD

In most applications and studies, the intensity of TMS is individually adjusted to the rest motor threshold (RMT), defined as the minimal intensity of a TMS pulse delivered to the motor cortex to elicit a reliable MEP of minimal amplitude ($>50\,\mu V$) in a target muscle at rest. Complete muscle relaxation can be controlled by checking the absence of EMG at high-gain amplification, either visually or by acoustic feedback or by both. In place of MEP recording, the RMT can also be determined on visual inspection of muscle twitches evoked by the stimulation. This "visual" method is easier to perform than the method based on MEP recording, but is associated with a greater variability and results in about 10% higher RMT values (Westin et al., 2014). An active motor threshold (AMT) can also be determined during a slight tonic contraction of the target muscle at approximately 20% of the maximal voluntary contraction force. The AMT corresponds to faster conducting axons of the corticospinal tract.

When using a figure-of-eight coil, its orientation and then the direction of the current flow induced in the brain is of critical importance for RMT determination (Kammer et al., 2001; Weyh et al., 2005). In any case, the lowest thresholds are found for hand muscles.

The procedure for RMT/AMT measurement using a figure-of-eight coil has been well defined (Groppa et al., 2012; Rossini et al., 2015). First, the "hot spot" is determined by stimulating the motor cortex with a fixed and relatively high intensity contralateral to the MEP recording side and orienting the coil 45 degrees away from the interhemispheric midline with the handle backwards. Second, at the hot spot, stimulation intensity is decreased to approximately 35% of the maximal stimulator output (MSO) and then gradually increased in steps of 5% MSO until TMS consistently evokes MEPs with peak-to-peak amplitude of more than $50\,\mu V$ in the target muscle at rest ($200\,\mu V$ in the case of actively contracted muscle) in each trial. Thereafter, stimulation intensity is gradually lowered in steps of 1% MSO until less than 5 positive response MEPs $\geq 50\,\mu V$ for RMT ($\geq 200\,\mu V$ for AMT) out of 10 trials are recorded. This stimulation intensity is then defined as the RMT (or AMT).

Adaptive methods based on threshold-tracking algorithms have also been proposed (Awiszus, 2003). They may provide a more accurate estimation of RMT with a smaller number of stimuli compared to the "classic" method (Awiszus, 2011; Qi et al., 2011). Adaptive methods use an S-shaped function to model the relationship between TMS intensity and the probability of eliciting an MEP. Examples of adaptive methods include parameter estimation by sequential testing (PEST) (Awiszus, 2003) and the maximum-likelihood regression tracking algorithm (Mishory et al., 2004).

INPUT–OUTPUT (STIMULUS–RESPONSE) CURVE

The stimulus–response relationship between TMS intensity and MEP amplitude can be determined by recording MEPs at gradually increasing intensity level, e.g., by steps of 10% increments from the RMT to 100% of MSO. Plotting MEP amplitude as a function of TMS intensity provides a stimulus–response curve (input–output (IO) curve), which has a sigmoid shape (Fig. 37.5) and can be fitted, e.g., to a Boltzmann function (Devanne et al., 1997). The first segment of the curve deviates from zero at the RMT (if assessed in a target muscle at rest). The second part of the sigmoid curve is an approximately linear ascending slope caused by an increase in MEP amplitude with increasing stimulation intensity (especially between 120% and 140% of RMT). A spectroscopy study revealed a positive correlation between this slope and cortical glutamate levels in the motor cortex (Stagg et al., 2011). The third segment of the IO curve is a plateau with no further increase in MEP amplitude despite increasing stimulation intensity, partly due to a phenomenon of phase cancellation of motor unit potentials.

Any change in corticospinal excitability, e.g., related to voluntary contraction, motor learning, training, disease-related loss of corticospinal neurones, or medications, may result in a rightward or leftward shift of the curve and/or a change in its slope. This is the reason why this sensitive testing is widely used as a TMS technique of investigation in neurophysiologic practice.

CORTICOSPINAL SILENT PERIOD AND IPSILATERAL SILENT PERIOD

When recorded in a tonically contracted muscle, a MEP produced by a TMS pulse delivered to the contralateral motor cortex is always immediately followed by a period of electrical silence. This silence has a mixed cortical and spinal origin (corticospinal silent period, CSP). Spinal mechanisms are involved in the early part of the CSP, i.e., about the first 50 ms (Fuhr et al., 1991), while the later part of the CSP takes its origin in intracortical inhibitory controls of the motor cortex with gamma-aminobutyric (GABA) mediation, involving mostly type B receptors (Siebner et al., 1998; Stetkarova and Kofler, 2013), particularly at high intensity of stimulation (Kimiskidis et al., 2006). On the whole, the CSP lasts for up to 100–300 ms and its duration gradually increases with TMS intensity up to a plateau (Kimiskidis et al., 2005). In contrast, the level of muscle contraction plays an insignificant role in CSP duration (Inghilleri et al., 1993) (Fig. 37.5).

The CSP is more usually measured from the onset of the MEP than from the end of the MEP, while the end of the CSP is always set at the recurrence of voluntary tonic EMG activity. Measurement may be facilitated by averaging five or six rectified EMG traces (Groppa et al., 2012).

The interhemispheric difference in CSP duration is very small, typically less than 10 ms, but interindividual differences as well as the intersession variability of the CSP duration are much larger, ranging between 20% and 35% (Cicinelli et al., 1997; Orth and Rothwell, 2004). In addition, the duration of the CSP is not always easy to determine, making this parameter difficult to use reliably in clinical routine.

The CSP is usually assessed when recording MEPs in a tonically contracted target muscle in response to focal TMS over the contralateral motor cortex. However, an interruption of ongoing voluntary EMG activity can also be observed in response to ipsilateral motor cortex stimulation, known as the ipsilateral silent period (iSP) (Ferbert et al., 1992; Meyer et al., 1995). This iSP is clearly smaller and more difficult to obtain than the CSP, and results from transcallosal projections of inhibitory controls between both motor cortices. Therefore, the recording of iSP has been proposed as a neurophysiologic tool for the diagnosis of corpus callosum lesions (Meyer et al., 1999).

PAIRED-PULSE TMS

Paired-pulse TMS techniques allow testing of various neural circuits involved in intracortical inhibition or facilitation. These techniques comprise a conditioning stimulus (CS) followed by a test stimulus (TS) with a variable interstimuli interval (ISI) between the CS and the TS. Then, the amplitude of the MEP produced by the paired pulse is compared to that produced by the TS alone. Due to the trial-to-trial variability of MEP produced by TMS pulses, at least 8–10 trials should be averaged at each ISI to obtain reliable values. The studies are usually done with the target muscle at rest, ascertained by monitoring background EMG activity. Muscle contraction strongly modifies paired-pulse TMS findings (Ridding et al., 1995).

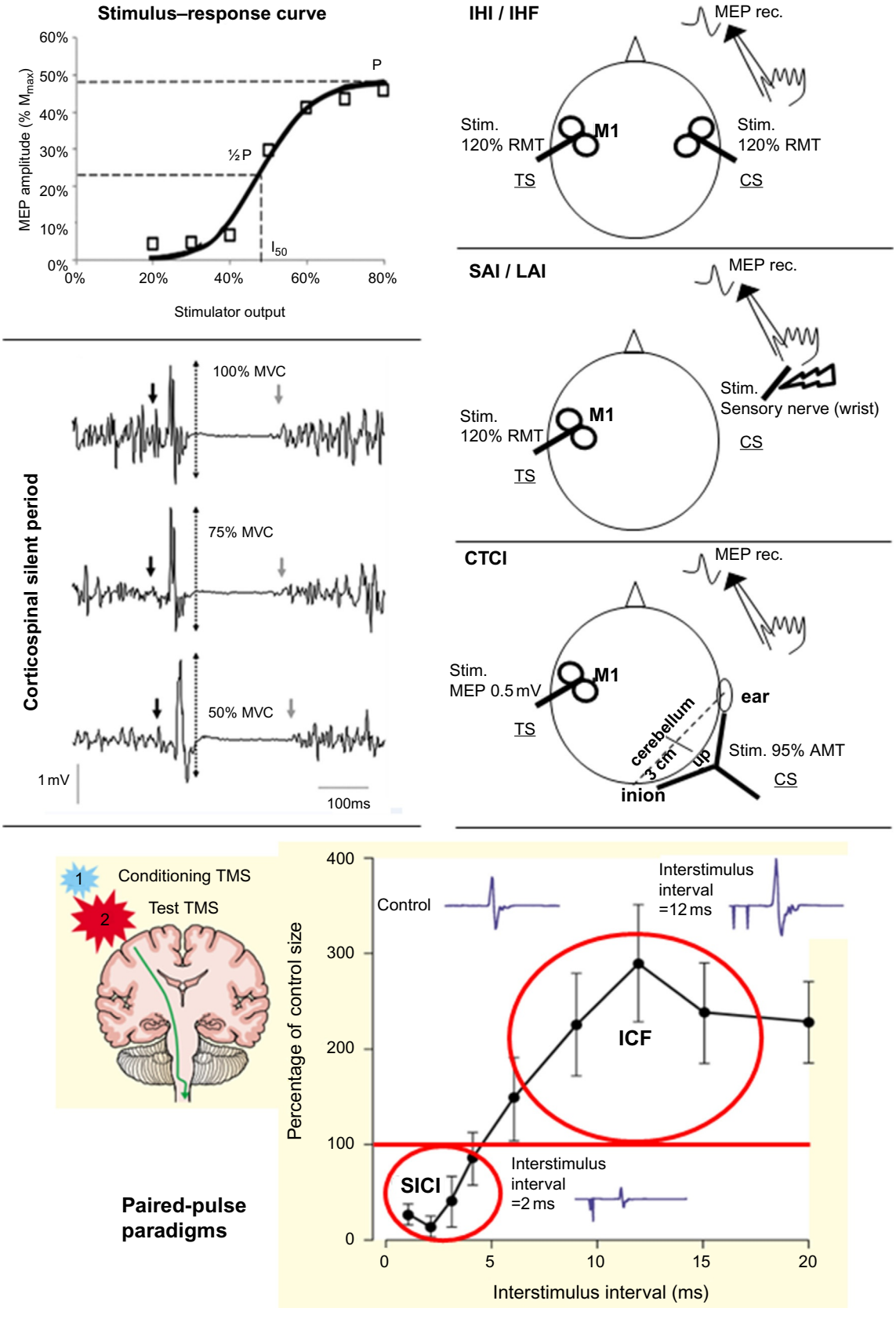

Fig. 37.5. See figure legend on next page.

Short interval intracortical inhibition and intracortical facilitation

In these paradigms, a paired-pulse is delivered to the motor cortex, usually with a figure-of-eight coil, with MEP recording in a muscle, usually at the hand (e.g., first dorsal interosseus muscle), contralateral to the stimulation. However, the technique can be performed with other types of coil (circular, double-cone) and MEP recordings in other muscles (e.g., lower limb muscles). In any case, the intensity of stimulation is set at 80% of RMT for the CS and at 120% of RMT for the TS. Alternatively, the intensity of stimulation for the TS can be adjusted to produce a MEP of 1 mV amplitude. The subthreshold CS pulse is able to recruit various types of intracortical control circuits, both inhibitory (GABAergic) and excitatory (glutamatergic). If the result of the GABA/glutamate balance provided by the CS pulse is inhibitory, the amplitude of the MEP evoked by the TS is smaller than following the TS alone. If the result of the GABA/glutamate balance provided by the CS pulse is excitatory, the amplitude of the MEP evoked by the TS is greater than following the TS alone. In practice, paired-pulse TMS results in MEP inhibition for an ISI between CS and TS ranging from 1 to 6 ms (short-interval intracortical inhibition, SICI) and in MEP excitation for an ISI ranging between 7 and 20 ms (intracortical facilitation, ICF) (Kujirai et al., 1993) (Fig. 37.5).

Regarding SICI at very short ISI (1 ms), neuronal refractoriness can be partly involved in the inhibitory phenomenon, but for ISI longer than 2 ms, MEP size reduction clearly reflects a process of synaptic inhibition mediated by GABA type A receptors (Ziemann et al., 1996; Di Lazzaro et al., 2007). However, the SICI is influenced by the intensity of stimulation used for the CS. Intracortical GABAergic circuits have a lower threshold than glutamatergic circuits (Ilic et al., 2002) and therefore increasing the CS intensity leads to greater SICI and then to an eventual MEP facilitation, as shown by the short-interval intracortical facilitation (SICF) paradigm (see next chapter). In fact, the relationship between the degree of SICI and CS intensity is a variable U-shaped curve, not easily predicted in all subjects (Chen et al., 1998). In routine practice, SICI appears as a very constant and reliable phenomenon, easy to record in all normal subjects, whereas ICF is more inconsistent and variable in amplitude in the population.

Short interval intracortical facilitation

Paired-pulse TMS with short ISI (less than 6 ms) can produce an increase in MEP size (SICF as defined in the previous section) if the CS is delivered at a suprathreshold intensity of stimulation, followed by a TS delivered at a suprathreshold intensity similar to CS (Tokimura et al., 1996) or just at the RMT level, preferentially (Ziemann et al., 1998). SICF occurs at three ISIs at around 1.5, 3, and 4.5 ms (Ziemann et al., 1998; Chen and Garg, 2000), likely due to the summation of different I-waves at cortical level, and then to an increase in the strength of the descending corticospinal volley (Hanajima et al., 2002). For each individual, the SICF should be assessed by testing various ISIs from 1 to 5 ms by steps of 0.2 ms to identify the optimal ISI for each SICF peak.

Long interval intracortical inhibition and late cortical disinhibition

This paradigm requires paired-pulse TMS with both CS and TS performed at the same suprathreshold intensity of stimulation with ISI ranging from 50 to 200 ms. In contrast to SICI, ICF, or SICF, the paired-pulse produces not one but two MEPs. The test compares the amplitude of the first MEP evoked by the CS to that evoked by the TS. Using this technique, a reduction of MEP amplitude to TS vs. CS is normally observed, called long-interval intracortical inhibition (LICI) (Valls-Solé et al., 1992; Wassermann et al., 1996; Sanger et al., 2001). The exact

Fig. 37.5. Main protocols of transcranial magnetic stimulation (TMS) to assess cortical excitability: stimulus–response (input–output) curve, plotting motor evoked potential (MEP) amplitude as a function of stimulation intensity; corticospinal silent period, showing the absence of influence of background contraction expressed as a percentage of maximal voluntary contraction (MVC) on the duration of the silent period; interhemispheric inhibition (IHI) or facilitation (IHF), resulting from condition and test stimuli (CS and TS) applied with a figure-of-eight coil to each motor cortex (M1) at an intensity set at 120% of the rest motor threshold (RMT) with MEP recording at the hand; short- and long-latency afferent inhibition (SAI and LAI), resulting from an electrical CS applied at the wrist over a sensory nerve and a TS applied with a figure-of-eight coil to contralateral M1 at 120% of RMT with MEP recording at the hand; cerebello-thalamo-cortical inhibition (CTCI), resulting from a CS applied with a double-cone coil over the cerebellum, lateral to the inion at 95% of the active motor threshold (AMT) and a TS applied with a figure-of-eight coil to contralateral M1 at an intensity producing MEPs of 0.5 mV amplitude with MEP recording at the hand; paired-pulse paradigms of short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF), resulting from subthreshold CS and suprathreshold TS applied with a figure-of-eight coil to M1 at various interstimulus intervals. Partially adapted from Kobayashi M, Pascual-Leone A. (2003). Transcranial magnetic stimulation in neurology. Lancet Neurol 2:145–156 and from Souron R, Farabet A, Millet GY et al. (2016). Reliability of the functional measures of the corticospinal pathways to dorsiflexor muscles during maximal voluntary contractions. J Neurol Sci 369: 368–374, with permission from Springer Nature.

ISI values to produce optimal inhibition may vary from one individual to another, but for a quick assessment, only two ISIs of 100 and 150 ms may be used. Following LICI, at ISIs longer than 200 ms, a period of late MEP facilitation, called late cortical disinhibition (LCD), has been described (Cash et al., 2010), preferentially if MEPs are recorded in voluntary contracted muscles (Caux-Dedeystère et al., 2014).

Interhemispheric inhibition and facilitation

In contrast to all the previously described variables (SICI, ICF, SICF, LICI, LCD), interhemispheric modulation is tested by applying the two TMS pulses at different cortical sites and not at the same site. Therefore, interhemispheric testing requires two figure-of-eight coils placed over both motor cortices, one coil delivering the suprathreshold CS to one motor cortex, followed by a suprathreshold TS over the contralateral one (Fig. 37.5). The resulting effect of the paired pulse (compared to the TS alone) varies with the ISI, MEP inhibition (interhemispheric inhibition, IHI, max −50%) being more pronounced at ISI of about 8–10 ms and 40–50 ms, referred to as short- and long-latency IHI (SIHI and LIHI) (Chen et al., 2003; Ni et al., 2009). At shorter ISIs (4–6 ms), a mild interhemispheric facilitation (IHF, max +15%) can be observed (Hanajima et al., 2001; Bäumer et al., 2006).

Both SIHI and IHF are cortical phenomena, produced by transcallosal projections between the two motor cortices (Ferbert et al., 1992; Wahl et al., 2007; Ni et al., 2009). In contrast, LIHI may represent a widespread inhibitory system projecting from various cortical areas, including the dorsolateral prefrontal, dorsal premotor, and somatosensory cortices, to the motor cortex (Ni et al., 2009). Interhemispheric facilitation from the premotor cortex to primary motor cortex has also been demonstrated (Bäumer et al., 2006).

Short latency and long latency afferent inhibition

The electrical stimulation of a cutaneous sensory or mixed peripheral nerve can be applied as CS preceding a subsequent suprathreshold TMS of the contralateral motor cortex as TS. The electrical CS usually delivered at the level of the hand or the fingers can modulate the amplitude of the MEPs recorded in the homotopic hand region (Fig. 37.5). The intensity of sensory stimulation may be set at two to three times sensory threshold (Ni et al., 2011). This type of paired associative stimulation results in MEP inhibition, according to two distinct periods. A first period of inhibition is observed for ISIs ranging between 20 and 25 ms (short-latency afferent inhibition, SAI, max −30%). In fact, the optimal ISI corresponds to the latency of the main cortical component of the somatosensory evoked potentials produced by the CS (N20) plus 2 ms (Mariorenzi et al., 1991; Bikmullina et al., 2009; Ni et al., 2011). Pharmacological studies showed that SAI involves mainly cholinergic circuits (Di Lazzaro et al., 2000), but also some mediation from GABA type A receptors (Di Lazzaro et al., 2005).

A second period of inhibition is observed for ISIs around 200 ms (long-latency afferent inhibition, LAI, max −50%) (Chen et al., 1999). Between these two periods of inhibition, the peripheral stimulation may result in a period of MEP facilitation, likely related to the production of long-latency transcortical responses (Mariorenzi et al., 1991; Tokimura et al., 2000).

Cerebello-thalamo-cortical motor inhibition

A TMS pulse delivered over the cerebellum as CS may produce a reduction in MEP amplitude in response to a subsequent TS delivered over the primary motor cortex (cerebello-thalamo-cortical motor inhibition, CTCI). While primary motor cortex stimulation requires a figure-of-eight coil, cerebellar should be preferentially performed with a type of coil (double-cone coil) dedicated to this use, placed 3 cm lateral to the inion, and oriented upwards (Ugawa et al., 1995; Werhahn et al., 1996) (Fig. 37.5). The CS intensity is set at 5% below the AMT and the TS intensity is adjusted to produce MEP of about 0.5 mV amplitude in hand muscle. A maximal MEP inhibition (max −40%) is observed for ISIs between cerebellar CS and cortical TS ranging from 5 to 8 ms. For shorter ISIs (3 ms), a facilitation may occur.

This inhibitory phenomenon is thought to be mediated by the activation of Purkinje cells in the cerebellar hemispheres, which leads to inhibiting pyramidal cells in the primary motor cortex via a di-synaptic pathway through relays in deep cerebellar nuclei (e.g., the dentate nucleus) and the ventral lateral thalamus (Ugawa et al., 1995; Pinto and Chen, 2001; Groiss and Ugawa, 2012).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Repetitive TMS (rTMS) was introduced in the early 1990s and required a specific set of stimulators able to overcome the recharging time of magnetic stimulators to maintain the same output level, even with extremely brief ISIs. Repetitive TMS has a modulatory effect on cortical excitability, which outlasts the stimulation period and can be used in a variety of indications, delivered to either motor or nonmotor brain regions. The impact of rTMS can be observed at the site of stimulation and mostly at a distance, according to the nature of the activated neural circuits. An international consensus

group has provided safety recommendations for the use of various forms of rTMS in various indications (Rossi et al., 2009).

There are two classic paradigms of rTMS: low-frequency rTMS (1 Hz or less), consisting of continuous trains of single pulses, and high-frequency rTMS (5 Hz and higher), consisting of bursts of stimuli that usually last for 5–10 s and are separated by pauses of 20–50 s (Fig. 37.6). In most therapeutic trials, the total duration of one rTMS session is about 20 min. Functional or clinical effects outlast the period of stimulation for minutes or hours, likely due to long-term depression (LTD) of synaptic transmission for low-frequency rTMS and long-term potentiation (LTP) for high-frequency rTMS (Chen et al., 1997; Pascual-Leone et al., 1998; Post et al., 1999). When applied to the motor cortex, low-frequency rTMS is able to reduce MEP size (Chen et al., 1997), while the reverse is produced by high-frequency rTMS (Pascual-Leone et al., 1994). However, it cannot be assumed from these MEP size changes that low- or high-frequency rTMS effects are due to the LTD or LTP process in all rTMS applications. Indeed, the direction of excitability changes induced by rTMS may vary according to the location of the cortical target (primary motor cortex versus other cortical areas) and to the prior state of activation of the recruited brain circuits. For example, whereas a majority of studies have reported a decrease in SICI following a high-frequency rTMS procedure in healthy subjects, a paradoxical SICI increase can be observed in pathological conditions, especially in patients with reduced SICI at baseline (Lefaucheur et al., 2006). Similarly, the effect of low-frequency rTMS on SICI or CSP is not consistent with highly contradictory effects reported across studies (Fitzgerald et al., 2006).

The repetition of the sessions can reinforce and prolong rTMS after-effects that are often weak, variable, and short-lasting following a single session, opening perspectives for the therapeutic use of rTMS. The therapeutic potential of rTMS was mainly demonstrated for chronic pain syndrome and depression (Lefaucheur et al., 2014). Beside these classic rTMS procedures, other TMS protocols have the potential to modulate cortical activities at a therapeutic level (Lefaucheur, 2009). The main protocols used so far are theta burst stimulation (TBS), quadripulse stimulation (QPS), and paired associative stimulation (PAS) (Fig. 37.6).

THETA BURST STIMULATION

TBS consists of short bursts of three low-intensity pulses with inner high frequency (50 Hz, within the gamma range) that are delivered every 200 ms, i.e., at 5 Hz (within the theta range) (Fig. 37.6). However, TBS protocols may vary across studies. For example, TBS delivered to the frontal eye field to modulate saccades (Nyffeler et al., 2006; Hubl et al., 2008; Schindler et al., 2008) consisted of three pulses at 30 Hz repeated at intervals of 100 ms (10 Hz).

Animal experiments suggest that TBS protocols can produce sustained changes in long-term synaptic excitability (Larson et al., 1986). When applied over the motor

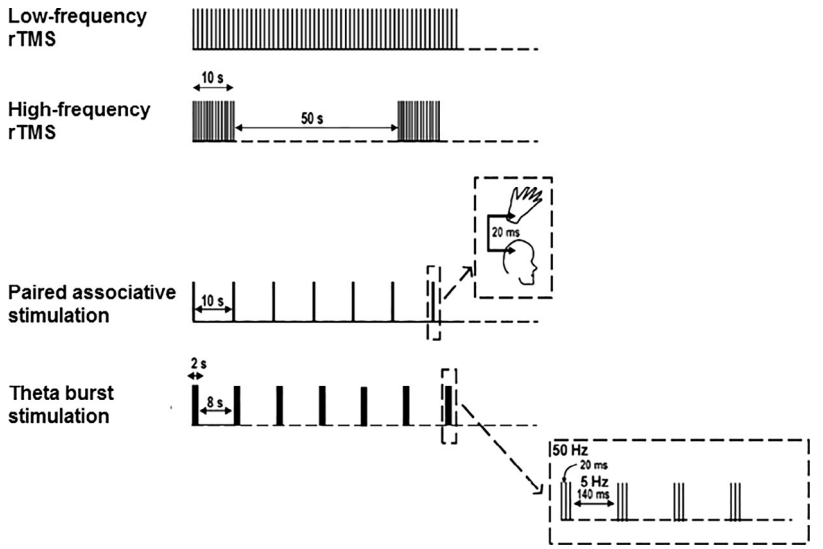

Fig. 37.6. Main protocols of repetitive transcranial magnetic stimulation (rTMS), including "classic" tonic low-frequency rTMS (≤1 Hz) and phasic high-frequency rTMS (5–20 Hz) paradigms, paired-associative stimulation (combining distal nerve peripheral electrical stimulation and magnetic cortical stimulation), and theta burst stimulation (intermittent application of short trains of three pulses at 50 Hz delivered every 200 ms, i.e., at 5 Hz, within the theta range). Partially adapted from Lefaucheur JP. (2009). Methods of therapeutic cortical stimulation. Neurophysiol Clin 39: 1–14.

cortex, an "intermittent" TBS protocol (iTBS; 2 s every 10 s, for a total stimulation time of 200 s) can result in MEP facilitation, whereas the continuous application of TBS (cTBS) for 40 s can result in MEP inhibition (Huang et al., 2005). Excitatory effects of iTBS build up within 1 s, whereas inhibitory effects of cTBS occur with a delay of several seconds and less consistency than the effects of iTBS. However, this dichotomy between "excitatory" iTBS versus "inhibitory" cTBS is not entirely satisfying, since, for example, doubling the duration of stimulation can reverse the effect produced by cTBS from inhibitory to excitatory (Gamboa et al., 2010). In addition, several studies reported similar rather than opposing physiologic and clinical effects of both types of TBS protocols when applied to motor or especially nonmotor cortical regions (Koch et al., 2005; Poreisz et al., 2008; Grossheinrich et al., 2009; Borckardt et al., 2011; Lefaucheur et al., 2012).

However, one important point is that TBS protocols, despite their extremely short duration, may produce greater and less variable effects on motor cortex excitability than conventional 1-Hz/10-Hz rTMS protocols (Huang et al., 2005). This can have a great impact on the practical aspects of using rTMS for therapeutic applications in clinical routine.

QUADRIPULSE MAGNETIC STIMULATION

QPS has been proposed to induce long-term effects on cortical excitability and plasticity with less interindividual variability (Hamada et al., 2008; Nakatani-Enomoto et al., 2012). This technique consists of trains of four monophasic TMS pulses delivered repetitively for a relatively long session duration (30 min). When delivered over the motor cortex, QPS facilitates MEPs when the four monophasic TMS pulses are separated by an ISI of 1.5–10 ms (usually 5 ms, QPS-5) and suppresses MEPs for an ISI of 30–100 ms (usually 50 ms, QPS-50) (Hamada et al., 2008). The ISI between two trains is set at 5 s (low stimulation frequency of 0.2 Hz) and then a "classic" QPS session delivers 360 trains of 4 pulses (1440 pulses). Although QPS is thought to be an effective approach to producing long-lasting cortical excitability changes and sustained clinical effects, this method was rather rarely used, especially for therapeutic purposes. Indeed, QPS requires a very specific device combining four magnetic stimulators connected with a specially designed synchronizing module.

PAIRED ASSOCIATIVE STIMULATION

Paired associative stimulation (PAS) is the association between a single electrical stimulus delivered at peripheral level (over a sensory or mixed nerve) and a single TMS pulse delivered over the contralateral motor cortex (Stefan et al., 2000). The two stimuli are separated by a fixed ISI to generate approximately synchronous events within the primary motor cortex, i.e., about 20–25 ms for a CS delivered to the median nerve at the wrist (Fig. 37.6). When this paired stimulation is applied at low frequency (0.02–0.1 Hz) for about 30 min (usually 90–180 stimuli), this leads to increased MEP amplitude lasting up to 60 min after the intervention (Stefan et al., 2000). The repetition of a PAS protocol for 3 days induces a strong expansion of the cortical representation of the stimulated muscle that persists for at least 2 days beyond the last stimulation session (McKay et al., 2002). When applied at 5 Hz, PAS also induces long-lasting somatotopic increase in corticospinal excitability (Quartarone et al., 2006).

PAS effects can be blocked by *N*-methyl-D-aspartate (NMDA) receptor antagonist, arguing for LTP-like phenomenon (Stefan et al., 2002). PAS can promote adaptive plasticity and functional reorganization of the motor cortex after brain injury, as shown in poststroke chronic hemiplegics (Uy et al., 2003). In this latter study, electrical stimulation of the common peroneal nerve at the leg was associated with single-pulse TMS delivered to the primary motor cortex corresponding to the lower limbs. Following 4 weeks of PAS, a significant clinical improvement was observed on several measurements.

TMS-EEG COREGISTRATION AND CLOSED-LOOP TMS

A promising tool of functional neuroimaging technique is to perform coregistration of EEG activity and TMS, thus providing the possibility to assess TMS-induced changes in cortical excitability and on-line connectivity (Ilmoniemi et al., 1997; Virtanen et al., 1999; Ilmoniemi and Kičić, 2010). This means that the impact of TMS-evoked neuronal activation can be appraised on scalp EEG activity changes and turned into a source of cerebral imaging. Although difficult to record without artifact contamination, several EEG responses to single-pulse TMS delivered over the motor cortex have been identified, i.e., negative and positive peaks whose latency ranges from 7 to 300 ms following a TMS pulse (Ilmoniemi and Kičić, 2010; Ferreri and Rossini, 2013). In addition, TMS pulses may modulate oscillatory brain rhythms and trigger event-related EEG synchronization/desynchronization or complex phenomena. A better knowledge of brain connectivity based on high-resolution EEG or diffusion tensor imaging studies could benefit the understanding of TMS-evoked EEG responses. Both local and distant effects of TMS can be obtained, even in contralateral hemisphere, via transcallosal connections (Ilmoniemi and Kičić, 2010; Ferreri and Rossini, 2013). The impact of

TMS on EEG response is also modulated by the initial state of the activated brain region (Ferrarelli et al., 2008; Casarotto et al., 2010; Karabanov et al., 2015).

On the other hand, the "brain-state" can be considered a critical factor regarding the possibility of inducing optimal plastic changes in the brain. Since "brain-state" may be reflected by some EEG features, EEG recordings could be used to provide biomarkers to determine the best moment to deliver TMS for promoting cortical plasticity. This is the principle of a closed-loop stimulation, coupling TMS to an EEG feedback. In fact, various studies have recently shown the technical possibility of such a montage, for instance delivering TMS pulses over the motor cortex, which were triggered online by oscillatory brain activity recorded in a 32-channel EEG set-up during cued kinesthetic motor imagery of hand opening (Gharabaghi et al., 2014). Various approaches to closed-loop interactions can be designed, such as a direct coupling of TMS to instantaneous EEG activity or the use of a "task dynamics" loop, in which goal-directed behavioral tasks are incorporated (Zrenner et al., 2016). One problem can be to identify a reliable biomarker to close the loop, with sufficient signal-to-noise ratio and timing precision as a single trial (with no need of averaging).

TRANSCRANIAL DIRECT CURRENT STIMULATION

In addition to TMS, various techniques of transcranial electrical stimulation are being used more and more to perform noninvasive cortical neuromodulation in the clinical domain. Among these techniques, transcranial direct current stimulation (tDCS), recently reintroduced in clinical neurophysiology (Priori et al., 1998; Nitsche and Paulus, 2000), is currently the most widely developed technique, at least regarding its therapeutic applications in a variety of neurological and psychiatric disorders (Lefaucheur et al., 2017). The usual tDCS technique consists of delivering weak direct currents by a large electrode (anode or cathode) placed on the scalp over a targeted cortical area with a return electrode of opposed polarity placed over the contralateral forehead, the chin, or the shoulder. Beyond this "classic" bipolar montage, more complex electrode montages are developed, including either highly focal stimulation by means of "high-definition" Laplacian montages (Borckardt et al., 2012) or multifocal stimulation of various interconnected cortical regions. In all cases, battery-driven portable stimulators can be used and the delivered current is set at a fixed intensity of 1–2 mA, applied continuously for 10–20 min. Currents of this magnitude cannot directly evoke action potentials in cortical axons but produce small polarizing changes in membrane potential and sustained modulation of cortical cell excitability (e.g., in spontaneous firing rates) that outlast the stimulation period (Filmer et al., 2014).

Cortical neurons have an exquisite sensitivity to weak DC fields that can produce local fluctuations in transmembrane ionic concentrations or conductance, leading to a variety of nonsynaptic changes (Jefferys, 1995; Ardolino et al., 2005). These changes can also affect glial cells (Ruohonen and Karhu, 2012). However, the main mechanism of action of tDCS is thought to result from plastic changes in synaptic connectivity, especially mediated by NMDA receptors (Liebetanz et al., 2002; Nitsche et al., 2003). By acting on neuronal networks (Francis et al., 2003), tDCS may interfere with oscillatory brain activities (Marshall et al., 2004).

A general opinion is that modulation of neuronal excitability by DC stimulation is a relatively simple function: cortical excitability is reduced by cathodal stimulation and increased by anodal stimulation, due to processes of neuronal hyperpolarization and depolarization. However, various factors can explain that in fact tDCS effects are more difficult to predict.

First, the resulting effect of DC stimulation highly depends on the orientation and distance of the axonal or dendritic-somatic axis with respect to the electric field (Gluckman et al., 1996). More recent experiments have showed that the spatial and temporal effects of DC fields can be more complex than expected from initial reports (Bikson et al., 2004). Therefore, little variation in the technique, e.g., in reference electrode placement or in stimulation intensity, can strongly influence the physiologic and clinical changes provided by tDCS (Nitsche and Paulus, 2000; Priori, 2003).

Second, although weak DC fields can coherently depolarize or hyperpolarize a neuronal network with respect to electrode polarity, the resulting effect of the stimulation depends on whether it affects an inhibitory (e.g., GABAergic) or excitatory (e.g., glutamatergic) brain circuit and also on the baseline activity of this network and its afferent synaptic inputs. All these factors could explain the variable clinical impact of tDCS according to the studies in pathological conditions.

Regarding the intensity of current produced into cortical layers, tDCS cannot be compared to TMS. Indeed, 2-mA tDCS with an anode of 25 cm^2 was shown to produce a mean current density of 0.1 A/m^2 (Miranda et al., 2006), whereas TMS yields current densities of 1.5–4.5 A/m^2 (Wagner et al., 2004). However, variations in tissue conductivity or distance between the target and the stimulating coil or electrode can greatly influence the resulting effect. In addition, the magnitude and location of current density can be altered in pathological versus normal conditions (Wagner et al., 2006, 2007).

Other techniques of transcranial electrical stimulation using low-intensity currents applied through scalp electrodes have been proposed for more than a century (Limoge et al., 1999; Paulus, 2011; Guleyupoglu et al., 2013), like nonpolarizing high-frequency pulsed biphasic balanced current, transcranial alternating stimulation (tACS), or random noise stimulation (tRNS). These techniques will not be detailed here.

NEURAL CIRCUIT ACTIVATION BY CORTICAL STIMULATION: SPATIAL ASPECTS

The strength-duration relationship of membrane properties makes fibers of passage more excitable than local cell bodies at the stimulation site (McIntyre and Grill, 2002; Nowak and Bullier, 1998). Therefore, one key feature of therapeutic brain stimulation is that fibers are more prone to be activated than cell bodies. The selective activation of neuronal cell bodies should require asymmetrical charge-balanced biphasic stimuli (McIntyre and Grill, 2002), but such a pattern of stimulation is not provided by standard neurostimulation techniques. The axonal excitation can give rise to both orthodromic and antidromic volleys. Orthodromic volleys induce postsynaptic excitation or inhibition in cortical or subcortical targets, whereas antidromic volleys reach the neural structures from which efferents arise, resulting in collision or network activation through collaterals, for example. However, both orthodromic and antidromic volleys can modulate the same structures through reciprocal interconnections. Although "local" effects may occur, the neural activity changes produced by cortical stimulation rather locate at a distance from the site of stimulation (Lefaucheur, 2008). Even if the site of stimulation is not the site of action, it must be precisely determined to allow between-study comparability and session repeatability. This goal is achieved in particular by using navigation systems dedicated for rTMS practice.

NEURAL CIRCUIT ACTIVATION BY CORTICAL STIMULATION: TEMPORAL ASPECTS

Fiber activation by cortical stimulation is able to generate various types of effects, developing or occurring during or beyond the time of stimulation. On one hand, there are acute or short-lasting effects, like MEP size changes in response to motor cortex stimulation. On the other hand, there are delayed and long-lasting effects, like therapeutic effects of cortical stimulation. For example, the analgesic effects produced by motor cortex stimulation in patients with chronic pain are delayed but prolonged for hours or days after the stimulation period using rTMS (Lefaucheur et al., 2001). This could be related to time-consuming neurochemical or neuroendocrine processes, expression of secondary messengers, and synaptic plasticity (Padberg et al., 2003).

In other types of neuromodulation, e.g., deep brain stimulation in tremor, clinical changes occur rapidly after switching the stimulator "on" or "off" or after modifying stimulation parameters. These rapid changes argue for stimulus-locked processes of activation, inhibition, or modification of disease-related (de)synchronization or oscillations, especially relevant for a closed-loop approach of brain stimulation. A careful assessment of the temporal relationship between clinical changes and stimulation time can provide valuable information on the mechanisms of action of a technique of neuromodulation. To summarize, neural changes occurring during stimulation can result from stimulus-locked activation, inhibition, or modification of oscillatory activities in cortico-subcortical networks. In contrast, plastic synaptic changes are considered to govern long-lasting after-effects.

PLASTICITY AND PRIMING

Synaptic plasticity depends on firing rate, spike timing, and temporal and spatial summations of the inputs arriving at presynaptic level. However, whether a synapse is strengthened or weakened by presynaptic activity also depends upon the level of activity in the postsynaptic neuron. The processes leading to depression of synaptic transmission are more effective when postsynaptic activity is high. Conversely, potentiation of synaptic transmission is more likely when postsynaptic activity is low. This is known as the Bienenstock–Cooper–Munro (BCM) model (Bienenstock et al., 1982). Generally speaking, previous neuronal activity modulates the capacity for subsequent plastic changes. This has been termed metaplasticity (Abraham and Tate, 1997). All these phenomena could concur in stabilizing neuronal networks and therefore contribute to "homeostatic plasticity" (Turrigiano and Nelson, 2004).

A study showed that rTMS effects on intracortical inhibition depended more on baseline individual values than on stimulation frequency (Daskalakis et al., 2006). Subjects with less inhibition before rTMS tended to have an increased inhibition post-rTMS (and vice-versa). A similar observation was made in patients with chronic pain who showed defective intracortical inhibition at baseline and increased inhibition following rTMS delivered at 10 Hz over the motor cortex (Lefaucheur et al., 2006).

Accordingly, priming cortical stimulation aimed at modulating the initial state of cortical excitability could influence subsequent rTMS-induced changes in cortical excitability. The priming stimulation can have no detectable effects per se on synaptic transmission. There are several reports of efficacious priming protocols in the

literature: subthreshold 6-Hz rTMS was found to reinforce the depression of motor responses induced by suprathreshold 1-Hz rTMS subsequently applied to the motor cortex (Iyer et al., 2003); the priming effect of iTBS was assessed on a subsequent 1-Hz rTMS session delivered to temporoparietal language areas during an auditory word-detection task (Andoh et al., 2008); the analgesic effects of "conventional" 10-Hz rTMS delivered to M1 was found to be enhanced by TBS priming, at least using iTBS (Lefaucheur et al., 2012); a PAS session was found to affect the changes in motor cortex excitability induced by a subsequent PAS session (Muller et al., 2007); tDCS was found to enhance or reverse the effects of 1-Hz or 5-Hz rTMS depending on stimulation polarity (Lang et al., 2004; Siebner et al., 2004), and so on. Thus, priming cortical stimulation surely is a potent way of improving rTMS efficacy in clinical practice.

Lesions and diseases can also be at the origin of preexisting homeostatic changes in the activity of a given cortical region. Therefore, the effects of cortical stimulation and priming strategies may differ between patients and healthy subjects. For example, PAS-induced potentiation of synaptic transmission is lacking in Parkinson's disease (Ueki et al., 2006) but enhanced in patients with focal dystonia (writer's cramp) (Quartarone et al., 2003) compared to normal controls. Differential effects of dorsolateral prefrontal cortical stimulation were observed between normal subjects and depressive patients regarding the type of mood changes with respect to the side of stimulation (George et al., 1996; Pascual-Leone et al., 1996). Actually, abnormal plastic responses and altered excitability changes to cortical stimulation have been found in numerous neuropsychiatric diseases. Various mechanisms other than preexisting homeostatic changes may also explain the differences in the responsiveness to cortical stimulation between healthy subjects and patients. These mechanisms include genetic factors (Edwards et al., 2006; Kleim et al., 2006), hormonal factors (Inghilleri et al., 2004), attentional capacities (Stefan et al., 2004), interindividual differences in brain anatomy, and possible shift of cortical areas of interest. The latter can now be corrected by determining the location of cortical stimulation targets with functional neuroimaging data integrated in a navigated approach.

CONCLUSION: SAFETY AND CONTRAINDICATIONS

As a conclusion, it should be emphasized that the adverse effects of noninvasive cortical stimulation, especially TMS, are rare and the contraindications sparse, as highlighted in various guidelines (Rossi et al., 2009; Lefaucheur et al., 2011; Antal et al., 2017). A mild and transient headache can be induced by TMS, but the main concern is to provoke seizure during an rTMS session, even if there is no evidence that a chronic epileptic disorder could be generated. The risk of inducing seizure depends on the intensity and the frequency of stimulation and also on the "brain-state" of the patient. In practice, this risk can be limited by following the published safety guidelines and by withdrawing drugs that reduce seizure threshold. The possibility of hearing after-effects, mainly hyperacusis, should also be taken into consideration, because the loud clicking sound evoked from the TMS coil may theoretically exceed limits for noise exposure. The use of hearing protection devices (earplugs) is recommended for rTMS sessions, especially in the case of temporal cortex stimulation. The other adverse effects are more hypothetical, including heating of the brain and effects on pulse rate, blood pressure, or hormone levels. The contraindications for TMS are similar to those of MRI, mainly involving intracranial ferromagnetic material. Cardiac pacemaker is usually considered a contraindication, although it is unlikely to be damaged by a TMS pulse delivered over the head.

The TMS techniques currently have a worldwide recognition and a major place in neurophysiologic practice, providing methods for diagnosis, pathophysiologic investigation, mapping procedure, or therapeutic applications.

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