2 Neurophysiological Bases and Mechanisms of Action of Transcranial Magnetic Stimulation

Vincenzo Di Lazzaro and Emma Falato

2.1 Introduction

Transcranial Magnetic Stimulation (TMS) is a neurophysiological technique that allows a noninvasive, painless stimulation of the human brain through the intact scalp.

Different brain areas can be targeted by TMS, depending on the position of the coil. TMS effects on motor areas have been better characterized compared to non-motor areas since the output produced by the stimulation of the primary motor area of one side can be easily recorded from muscles of the contralateral side of the body.

The application of noninvasive TMS to the human brain for assessing central motor pathways was described for the first time in 1985, in the *Lancet* journal, by A.T. Barker, R. Jalinous and I.L. Freeston, from the University of Sheffield [1].

The new TMS technique had a unique potential and some advantages compared to noninvasive transcranial electrical stimulation (TES), which was developed in 1980 by P.A. Merton and H.B. Morton [2]. Compared to TMS, TES requires high current densities to overcome the skull and to generate action potentials, resulting in painful and low tolerable stimulation.

The interest in TMS raised during the years and a consistent number of studies on this topic have advanced our knowledge of the human brain [3], even if many limitations exist due to the artificial nature of the stimulation. So far, many protocols of TMS stimulation have been tested and described, and different cortical circuits activated by TMS have been characterized [4, 5]. TMS can be used alone or in combination with other techniques in order to test corticospinal and cortico-cortical connectivity and brain plasticity, to map brain functions, and study specific cortical functions by inducing a "virtual lesion" in a targeted area [6–8].

V. Di Lazzaro (✉) · E. Falato
Unit of Neurology, Neurophysiology and Neurobiology, Università Campus Bio-Medico, Rome, Italy
e-mail: V.DiLazzaro@unicampus.it

B. Dell'Osso, G. Di Lorenzo (eds.), *Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences*,
https://doi.org/10.1007/978-3-030-43356-7_2

A milestone in TMS history has been the demonstration that protocols based on repetitive TMS (rTMS) can induce prolonged effects, which outlast the period of stimulation [9, 10]. This evidence opened exciting research and clinical scenarios in which rTMS protocols are used for neuromodulatory/therapeutic purposes.

To date, TMS has a recognized role in the clinical and research settings. Stimulation protocols have been standardized, and safety limits of TMS stimulation have been established [11, 12]. Indeed, specific rTMS protocols received Food and Drug Administration (FDA) approval for the treatment of drug-resistant unipolar major depression.

In this chapter, we will review the evidence and the hypotheses on the neurophysiological bases and on the mechanisms of action of TMS, focusing on TMS application to the primary motor cortex.

2.2 How TMS Is Delivered

TMS is based on the Faraday's principle of electromagnetic induction, according to which a time-varying magnetic field will induce an electric current [13]. In TMS, a brief electric current is delivered through a capacitor to a coil, made of loops of copper wire embedded in a plastic case. Perpendicularly to the coil plane, a focal magnetic field is induced, which penetrates the scalp and the skull without attenuation and generates an electric current. If sufficiently strong, the induced electric current will change the electrical potential of the conductive superficial neuronal membranes leading to an action potential [14, 15].

The most widespread TMS devices can provide monophasic or biphasic pulse shapes with a determined width. More recently, TMS devices with controllable pulse parameters have been introduced [16].

Different types of coil exist, for superficial and deep targets of stimulation, and their effects have been modelled [17, 18]. Among the most frequently used coils, there are the figure-of-eight coil (which induces a more focal stimulation) and the circular coil (which induces a nonfocal stimulation of the brain) [4].

Focal coils can be oriented so as to induce currents in the brain with different directions: more commonly, the coil is kept perpendicularly to the central sulcus, and a posterior-to-anterior (PA) directed current is induced in the brain.

TMS spatial resolution and corticospinal output vary depending on several factors, including the shape of the stimulating coil, its position above the scalp, coil orientation, stimulation intensity, pulse waveform, ongoing voluntary muscle contraction, and other variables [19–22].

2.3 Single-Pulse TMS

The responses that can be recorded at the muscular level after TMS are named as motor-evoked potentials (MEPs) [1, 23–25] (Fig. 2.1). The optimal scalp location to evoke MEPs in the targeted muscle is defined as “hot-spot”, while the minimum

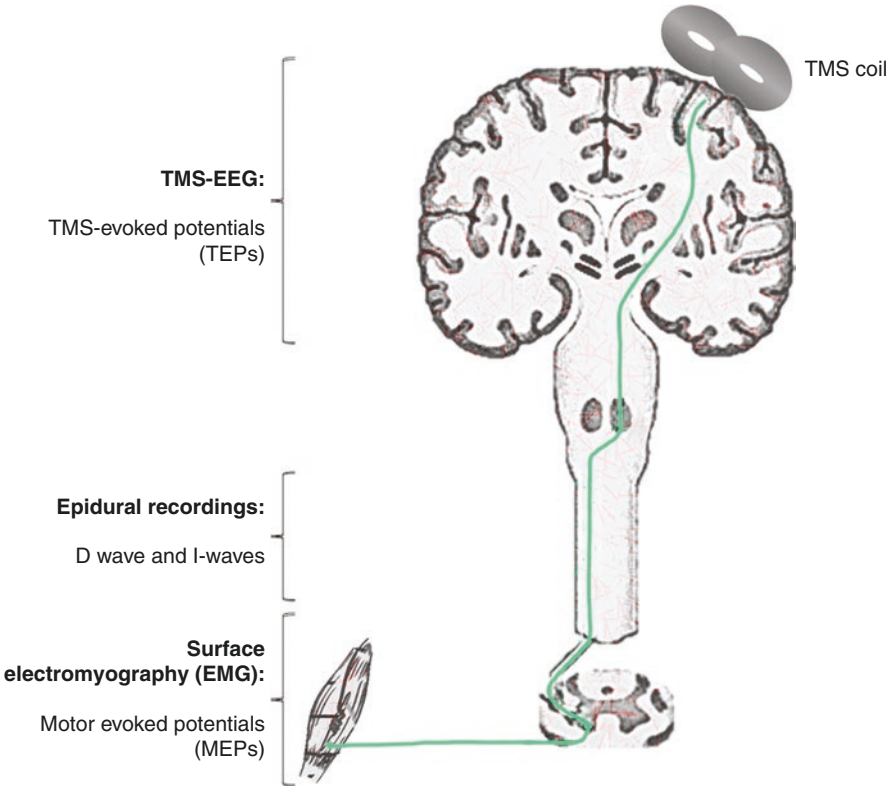

Fig. 2.1 TMS-induced responses at different recording levels

TMS stimulation intensity able to elicit consistent MEPs (with peak-to-peak amplitudes of at least 50 μV in each trial) in at least 5 out 10 consecutive TMS stimuli at rest is defined as resting motor threshold or RMT [12]. For each MEP, objective measures such as onset latency, peak latency, amplitude, and area can be obtained (Fig. 2.2). MEP amplitude, usually measured peak-to-peak, has an intrinsic variability of multifactorial origin [26, 27]. The mechanisms through which primary motor cortex TMS produces MEPs are partially understood due to the complexity of cortical circuits and the difficulty in assessing the interactions between the induced current in the brain and the neural networks, which are composed of different cell types, with different orientations and sizes. The physiological effects produced by motor cortex stimulation have been characterized first in animals, using direct electrical stimulation of the motor cortex together with the direct recording of the evoked corticospinal activity from the high cervical cord. These recordings revealed that a single electrical stimulus delivered to the motor cortex could produce a high-frequency (>600 Hz) repetitive discharge of corticospinal axons originating both from direct and indirect activation of corticospinal cells [28–30]. The earliest wave that is still recordable after cerebral cortex ablation was

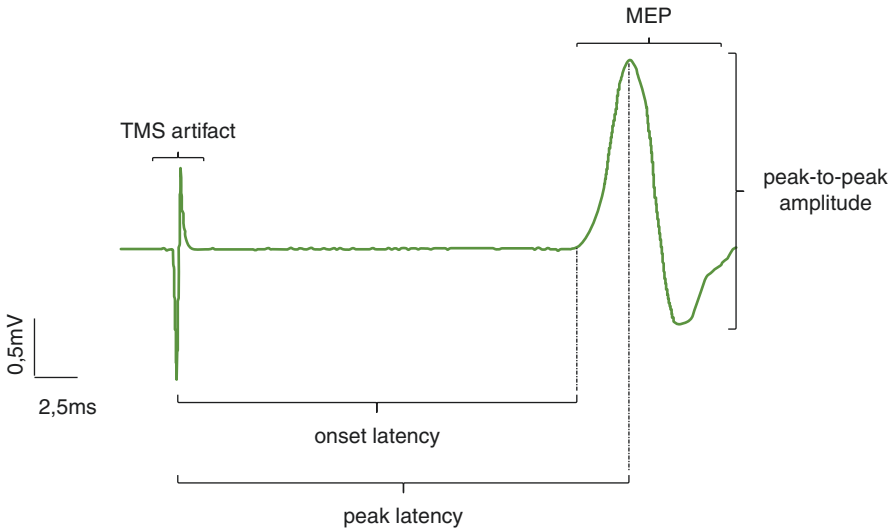

Fig. 2.2 Motor-evoked potential (MEP) elicited by single-pulse Transcranial Magnetic Stimulation (TMS) at 110% resting motor threshold (RMT) intensity, recorded from superficial electromyography (EMG) at the level of the contralateral first dorsal interosseous muscle

thought to originate from direct activation of the corticospinal axons and has therefore been termed the "D" wave [29]. The following waves that require the integrity of the cerebral cortex were thought to originate from indirect, trans-synaptic, activation of corticospinal neurons and were termed "I" waves. They were numbered in order of their appearance (I1, I2, I3, …). The interval between I-waves is about 1.5 ms, which corresponds to a discharge frequency of about 600 Hz. The same high-frequency corticospinal activity was subsequently recorded in humans after motor cortex TMS through epidural high cervical electrodes implanted for the treatment of chronic pain. This unique setting has provided relevant insight [31]. Indeed, it has been shown that also in humans the TMS-induced corticospinal descending activity is made by multiple descending high-frequency waves. Several studies showed that the composition of the corticospinal volleys in terms of D- and I-waves is influenced by the parameters of stimulation (stimulation intensity, coil type, and coil orientation) and by changes in cortical excitability (e.g., changes induced by voluntary contraction) [31, 32]. When the stimulating coil is aligned to induce a current perpendicularly to the line of the central sulcus (approximately posterior–anterior in the brain; PA), TMS evokes the earliest trans-synaptic response that, in analogy with animal recordings, is termed I1-wave. At higher intensities, this wave is followed by later waves numbered in order of their appearance (I2, I3, etc.) [31]. Only at very high stimulus intensity, a short-latency D-wave is evoked. When the induced current flows parallel to the line of the central sulcus (approximately lateral-to-medial in the brain; LM), only a D-wave is preferentially recruited. If the orientation of the induced current is kept perpendicular to the line of the central sulcus, but it is reversed (approximately anterior–posterior in the

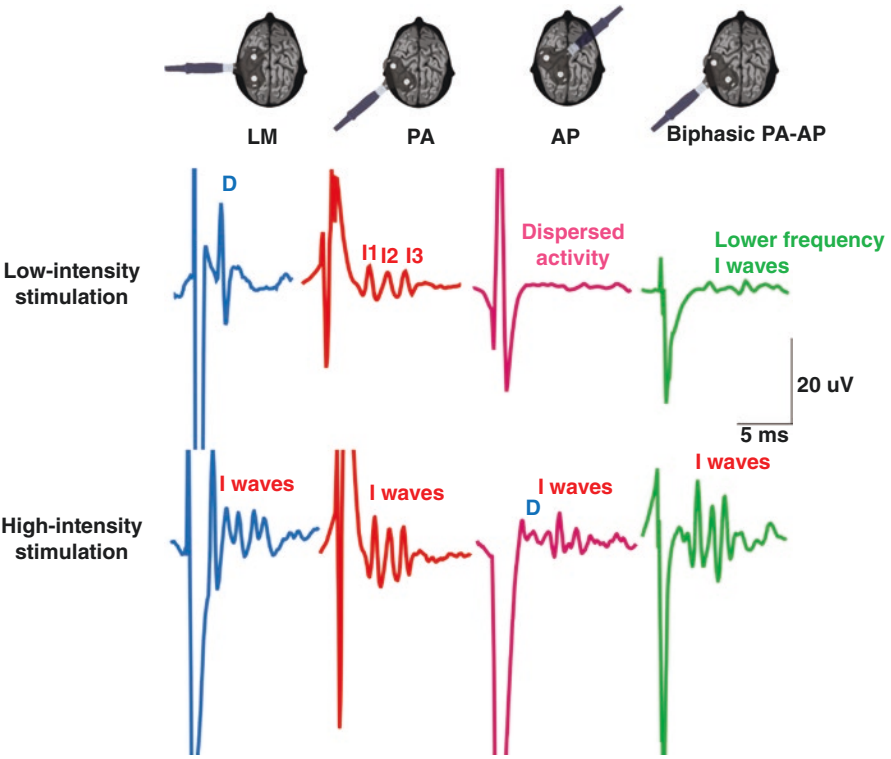

Fig. 2.3 Epidural recordings from the cervical cord of descending volleys evoked by lateromedial (LM), posterior–anterior (PA), anterior–posterior (AP), or biphasic (PA-AP) transcranial magnetic stimulation (TMS) at low and high intensity in patients with cervical epidural electrodes. At lower intensities of stimulation, the different orientations of the induced current evoke different corticospinal activities: LM TMS evokes D-waves; PA TMS elicits three I-waves; AP TMS evokes a dispersed activity, and no clear waves can be identified; biphasic TMS (PA followed by AP) evokes longer latency and lower frequency I-waves. At high intensity, all the directions of the induced current only evoke the high-frequency I-waves

brain; AP), the evoked activity is less synchronized, with some later peaks of latencies compared to those of the I-waves evoked by PA stimulation [31]. Similar findings have been obtained with biphasic stimulation (a PA-induced current followed by an AP-induced current): using biphasic TMS discharges, a corticospinal activity with a frequency that is half of that of the I-waves (about 330 Hz) has been recorded in some patients [4] (Fig. 2.3). These findings suggest that motor cortex TMS may activate not only the corticospinal neurons responding with a high-frequency discharge at I-wave frequency, but also different populations of corticospinal neurons responding at lower frequencies. However, these activities are usually not evident in volleys recorded at the epidural level because, as in animals, these volleys are dominated by fast conducting axons whose discharge is larger and more synchronous, particularly at high stimulation intensity. Only at lower intensities, different corticospinal outputs can be detected. Indeed, at high intensities of stimulation, the

high-frequency I-waves represent the only output that is recorded with all the directions of the induced current in the brain and by both focal and nonfocal coils [4, 31] (Fig. 2.3).

Thus, the direct recording of corticospinal activity in humans and in animals demonstrates that different activities can be produced by transcranial stimulation, suggesting the presence of multiple independent cortical circuits within the motor cortex projecting to the lower motor neurons [4].

Interestingly, the simultaneous recording of TMS and electroencephalography (EEG), known as TMS-EEG, is emerging as a very useful clinical tool to assess cortico-cortical connectivity together with corticospinal connectivity. In this case, the TMS-evoked responses are recorded through the EEG electrodes as positive and negative deflections in the EEG signal and are called TMS-evoked potentials (TEPs) [33].

2.4 Paired-Pulse Stimulation

In paired-pulse TMS protocols, pairs of stimuli are delivered using two connected TMS stimulators. Depending on the interstimulus interval and stimulus intensity, the interaction between pairs of stimuli delivered to the primary motor cortex can be inhibitory or facilitatory, as assessed by MEP amplitude.

Specific paired-pulse TMS protocols have been described. Among the most frequently used in research, for their proposed role as an indirect measure of interneuronal function, there are the short-interval intracortical inhibition (SICI) and the intracortical facilitation (ICF) protocols. SICI and ICF are elicited by pairing a subthreshold conditioning stimulus and a suprathreshold test stimulus, delivered at 1–5 ms (SICI) or 8–30 ms (ICF) interstimulus interval (ISI), respectively. The result is a suppression (SICI) or a facilitation (ICF) of MEP amplitude [34, 35]. SICI has been mainly related to the activation of GABA-A receptors and to a reduction of late I-waves [36–38], while ICF has been in part attributed to glutamatergic NMDA receptor activation, even if it is less well understood [39, 40]. Other paired-pulse protocols are the short-interval intracortical facilitation (SICF) and the long-interval intracortical inhibition (LICI) (for more details see [4]).

Several other TMS protocols are used in research, being TMS a very versatile tool. These protocols include the interhemispheric inhibition (IHI), in which two TMS coils (one for each hemisphere) are used, and the very interesting protocols in which TMS is paired with peripheral electrical stimulation: short-latency afferent inhibition (SAI), long-latency afferent inhibition (LAI), and paired associative stimulation (PAS). For a more comprehensive list and description of TMS protocols, see [12]. Interestingly, epidural recordings in humans have shown that inhibitory protocols only suppress the later components of the corticospinal volley with no effect on the I1-wave [4]. This observation provides further support to the existence of independent cortical circuits producing different corticospinal activities with only some of them under a GABAergic inhibitory control.

2.5 Repetitive TMS (rTMS)

In rTMS, a repetitive stimulation, with biphasic or monophasic stimuli, is delivered over the scalp. rTMS targeting primary motor area showed to be able to induce prolonged effects on corticospinal excitability, which outlasted the stimulation from several minutes to some hours [9, 41]. The mechanisms underlying rTMS effects are still largely unknown. rTMS application on motor areas is commonly studied through the analysis of MEPs size before and after rTMS stimulation. In contrast, rTMS effects over nonmotor areas have more indirect outcome measures, including EEG and MRI connectivity measures and behavioral tests, whose interpretation requires more caution.

To date, existing evidence suggests that rTMS might induce changes in cortical and subcortical neurotransmitter release, with consequent prolonged changes in synaptic activity [42, 43].

rTMS applied to the dorsolateral prefrontal cortex (DLPFC), as in the treatment of depression, is thought to act not only on the stimulated area but also in distant regions, which are anatomically and/or functionally connected [44, 45].

rTMS classical protocols include low-frequency (LF) rTMS (≤1 Hz) and high-frequency (HF) rTMS (>1 Hz). Other popular rTMS protocols are the continuous theta-burst stimulation (cTBS) and the intermittent theta-burst stimulation (iTBS) (Fig. 2.4). Classically, LF rTMS and cTBS were considered inhibitory protocols,

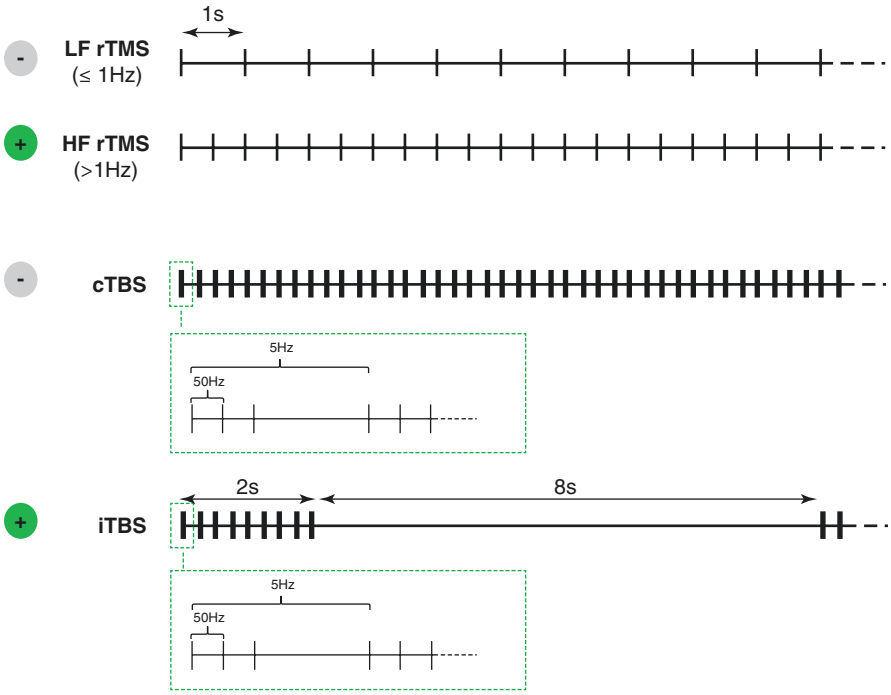

Fig. 2.4 Protocols of repetitive Transcranial Magnetic Stimulation (rTMS). Cf. text for details

able to induce long-term depression (LTD)-like plasticity, whereas HF rTMS and iTBS were considered excitatory protocols, able to induce long-term potentiation (LTP)-like plasticity [9]. However, it is now known that their effect is mixed and it depends on many variables, including the number of stimuli [46, 47], the intensity of stimulation, and the baseline cortical activation state [9, 48]. The after-effects of the different rTMS protocols are commonly described in terms of the changes that are produced in threshold or size of evoked MEPs, and the different protocols are simply classified as inhibitory or facilitatory, assuming that the physiological basis of all the inhibitory and of all the excitatory protocols are similar. However, epidural recordings in humans, performed before and after different rTMS protocols, have shown that, even though most protocols selectively modulate the late components of the corticospinal volleys, some of them could selectively modulate the earliest component or the inhibitory cortical circuits [25]. Thus, epidural recordings revealed that the effects of different protocols on cortical circuits are not homogeneous and that distinct protocols can modulate specific neural elements in distinct layers of the cortex. Different patterns of modulation have been demonstrated: (1) the most commonly observed change after rTMS is a selective modulation of late I-waves with no change in the amplitude of the I1-wave (i.e., inhibition is obtained after low-frequency rTMS (1 Hz), while a selective enhancement of late I-waves with no change in the amplitude of the I1-wave is observed after iTBS). This pattern indicates a more pronounced effect on cortico-cortical interneurons projecting on corticospinal cells with no change in the excitability of corticospinal cells; (2) after high-frequency rTMS (5 Hz), all the volleys are enhanced including the D-wave. This pattern highlights how that the excitability of corticospinal neurons is enhanced; (3) the cTBS protocol suppresses the I1-wave selectively, while later I-waves are much less affected. This suggests that cTBS has its major effect on a single source of inputs to corticospinal cells, which is responsible for the I1-wave production; (4) a very low-intensity and high-frequency stimulation has no effect on corticospinal volleys but suppresses intracortical inhibitory activity, as evaluated with paired-pulse stimulation, suggesting that this form of stimulation selectively modulates the excitability of GABAergic inhibitory networks in the motor cortex [25]. Thus, epidural recordings have shown that it might be possible to modulate specific cortical circuits using rTMS, and this could be extremely relevant because neural circuits that are differentially affected in various neuropsychiatric disorders can be targeted quite selectively with rTMS.

Extensive evidence supports the potential therapeutic applications of rTMS in specific neurological and psychiatric disorders [9].

The main clinical application of rTMS is drug-resistant unipolar major depression, for which rTMS received FDA approval in 2008. The optimal stimulation parameters for a safe and effective administration of rTMS in the treatment of depression have been recently reviewed [49]. The standard rTMS protocol used for the treatment of depression is the 10 Hz stimulation (trains of 4-second duration, with an intertrain interval of 26 seconds) delivered through a figure-of-eight coil, over the left DLPFC at an intensity of 120% relative to RMT. The total number of

pulses per session is 3000. Each session lasts about 37 minutes. The total number of sessions is 20 (5 working days/week for 4 consecutive weeks).

In 2018, a randomized noninferiority trial, which included more than 400 patients (the largest trial of brain stimulation ever done), demonstrated that iTBS effectiveness is noninferior to that of the 10 Hz treatment, with very similar tolerability and safety profiles [50].

Since one iTBS session has a duration of about 3 minutes, approximately 10 times shorter than the standard 10 Hz rTMS session, the new protocol is advantageous in practical terms. However, the total number of sessions tested in the trial is still 20, which requires high patients' compliance.

Systematic clinical studies are still needed to define all the clinical indications of therapeutic rTMS and to identify effect predictors. Further research is also needed to clarify the mechanisms of action and to optimize the stimulation parameters.

References

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106–7.
2. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature. 1980;285(5762):227.
3. Geddes LA. History of magnetic stimulation of the nervous system. J Clin Neurophysiol. 1991;8(1):3–9.
4. Di Lazzaro V, Rothwell J, Capogna M. Noninvasive stimulation of the human brain: activation of multiple cortical circuits. Neuroscientist. 2018;24(3):246–60.
5. Di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. Front Neural Circuits. 2013;7:18.
6. Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res. 2003;148(1):1–16.
7. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55(2):187–99.
8. Hallett M, Di Iorio R, Rossini PM, Park JE, Chen R, Celnik P, et al. Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. Clin Neurophysiol. 2017;128(11):2125–39.
9. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125(11):2150–206.
10. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45(2):201–6.
11. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008–39.
12. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126(6):1071–107.
13. Faraday M. Experimental researches in electricity. Second Series. Phil Trans Roy Soc London. 1832;122, 163.
14. Eldaief MC, Press DZ, Pascual-Leone A. Transcranial magnetic stimulation in neurology: a review of established and prospective applications. Neurol Clin Pract. 2013;3(6):519–26.

15. Holtzheimer PE, McDonald W. A clinical guide to transcranial magnetic stimulation. Oxford: Oxford University Press; 2014.
16. Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul. 2012;5(4):435–53.
17. Deng ZD, Lisanby SH, Peterchev AV. Coil design considerations for deep transcranial magnetic stimulation. Clin Neurophysiol. 2014;125(6):1202–12.
18. Deng ZD, Lisanby SH, Peterchev AV. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul. 2013;6(1):1–13.
19. Di Lazzaro V, Oliviero A, Mazzone P, Insola A, Pilato F, Saturno E, et al. Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans. Exp Brain Res. 2001;141(1):121–7.
20. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Insola A, Mazzone P, et al. Descending volleys evoked by transcranial magnetic stimulation of the brain in conscious humans: effects of coil shape. Clin Neurophysiol. 2002;113(1):114–9.
21. Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, et al. Effects of voluntary contraction on descending volleys evoked by transcranial electrical stimulation over the motor cortex hand area in conscious humans. Exp Brain Res. 1999;124(4):525–8.
22. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res. 1998;119(2):265–8.
23. Hess CW, Mills KR, Murray NM. Responses in small hand muscles from magnetic stimulation of the human brain. J Physiol. 1987;388:397–419.
24. Berardelli A, Inghilleri M, Cruccu G, Manfredi M. Descending volley after electrical and magnetic transcranial stimulation in man. Neurosci Lett. 1990;112(1):54–8.
25. Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol. 2014;592(19):4115–28.
26. Kiers L, Cros D, Chiappa KH, Fang J. Variability of motor potentials evoked by transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol. 1993;89(6):415–23.
27. Torrecillos F, Falato E, Pogosyan A, West T, Di Lazzaro V, Brown P. Motor cortex inputs at the optimum phase of beta cortical oscillations undergo more rapid and less variable corticospinal propagation. J Neurosci. 2019;40(2):369–81.
28. Adrian ED, Moruzzi G. Impulses in the pyramidal tract. J Physiol. 1939;97(2):153–99.
29. Patton HD, Amassian VE. Single and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol. 1954;17(4):345–63.
30. Kernell D, Chien-Ping WU. Responses of the pyramidal tract to stimulation of the baboon's motor cortex. J Physiol. 1967;191(3):653–72.
31. Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A, et al. I-wave origin and modulation. Brain Stimul. 2012;5(4):512–25.
32. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. J Physiol. 1998;508(Pt 2):625–33.
33. Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS-EEG. Clin Neurophysiol. 2019;130(5):802–44.
34. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993;471:501–19.
35. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol. 1996;496(Pt 3):873–81.
36. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, et al. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clin Neurophysiol. 2000;111(5):794–9.

37. Di Lazzaro V, Pilato F, Dileone M, Profice P, Ranieri F, Ricci V, et al. Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: a TMS study. Clin Neurophysiol. 2007;118(10):2207–14.
38. Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, et al. Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J Physiol. 1998;509(Pt 2):607–18.
39. Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al. TMS and drugs revisited 2014. Clin Neurophysiol. 2015;126(10):1847–68.
40. Di Lazzaro V, Pilato F, Dileone M, Saturno E, Oliviero A, Marra C, et al. In vivo cholinergic circuit evaluation in frontotemporal and Alzheimer dementias. Neurology. 2006;66(7):1111–3.
41. Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F, Tononi G. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. Brain Res Bull. 2006;69(1):86–94.
42. Fitzgerald PB, Daskalakis ZJ. The mechanism of action of rTMS. Repetitive transcranial magnetic stimulation treatment for depressive disorders: a practical guide. Berlin: Springer; 2013. p. 13–27.
43. Soundara Rajan T, Ghilardi MFM, Wang HY, Mazzon E, Bramanti P, Restivo D, et al. Mechanism of action for rTMS: a working hypothesis based on animal studies. Front Physiol. 2017;8:457.
44. Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat Rev Neurosci. 2017;18(11):685–93.
45. Anderson RJ, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for treatment resistant depression: re-establishing connections. Clin Neurophysiol. 2016;127(11):3394–405.
46. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res. 2010;204(2):181–7.
47. Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci. 2014;34(20):6849–59.
48. Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topogr. 2008;21(1):1–10.
49. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79(1).
50. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018;391(10131):1683–92.