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Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS)

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alexandra.lackmy@upmc.fr

Wanalee Klomjai[a], Rose Katz[b, c], Alexandra Lackmy-Vallée[b, ,]
[a] Faculty of Physical Therapy, Mahidol University, 73170 Nakonpathom, Thailand
[b] UPMC Université Paris 06, CNRS, Inserm, laboratoire d'imagerie biomédicale, Sorbonne universités, 75013 Paris, France
[c] Service de médecine physique et réadaptation, groupe hospitalier Pitié-Salpêtrière, AP–HP, France

Abstract

Transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) are indirect and noninvasive methods used to induce excitability changes in the motor cortex via a wire coil generating a magnetic field that passes through the scalp. Today, TMS has become a key method to investigate brain functioning in humans. Moreover, because rTMS can lead to long-lasting after-effects in the brain, it is thought to be able to induce plasticity. This tool appears to be a potential therapy for neurological and psychiatric diseases. However, the physiological mechanisms underlying the effects induced by TMS and rTMS have not yet been clearly identified. The purpose of the present review is to summarize the main knowledge available for TMS and rTMS to allow for understanding their mode of action and to specify the different parameters that influence their effects. This review takes an inventory of the most-used rTMS paradigms in clinical research and exhibits the hypotheses commonly assumed to explain rTMS after-effects.

Key words: transcranial magnetic stimulation (TMS), human, cortex

Introduction

Over the past decades, neuroscience researchers have benefited from technical advancements in non-invasive brain stimulation in humans. Transcranial magnetic stimulation (TMS) is one method used to deliver electrical stimuli through the scalp in conscious humans. In general, single-pulse TMS (including paired-pulse TMS) is used to explore brain functioning, whereas repetitive TMS (rTMS) is used to induce changes in brain activity that can last beyond the stimulation period. Non-invasive TMS of the motor cortex leads to a twitch in the target muscle evoking a motor-evoked potential (MEP) on electromyography (EMG). The MEP is usually used to assess the corticospinal tract excitability. The physiological bases underlying modulations induced by TMS and rTMS have not been elucidated. The main knowledge is still from animal studies and *in vitro* experiments performed on hippocampal slices. The purpose of the present review is to discuss the main points of TMS to allow for a better understanding of its mechanisms.

Animal experiments

During the 20th century, animal studies provided the first evidence of the effect of a single electrical pulse given by a probe directly applied over the motor cortex [1]. In these experiments, the skull was removed to expose the brain. This setup with implanted electrodes allowed for recording the discharges from subcortical fibers and fibers of the pyramidal decussation. Later, Patton and Amassian showed that the response evoked in pyramidal fibers by electrical stimulation of the motor cortex were spaced from 1 to 2 ms [2]. At a response threshold, anodal stimulation evoked a first volley in the pyramidal tract, which was followed, with increasing stimulation intensity, by later volleys separated by a periodicity of 1.5 ms. Different conditions were tested to determine the origins of these descending volleys induced by anodal stimulation. The first volley recruited appeared not to be affected by cortex cooling and was maintained after removal of the cortical grey matter, whereas later volleys were depressed by cortex cooling and disappeared when the grey matter was removed. The authors hypothesized that the first volley resulted from direct stimulation of pyramidal tract axons, called direct wave (D-wave), whereas later volleys came from synaptic activation of the same pyramidal tract neurons, called indirect waves (I-waves). The recruitment order of descending volleys evoked in the pyramidal tract by anodal stimulation was accurately defined by Kernell and Chien-Ping, who confirmed that the D-wave was the first volley recruited and showed that it was followed 3 and 4.5 ms later by an I_2-wave and I_3-wave, respectively [3]. However, an I_1-wave occurring 1.5 ms later than the D-wave was evoked only with high stimulation intensities. The authors also found that the amplitude of descending volleys induced in the pyramidal neurons increased in parallel with stimulation intensity of the motor cortex.

First experiments of transcranial stimulation in humans

In 1980, Merton and Morton succeeded in electrically stimulating the motor cortex through the scalp in conscious humans by using transcranial electrical stimulation (TES) [4]. The electrical impulse was given by 2 electrodes placed over the scalp, one applied over the arm motor area and the other 4 cm above the first one. Electrodes were connected to a high-capacity condenser (0.1 µF) charged up to 2000 V. TES led to a twitch in contralateral arm muscles, which evoked an MEP on EMG. However, TES appeared to be uncomfortable and painful. Only some fraction of the current was thought to pass through the scalp and reach the cortex, whereas the main fraction of the current spreading between the 2 electrodes was considered to evoke contraction of the scalp muscles and induce local pain. In 1985, Baker

and colleagues proposed replacing TES with TMS [5]. TMS directs a magnetic field of several Teslas via a wire coil. In 1990, Tofts proposed a model of the distribution of TMS-induced currents in the central nervous system [6]. He suggested that as the magnetic field changes rapidly, circular electrical currents are induced. The currents flow in a plane perpendicular to the magnetic field. So, current flows induced by TMS are in an annulus underneath the coil. If the circular coil is placed flat on the scalp, currents flow in a plane parallel to both the coil and the scalp. The force of magnetic field induced by TMS can be reduced by extracerebral tissues (scalp, bone, meninges); however, it is still able to induce an electrical field sufficient to depolarize superficial axons and to activate networks in the cortex [7]. However, because the impedance of gray matter is greater than that of white matter, electrical currents in subcortical structures are weaker than in superficial layers, so subcortical structures such as the basal ganglia and thalamus are not activated by TMS.

Spinal motoneuron recruitment in response to TMS

On the basis of the Tofts' model [6], TMS preferentially activates neurons oriented horizontally in a plane that is parallel to both the coil and the brain surface. As with TES, TMS applied over the motor cortex induces descending volleys in the pyramidal tract projecting on spinal motoneurons, also termed corticospinal tracts. Motor-neuron activation in response to corticospinal volleys induced by TMS evokes an MEP on EMG recorded by using surface electrodes applied over the muscle belly. In practice, the peak-to-peak amplitude of the MEP and the motor threshold (MT), defined by the minimum TMS intensity required to evoke an MEP of at least 50 μV in about 50% of 5 to 10 consecutive trials [8], are both parameters used to estimate the excitability of corticospinal pathways (Fig. 1). In 1987, a study showed that the first motor unit recruited during minimal voluntary contraction was also that recruited by TMS of the motor cortex; the order of recruitment was the same with TMS and with voluntary contraction [9]. Motor units are recruited in an orderly sequence from the smallest to the largest according to the size principle [10].

Physiological bases of TMS measures used to estimate corticospinal excitability

From pharmacolocial studies with healthy volunteers, TMS measures used to estimate motor cortical and corticospinal excitability such as MT and MEP are assumed to rely on different physiological mechanisms. Thus, the MT, which depends on excitability of cortico-cortical axons and their excitatory contacts to corticospinal neurons, is influenced by agents blocking voltage-gated sodium channels that are crucial in regulating axon excitability [11] and by

agents acting on ionotropic non-N-methyl-D-aspartate (non-NMDA) glutamate receptors such as ketamine that are responsible for fast excitatory synaptic transmission in the cortex [12]. In contrast, other neurotransmitters and neuromodulator systems such as GABA, dopamine, norepinephrine, serotonin or acetylcholine have no effect on MT. As for MT, the MEP can be depressed by agents that inactivate sodium channels such as volatile anesthetics [13]. MEP reduction is hyposthesized to result from reduced excitability of I-waves due to sodium-channel inactivation, which leads to decreased action potential firing and in turn reduces calcium entry at the presynaptic terminal and finally synaptic transmission [14]. Moreover, MEP amplitude was found to vary after the application of modulators of inhibitory and excitatory transmission in neuronal networks. For instance, the MEP is depressed by modulators of $GABA_A$ receptors or increased by dopamine agonists and various norepinephrine agonists. Of note, changes in MEP amplitude can occur without significant changes in MT, which supports the notion of a fundamental difference in physiology between the 2 measures. [15].

Descending volleys induced in the corticospinal tract

In 1990, direct epidural recordings were performed in anesthetized subjects to compare descending volleys evoked by TES and TMS in the corticospinal tract [16]. The pattern of recruitment of corticospinal volleys evoked by TES seemed to closely resemble that evoked in animals by anodal electrical stimulation of the motor cortex: D-wave, late I-waves, then early I-wave. This finding suggests that TES preferentially activates cortical neurons in a plane vertical to the surface brain. The D-wave induced by TES is thought to result from excitation of pyramidal tract axons at the initial segment [17-18]. Consistent with the Tofts' model [6], the recruitment pattern of corticospinal volleys induced by TMS differed from that evoked by TES, as attested by epidural recordings. With increasing TMS intensity, the I_3-wave was first recruited, followed by the I_2-wave, then I_1-wave. In a few subjects, the D-wave could be evoked with high TMS intensities. These results confirmed that TMS preferentially activates cortical interneurons relaying excitatory inputs to pyramidal neurons.

Variability of TMS-induced responses

The path and strength of an electrical field generated in the brain by TMS depends on many physical and biological parameters such as magnetic pulse waveform; shape and orientation of the coil; intensity, frequency and pattern of stimulation; orientation of the current lines induced in the brain; and excitable neural elements. TMS can deliver a monophasic pulse or

biphasic pulses. Monophasic magnetic pulses are commonly used for single-pulse experiments, whereas biphasic stimulus waveforms are usually required in rTMS experiments because of the lower energy requirements [19]. The effect of mono- and biphasic pulses can be compared if the second and decisive phase of the biphasic pulse is taken as the equivalent of the initial monophasic pulse [7]. The effectiveness of stimulation appears to vary according to the direction of currents induced in the motor cortex [20].

Various kinds of coils with different geometries and sizes have been developed and include the circular coil, figure-of-eight coil, double-cone coil, air-cooled coil and, more recently, the Hesed coil [21], c-Core coil and circular crown coil [7]. Currents induced by circular coils widely spread under the windings and activate superficial cortical layers. Circular coils are recommended for stimulating large and superficial motor areas such as upper-limb motor areas. However, the figure-of-eight coil provides a focused stimulation; the electric field is at its maximum under its center (hot spot), where the 2 uwindings meet, for a more accurately defined area. The electric field of double-cone coils can reach deep cortical layers. This coil is mainly recommended for stimulating the motor areas of lower limbs that are located deep inside the inter-hemispheric fissure [22]. Nevertheless, the double-cone coil is not focal. A single TMS via a double-cone coil over M1 evokes bilateral responses in upper and lower limbs and also a contraction in facial muscles. The direction of current lines derives from the orientation and position of the coil over brain gyri and sulci. In most studies, TMS is used to stimulate M1. If the figure-of-eight coil over M1 is oriented parallel to the inter-hemispheric fissure, current flows in the posterior–anterior direction and activates the pyramidal tract indirectly via the recruitment of excitatory interneurons. Thus, posteriorly directed currents in the brain preferentially elicit late volleys in the corticospinal tract. However, if the figure-of-eight coil is oriented perpendicular to the inter-hemispheric fissure, an early I-wave and even a D-wave can be recorded [23].

Recently, navigated brain stimulation (NBS) has been developed to facilitate the use of TMS. NBS devices consist of an infrared camera detecting trackers placed on a headband worn by the subject and on the coil. From MRI brain data, NBS is able to rebuild the subject's head in 3-D and to record the coil position. Some devices can measure the strength and direction of the electric field induced in the brain by TMS. More than just being an improvement of TMS measurement, NBS offers the possibility of reliably stimulating other brain areas such as the premotor cortex, cerebellum, sensory areas and cognitive areas.

Paired-pulse TMS methods

Paired-pulse TMS methods have been developed since the late 20th century. Paired-pulse TMS consists of 2 successive pulses through the same coil, delivered with a short inter-stimulus interval (ISI) of a few milliseconds or a long ISI (from tens to hundreds of milliseconds). In practice, both pulses are applied over the same point of the dominant hemisphere over the motor cortex. This method is used to explore inhibitory or excitatory intracortical networks depending on the intensity and ISI used [24-26]. Nevertheless, paired-pulse TMS can reveal inhibitory cortical networks more easily than excitatory networks, which are less investigated. Two TMS pulses can also be delivered over each hemisphere at the same point of the motor cortex so as to explore inter-hemispheric inhibition (or transcallosal inhibition) [27].

rTMS methods

Contrary to single-pulse TMS, rTMS is able to change and modulate cortical activity beyond the stimulation period, for a potential method for the treatment of neurological and psychiatric disorders. The physiological bases of rTMS after-effects have not yet been clearly identified. Many arguments support the idea that the mechanisms underlying rTMS after-effects resemble long-term potentiation (LTP) and long-term depression (LTD) described in animals.

Potential cellular mechanisms inducing LTP and LTD

LTP and LTD are broad terms that traduce long-term changes in synaptic strength that can occur in experimental conditions after brief high-frequency stimulation. LTP is defined as an increase in synaptic strength, whereas LTD reflects a decrease in synaptic strength. These concepts were introduced in 1973 by Bliss and Gardner-Medwin, who showed in rabbits that trains of high-frequency stimulation delivered to pyramidal cell axons in the hippocampus led to a long-lasting increase in the amplitude of excitatory postsynaptic potentials [28]. Thus if weak and strong inputs were activated together, the temporal order of the pre- and post-synaptic spiking determined whether LTP or LTD was induced. On stimulating first the presynaptic neuron, then the postsynaptic neuron (pre–post) within an interval of tens of milliseconds, LTP is induced, whereas with stimulation in the reverse order (post–pre), LTD is induced. No changes in the synaptic strength were observed if the ISI was longer than 100 ms [29]. The extensive literature on this issue stresses that plasticity changes depend on the synapses and the circuits in which they operate. Several arguments suggest that LTP can be induced by activation of N-methyl-D-aspartate (NMDA) receptors. This post-synaptic

receptor has an intrinsic cation-channel blocked by Mg ions when the cell is at its normal resting potential. When the synaptic neuron is sufficiently depolarized, Mg^{2+} ions are ejected to open the NMDA-receptor cation-channel. The calcium entrance in post-synaptic cells activates a calcium-sensitive signaling pathway, which has many downstream targets that induce changes in pre- and post-synaptic neurons leading to increased synaptic strength. One of these effects is increased post-synaptic neuron sensitivity to glutamate according to a mechanism involving alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [30]. Moreover, experiments with hippocampal slices revealed that nitric oxide (NO), a membrane-soluble neuronal messenger, could contribute to synaptic plasticity in the brain. Inhibitors of NO synthase (NOS) could suppress the induction of LTP in the hippocampus and block LTD in the cerebellum [31]. The NO contribution to synaptic plasticity depends on the strength (i.e., intensity, frequency or duration) of tetanic stimulation. Thus, LTP induced by weak tetanic stimulation would be blocked by NOS inhibitors, whereas stronger tetanic stimulation would lead to NO-independent potentiation [32]. Moreover, NO paired with low-frequency stimulation (0.25 Hz) produces long-lasting depression rather than potentiation [33]. Whether NO affects plasticity by facilitating potentiation mechanisms or contributes to LTP induction by inhibiting LTD is unclear.

Concerning LTD, its induction reverses the LTP effects or LTD is induced *de novo*. Several hypotheses suggest that LTD induction also results from activation of NMDA receptors, thereby leading to increased Ca^{2+} concentration. Contrary to LTP induction, which would be due to a large and fast increase in Ca^{2+} concentration, LTD induction would arise from a small and slow increase in Ca^{2+} content. *In vitro*, LTD is induced by low-frequency stimulations delivered for long periods (600-900 pulses), whereas LTP occurs after short train stimulations delivered at high frequencies. Changes in synaptic strength resulting from LTP or LTD are commonly divided into 2 phases: 1) a short phase (early LTP or LTD) when changes last for only 30 to 60 min and 2) a long-l phase (late LTP or LTD) when modifications of protein synthesis occur [30].

rTMS protocols

Numerous rTMS protocols have reported different after-effects. An after-effect induced by rTMS depends on stimulation frequency and duration of the stimulation period [34]. Low-frequency stimulation (< 1 Hz) has inhibitory effects, whereas high-frequency stimulation (> 5 Hz) leads to excitatory effects in the brain. The duration of the after-effects seems to vary in

parallel with the length of the stimulation. A longer stimulation induces a longer duration of after-effects.

Simple rTMS protocols have individual stimuli that are spaced by identical ISI (Fig. 2). In most low-frequency rTMS studies, the stimulation frequency is usually set at 1 Hz, with stimulation intensity and pulse number varying among studies. Low-frequency rTMS (1 Hz) is considered to have an inhibitory effect but at low intensities (less than MT), 1-Hz rTMS often fails to have measurable effects on motor excitability. Some findings indicate that variability of response to 1-Hz rTMS might be related to the level of motor cortex excitability of the targeted muscle. 1-Hz rTMS suppresses MEP only when the target muscle is at rest. The depression of MEP could be increased if 1-Hz rTMS is preceded by a high-frequency subthreshold stimulation as compared to no preconditioning stimulus. This increase in cortical depression lasts for at least 60 min [35]. In contrast, high-frequency rTMS (5-25 Hz) is thought to increase cortical excitability. Berardelli et al. reported that 5-Hz rTMS set at 120% of the MT facilitated MEP for 1 s [36]. However, the duration of effects induced by high-frequency rTMS varies according to stimulation intensity, pulse number and stimulation frequency. High-frequency rTMS after-effects can persist up to 90 min after stimulation in some cases. However, after-effects induced by high-frequency rTMS could be reversed because of stimulation intensity. Low intensity (less than MT) tends to decrease cortical excitability, whereas high intensity (greater than MT) increases cortical excitability [37]. As for low-frequency rTMS, modulations induced by high-frequency rTMS depend on the level of excitability of motor neurons of the target muscle. If subjects perform a brief isometric contraction of the target muscle, the MEP facilitation induced by 5-Hz rTMS is longer than that observed in subjects at rest [38].

Besides simple rTMS protocols, new rTMS protocols have been developed. The most used is theta burst stimulation (TBS), which has been used in animal studies to induce synaptic plasticity. The pattern of TBS is based on the brain's natural theta rhythm occurring in the hippocampus. TBS consists of bursts of high-frequency stimulation (Fig. 2). The intensity is subthreshold, usually set at 80% of the MT. Different patterns of TBS produce different effects on motor cortex excitability. An intermittent TBS (iTBS) protocol, with TBS applied for 2 s and then repeated every 10 s, increases motor cortex excitability [34, 39-40]. A continuous TBS (cTBS) protocol, with TBS repeated for 40 s without any pause, induces a consistent depression of the MEP. The duration of the TBS after-effects depends on stimulation. iTBS applied for a total of 190 s increases MEP for at least 15 min, whereas 40 s of cTBS depresses the MEP for approximately 60 min. TBS is assumed to produce a mixture

of facilitatory and inhibitory effects, facilitation building up faster than inhibition [39]. Of note, results of TBS protocols seem more consistent than those of simple rTMS protocols, likely due to the fact that in TBS studies, stimulation intensity and number of pulses applied are approximately equal, which is not the case in simple rTMS studies [30].

The last TMS protocol detailed in this review is termed paired associative stimulation (PAS), introduced by Stefan, in 2000. PAS protocols combine a repetitive stimulation of somatosensory afferents with TMS over the contralateral motor cortex [34] (Fig. 2). PAS is based on models of associative LTP or the Hebbian concept described in animals. This model supports that converging inputs from various sources, including local intracortical fibers and corticocortical or thalamocortical afferents, could interact to reshape local representational cortical patterns [41]. In this concept, the temporal order of the presynaptic and postsynaptic spiking determines whether LTP and LTD is induced when a weak and strong input are activated together [29]. In humans, the nature of effects induced by PAS depends on the ISI between the electrical peripheral nerve stimulation and cortical stimulation. If the ISI is shorter than the afferent delay (time required for the peripheral afferent input to reach the brain), PAS depresses the excitability in the motor cortex. In contrast, if ISI is longer than the afferent delay, PAS increases cortical excitability [42]. Pharmacological studies support that PAS after-effects would rely on mechanisms depending on NMDA and $GABA_B$ receptors. Furthermore, dopamine could also play a role in inducing PAS after-effects [30].

Conclusion

The aim of the present review was to summarize the main knowledge about the physiological bases of TMS and rTMS. Given the numerous physical and biological parameters that influence TMS responses, effects induced by TMS and rTMS differ among studies, so calibrated paradigms need to be defined to increase reproducibility. The great variability in results questions the use of TMS and rTMS in clinical trials. However, this question is addressed in detail in the next review [43].

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Figure legends

Figure 1. Transcranial magnetic stimulation (TMS) applied over the motor cortex preferentially activates interneurons oriented in a plane parallel to the brain surface. This placement leads to a transynaptic activation of pyramidal cells evoking descending volleys in the pyramidal axons projecting on spinal motoneurons, also termed the corticospinal tract. Motoneuron activation in response to corticospinal volleys induced by TMS leads to a contraction in the target muscle evoking a motor-evoked potential (MEP) on electromyogram (EMG) recorded by using surface electrodes applied over the muscle belly. Its peak-to-peak amplitude is used to estimate excitability of the corticospinal tract.

Figure 2. Simple repetitive TMS (rTMS) protocols consist of identical stimuli spaced by an identical inter-stimulus interval (ISI). Effects depend on stimulation frequency: at low frequency (LF rTMS < 1 Hz), rTMS depresses excitability in the motor cortex, whereas at high frequency (HF rTMS > 5 Hz), cortical excitability is increased. Theta burst stimulation (TBS) involves bursts of high-frequency stimulation (3 pulses at 50 Hz) repeated with an ISI of 200 ms (5 Hz). In an intermittent TBS (iTBS) protocol, bursts are delivered for 2 s, then repeated every 10 s (2 s of TBS followed by a pause of 8 s). However, in a continuous TBS protocol (cTBS), bursts are repeated for 40 s without any pause. Paired associative stimulation (PAS) protocols combine a repetitive stimulation of peripheral nerve afferents of the target muscle with TMS over its motor area. Intervention consists of 90 to 100 PAS.

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Simplified scheme of mechanism of action of TMS of the motor cortex

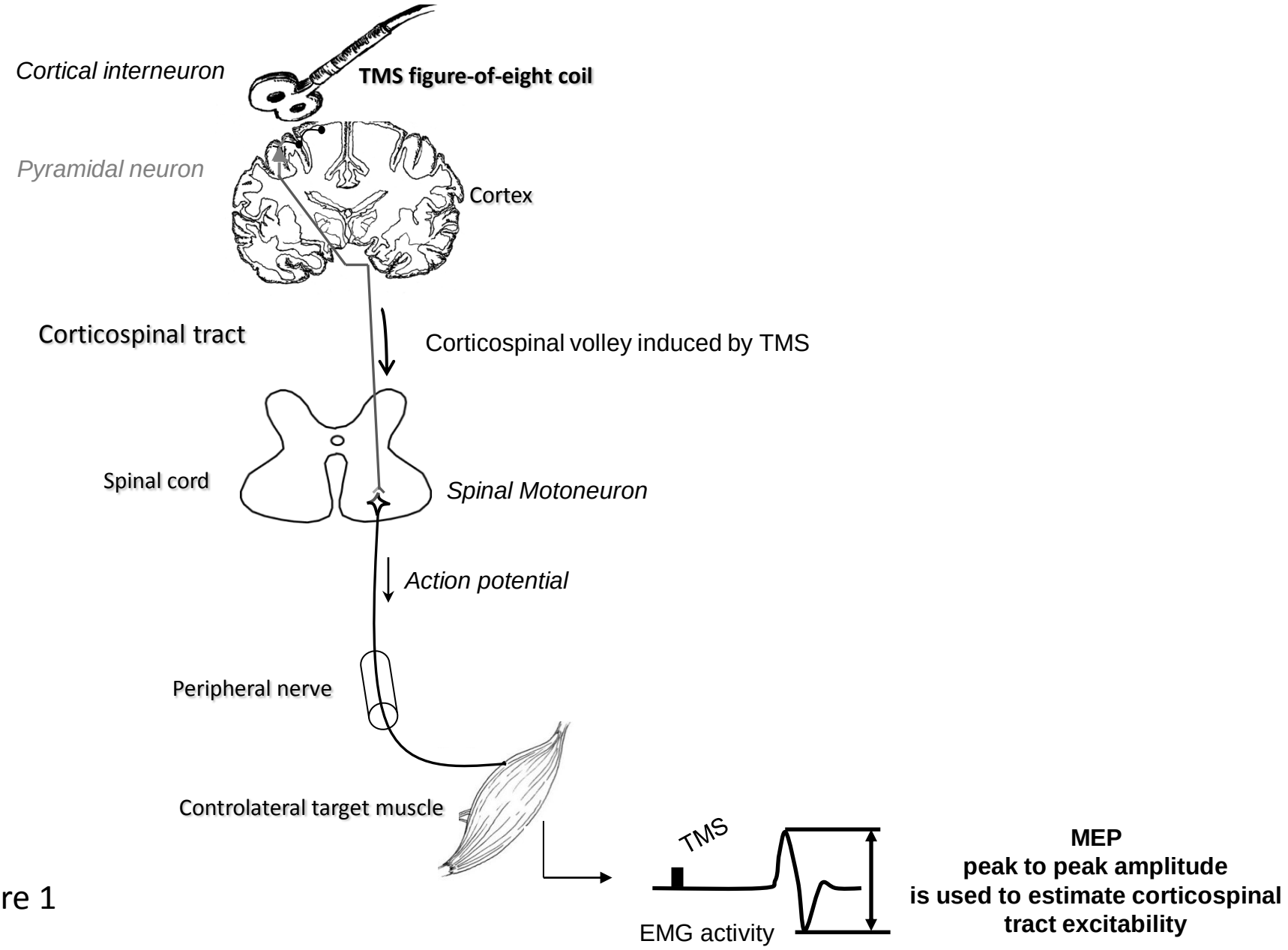

figure 1

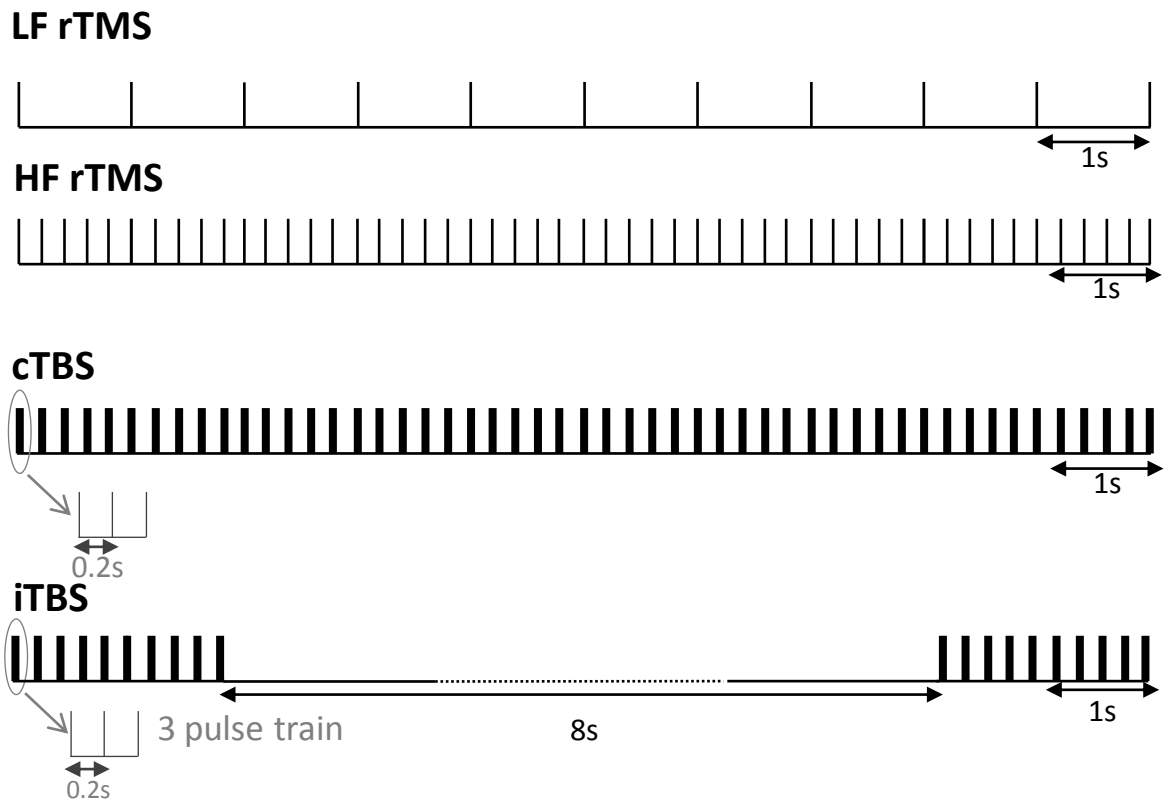
LF rTMS
1s
HF rTMS
1s
cTBS
1s
0.2s
iTBS
3 pulse train
8s
1s
0.2s
PAS
TMS
TMS
TMS
Peripheral
nerve stimulation
pre
90 paired-stimulations
ISI > afferent delay
ISI < afferent delay
post

figure 2