Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences

Bernardo Dell'Osso
Giorgio Di Lorenzo
Editors

Springer

Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences

Bernardo Dell'Osso • Giorgio Di Lorenzo
Editors

Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences

Springer

Editors
Bernardo Dell'Osso
ASST Fatebenefratelli Sacco
University of Milan
Milano
Italy

Giorgio Di Lorenzo
University of Rome Tor Vergata
Roma
Italy

ISBN 978-3-030-43355-0 ISBN 978-3-030-43356-7 (eBook)
https://doi.org/10.1007/978-3-030-43356-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences, edited by Bernardo Dell'Osso and Giorgio Di Lorenzo, and published by Springer, is a timely and authoritative text and a rare combination of a cutting-edge and user-friendly guide to TMS and tDCS. It includes seminal contributions from world renowned experts in this emerging field. Building on a foundational understanding of the mechanism of action of brain stimulation techniques, the book then translates these insights into clinical applications across a fascinating range of neuropsychiatric conditions. It carefully weighs the efficacy and safety of these approaches. These new treatments may be especially promising for depression and anxiety disorders, OCD, ADHD, addiction, as well as developmental disorders and dementia. This work spearheads the development of novel clinical neuroscience treatments based on the emerging understanding of underlying neural circuits and human behavior.

Eric Hollander
Albert Einstein College of Medicine,
Psychiatric Research Institute at Montefiore-Einstein
The Bronx, NY, USA

Foreword

This volume provides updated, cutting-edge information about the different brain stimulation technologies and lays out the neuroscience beyond NIBS. It brings essential guidance to clinicians on how to use NIBS in different diagnoses, including depression, psychosis, OCD, ADHD, Tourette, addictions, dementia, and anxiety. The Editors and the Contributors summarize in a clear, yet scientifically accurate and clinically useful, manner the state of the art of this exciting development in psychiatry in recent years. The Reader will come up with both an understanding of the neuroscience basis and how to clinically use those important tools that are currently available. This volume is an important addition to the bookshelves of every professional who is interested in understanding and treating disorders of the brain.

Joseph Zohar
Chaim Sheba Medical Center
Tel HaShomer, Israel

Acknowledgements

The Editors acknowledge the valuable contribution of Doctors Eleonora Piccoli, Federica Giorgetti, Laura Molteni, Rita Cafaro and Monica Macellaro of the University of Milan (Sacco Hospital) and Doctors Tommaso B. Jannini, Lucia Longo and Rodolfo Rossi of the University of Rome Tor Vergata in relation to proofs revision.

In recognition of the ongoing collaborations and contributions to the present volume, Editors acknowledge the following organizations:

– "Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Milan, Italy;
– Associazione Italiana per le Terapie Somatiche in Psichiatria (AITESP);
– BrainTrends Ltd, IRCCS Fondazione Santa Lucia, Rome, Italy;
– European College of Neuropsychopharmacology (ECNP) Thematic Working Group on Neuromodulation;
– European Conference on Brain Stimulation in Psychiatry;
– Società Italiana di Psichiatria (SIP), Gruppo di Brain Stimulation in Psichiatria.

Contents

NIBS 2020: How TMS and tDCS Acquisitions Have Set New Standards in Clinical Neuroscience

1

Bernardo Dell'Osso and Giorgio Di Lorenzo

At the beginning of the millenium, not many neuroscientists and even less patient treating doctors could have predicted such a massive development in the field of non-invasive brain stimulation—otherwise known as "NIBS"—which became an innovative tool for neurophysiologic research, psychological and cognitive investigation, and, ultimately, clinical treatment of a wide spectrum of neuropsychiatric conditions. Indeed, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)—the main NIBS techniques—have become the mainstay of translational neuroscience as research tools for understanding cognitive and behavioral states. In addition, their efficacy has been acknowledged within guideline-recommended algorithms for the treatment of different neurological conditions and psychiatric disorders [1–3].

There are many reasons regarding the unprecedented growth of preclinical and clinical investigation with NIBS techniques. One of these is represented by their accessibility and possibility to be associated with other research methodologies and clinical devices, including structural and functional neuroimaging, electroencephalography, genetics, and epigenetics investigation. This has permitted our increased understanding of the network activity underlying both healthy human brain

B. Dell'Osso (✉)
Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, ASST Fatebenefratelli-Sacco, Milan, Italy

'Aldo Ravelli' Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, University of Milan, Milan, Italy

Department of Psychiatry and Behavioural Sciences, Stanford University, Stanford, CA, USA
e-mail: bernardo.dellosso@unimi.it

G. Di Lorenzo
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

IRCCS Fondazione Santa Lucia, Rome, Italy

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_1

functions as well as connectivity changes associated with dysfunctional states characterizing neuropsychiatric disorders.

On the other hand, as the acronym "NIBS" literally indicates, TMS and tDCS are considered safe and well-tolerated interventions for the investigation of neurophysiology, cognitive, affective, and other behavioral domains in healthy controls, as well as for the treatment of patients affected by different neuropsychiatric disorders. Indeed, the use of NIBS in neuroscience research not only allows us to investigate cortical excitability, cerebral connectivity, and neuroplasticity [4, 5] but, in relation to the clinical use of NIBS as therapeutic interventions, TMS and tDCS are considered by many clinicians and patients better tolerated than many psychotropic drugs, in light of their lack of systemic side-effects, including weight gain and sexual dysfunctions, which are often responsible for poor therapy compliance and treatment withdrawal in medicated patients. The favorable safety and tolerability profile of NIBS, however, is not to be claimed at the expense of the clinical efficacy of these interventions. For instance, since 2008, the American F.D.A. approved four different TMS devices for the treatment of Major Depressive Disorder with poor response to standard antidepressants. Lastly, NIBS techniques may also serve as adjuvants to support therapeutic activities across various disciplines, including re-learning or rehabilitative approaches, with encouraging results from field studies.

On this basis, the present book was conceived as a compendium of the latest acquisitions in the evolving field of NIBS, through the valuable contributions of a series of international experts in the areas of brain stimulation and neurophysiology, clinical psychology, neurology, and psychiatry. Across three sections, respectively, focused on (1) basic mechanisms of actions and rationale for the application of NIBS techniques in clinical neuroscience; (2) efficacy and safety of TMS; and (3) tDCS for the investigation and treatment of neuropsychiatric conditions and behavioral alterations, we sought to present a comprehensive and updated state of the art for NIBS in the aforementioned fields.

Because the unprecedented development of NIBS opened new ways for neuroscience by allowing researchers to validate their correlational theories through the direct manipulation of brain function for the first time [6], and for clinicians to safely approach difficult-to-treat conditions, we firmly believe that it deserves a place of priority in the modern education and wealth of knowledge of neuropsychiatrists, neurophysiologists, clinical psychologists, and other professionals involved in the study of neural mechanisms underlying emotions, cognition, and behavioral alterations.

Whether NIBS research in clinical neuroscience will contribute to the identification of biomarkers for specific diseases in the future still represents one of the greatest challenges; however, clinicians are currently focusing their efforts in identifying the best candidates and predictors of response to TMS and tDCS, optimizing stimulation parameters and anatomical targets. Notably, we have already been noticing the use of NIBS as therapeutic interventions for conditions that have been traditionally considered poor targets for psychotropic medications like, for instance, addictive behaviors and eating disorders with remarkable results [7].

Under these premises, we hope the present book will succeed in representing the uniqueness of NIBS as a translational research tool in clinical neuroscience through the peculiar capacity of TMS and tDCS to embrace different clinical and preclinical disciplines advancing their mutual understanding of brain functioning and alterations.

References

1. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92s.
2. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125(11):2150–206.
3. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatr. 2016;61(9):561–75.
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. Reinhart RM, Cosman JD, Fukuda K, Woodman GF. Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. Atten Percept Psychophys. 2017;79(1):3–23.
6. Farzan F, Vernet M, Shafi MM, Rotenberg A, Daskalakis ZJ, Pascual-Leone A. Characterizing and modulating brain circuitry through transcranial magnetic stimulation combined with electroencephalography. Front Neural Circuits. 2016;10:73.
7. Yavari F, Shahbabaie A, Leite J, Carvalho S, Ekhtiari H, Fregni F. Noninvasive brain stimulation for addiction medicine: from monitoring to modulation. Prog Brain Res. 2016;224:371–99.

Part I

Introducing NIBS: From Research to Clinical Practice

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

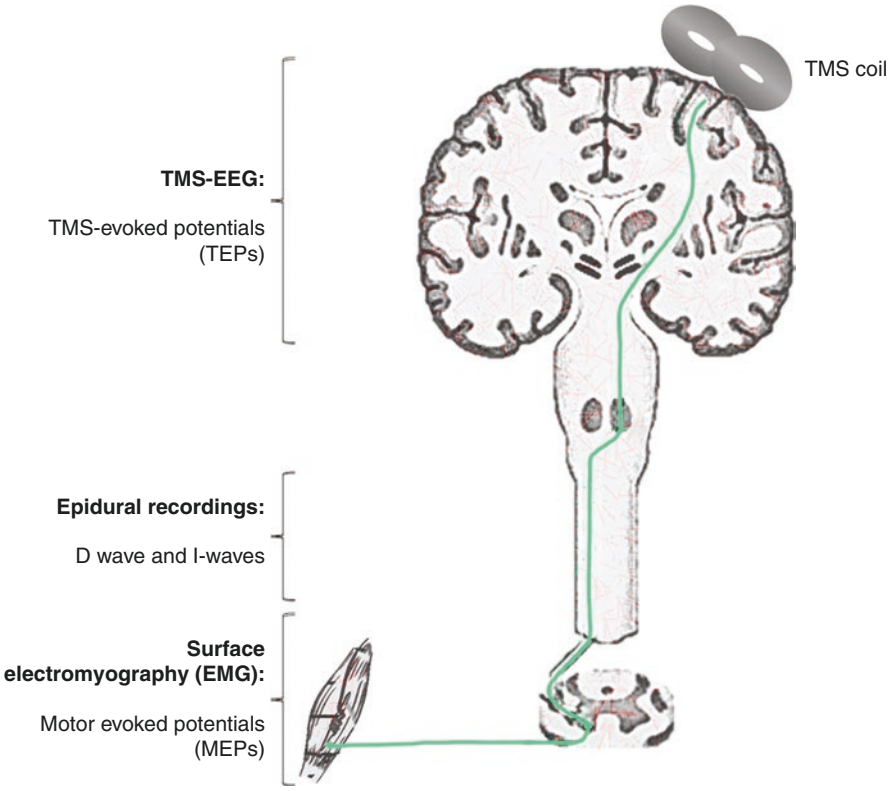

Fig. 2.1 TMS-induced responses at different recording levels

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

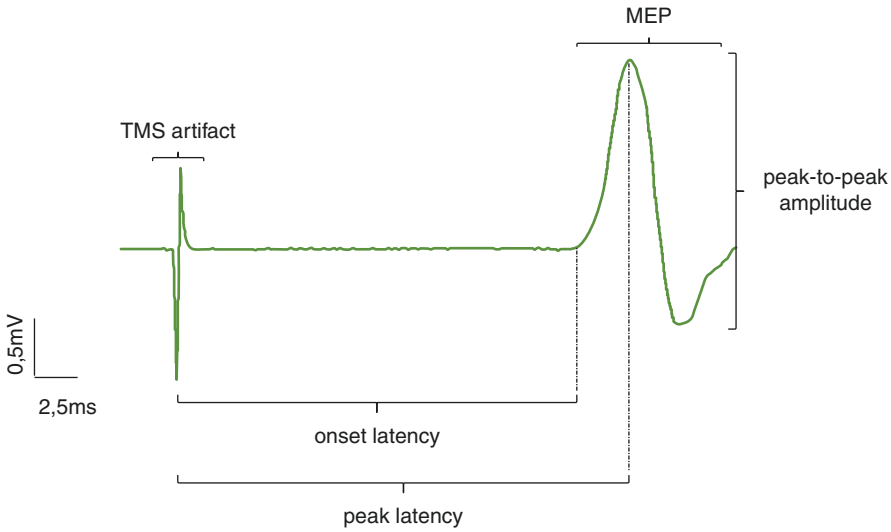

Fig. 2.2 Motor-evoked potential (MEP) elicited by single-pulse Transcranial Magnetic Stimulation (TMS) at 110% resting motor threshold (RMT) intensity, recorded from superficial electromyography (EMG) at the level of the contralateral first dorsal interosseous muscle

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

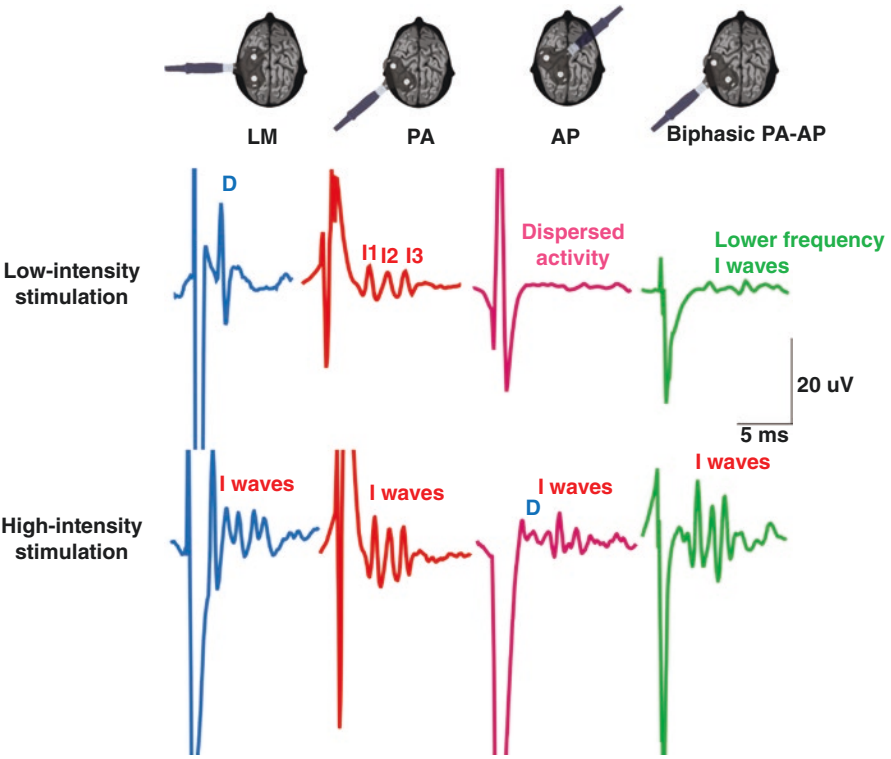

Fig. 2.3 Epidural recordings from the cervical cord of descending volleys evoked by lateromedial (LM), posterior–anterior (PA), anterior–posterior (AP), or biphasic (PA-AP) transcranial magnetic stimulation (TMS) at low and high intensity in patients with cervical epidural electrodes. At lower intensities 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,

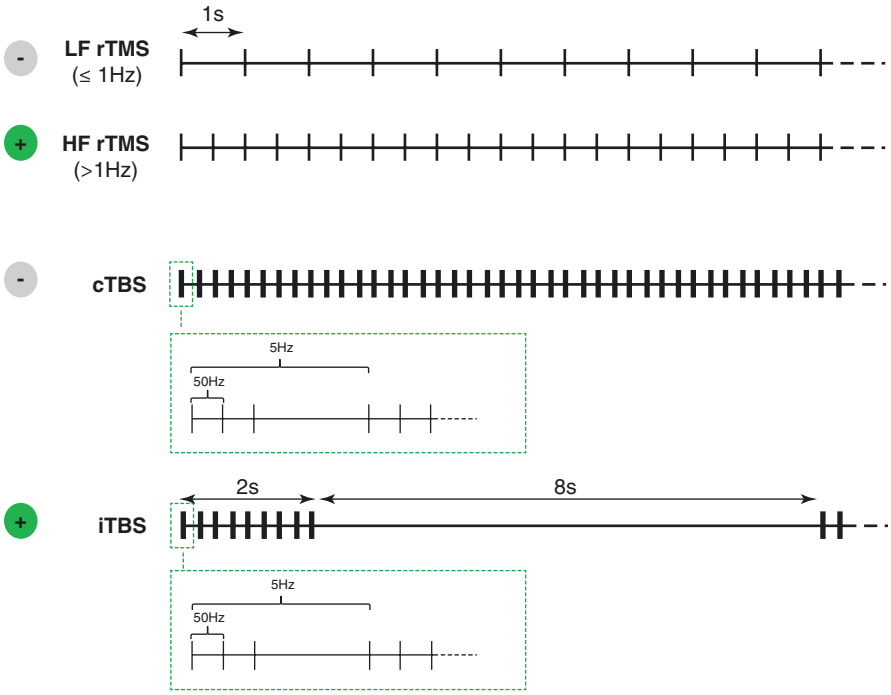

Fig. 2.4 Protocols of repetitive Transcranial Magnetic Stimulation (rTMS). Cf. text for details

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.

3 Neurophysiological Bases and Mechanisms of Action of Transcranial Direct Current Stimulation (tDCS)

Tommaso Bocci, Roberta Ferrucci, and Alberto Priori

3.1 Overview

Transcranial Direct Current Stimulation (tDCS) of the brain has emerged in the past two decades as a novel, noninvasive, cheap, and safe technique to modulate cortical excitability in humans, both in health and disease. Clinical applications ranged from post-stroke recovery [1] and movement disorders [2] to pain syndromes [3] and neuropsychiatric diseases [4, 5]. Recently, tDCS has also been proposed for pediatric use, showing promising results for the treatment of cerebral palsy [6, 7], refractory epilepsies [8], and Attention Deficit Hyperactivity Disorder [9].

tDCS commonly uses subthreshold currents (1.0–2.5 mA), too weak to induce neuronal activity independent from afferent input, but sufficient *per se* to alter both the excitability and spontaneous neuronal firing rate.

Despite a growing body of literature, putative mechanisms of action remain to be completely elucidated, both at molecular and cellular levels (see Fig. 3.1). Moreover, some questions are still unanswered: (1) whether tDCS can interfere with gene expression and protein folding; (2) how neuronal activity is modulated during and following tDCS (online effects versus offline aftereffects); and (3) how long neuronal and subsequent behavioral changes persist. In this chapter, we encompass the current knowledge about tDCS action in humans, suggesting novel mechanisms underlying its use in neuropsychiatric disorders and strengthening the importance of neurophysiological monitoring in human diseases.

T. Bocci (✉) · R. Ferrucci · A. Priori
"Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health Sciences, Neurology Unit, University of Milan, San Paolo University Hospital, Milan, Italy
e-mail: tommaso.bocci@unimi.it; roberta.ferrucci@unimi.it; alberto.priori@unimi.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_3

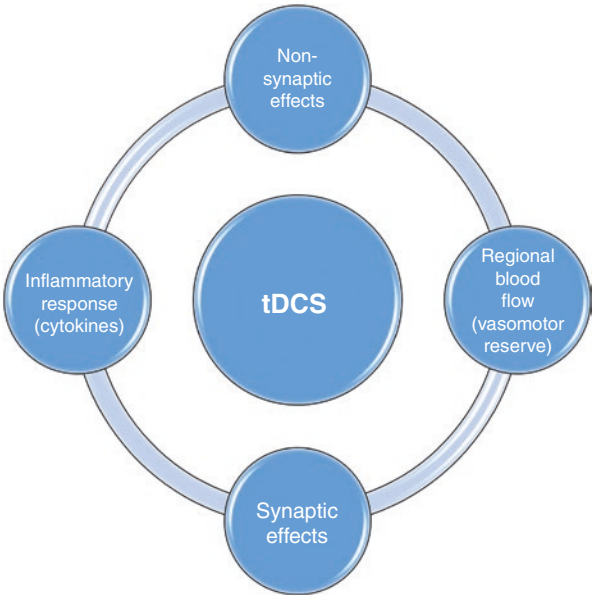

Fig. 3.1 An overview of tDCS mechanisms of action. tDCS exerts both nonsynaptic and synaptic changes, modulating at the same time the inflammatory response and regional blood flow

3.2 Basic tDCS Effects

Overall, tDCS effects are cumulative, nonlinear, and polarity-dependent [10–14]. From a molecular point of view, tDCS shows both short- and long-term effects; the first ones usually outlast the end of stimulation for only a few minutes and involve nonsynaptic mechanisms, comprising changes in membrane polarity, migration, and steric conformation of transmembrane proteins; conversely, the long-term after-effects are mainly mediated by synaptic modifications (Fig. 3.2). In particular, among synaptic changes, anodal and cathodal tDCS seem to have similar effects on different brain neurotransmitters: while anodal tDCS reduces GABA and increases myoinositol, cathodal tDCS decreases glutamate levels [15, 16], respectively, driving long-term potentiation and depression-like phenomena (LTP, LTD).

Nonetheless, the relationship between inhibition and stimulation is not so linear as previously described; the intra- and interindividual variability of tDCS action also depends on genetic polymorphisms [13], as well as on the preexisting excitability state of the cortex, a phenomenon referred to as "metaplasticity" and primed by *N*-methyl-D-aspartate receptors [17, 18]. In healthy humans, the existence of "metaplasticity" has been demonstrated by using neurophysiological methods, both in the primary motor [17] and visual cortex [18]. This kind of plasticity could explain, at least in part, some paradoxical effects, in that anodal tDCS can actually lead to dampened excitability when the stimulation time is increased [19], and cathodal tDCS can sometimes increase excitability when intensity is improved [20].

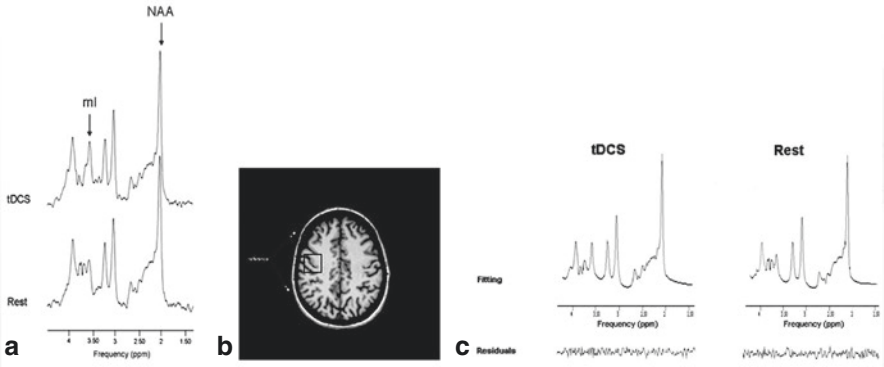

Fig. 3.2 tDCS and nonsynaptic effects. Active tDCS (anodal) over the right frontal lobe induces an increase in myoinositol (mI) content in healthy humans, as proved by the analysis of MRS spectra; given that tDCS alters biophysical properties of the membrane, it influences phospholipid's metabolism and, in turn, mI concentration (modified from Rango *et al.,* 2008, with permission)

From a cellular perspective, both synaptic and nonsynaptic effects of direct polarization ultimately lead to changes in phenotypic and functional aspects, such as morphology, orientation, migration, and cellular growth, as recognized for nearly a century [21]. The possibility to interfere with cells' migration is of particular interest for the development of nonneural cells (e.g., microglia) and for the modulation of immune responses in the human brain, even in adulthood, as discussed below in more detail.

Finally, although tDCS has been primarily studied for its cortical effects, recent animal data have suggested that direct polarization (1–4.16 A/m^2) may also affect subcortical white matter structures, such as the red nucleus, medial longitudinal fascicle [22, 23], and thalamus, likely through changes in regional blood flow and cerebral vasomotor reserve [24, 25].

3.3 Nonsynaptic Mechanisms

tDCS exerts nonsynaptic mechanisms of action. These effects involve changes at different levels, as proved in humans by historical neurophysiological evidence [11]. One of these is the ability to modify neuronal membrane polarity and its threshold for action potential generation, likely affecting the spike timing of individual neurons receiving suprathreshold inputs [26–28]. This effect critically depends on the orientation of the axons relative to the electric field [14, 29], thus driving the direction of tDCS modulation (excitation versus inhibition). For instance, when the electrical field is perpendicular to the axons, the physiological effects of stimulation are negligible, whereas if the current flows longitudinally, these effects

are more pronounced, as larger membrane compartments are homogeneously polarized [30]. Together with the abovementioned "metaplasticity", this is another critical source of variability to predict behavioral effects of tDCS in humans, as in complex brain structures, synapses are not always oriented in the same direction.

3.4 Synaptic Mechanisms (Neuroplastic Changes)

Long-lasting tDCS aftereffects are recognized to be driven mainly by synaptic changes. GABA and glutamate, especially through NMDA receptors (NMDARs), are the most studied neurotransmitters regarding tDCS aftereffects in humans. This is of particular interest because a huge amount of evidence indicates abnormalities of glutamatergic neurotransmission or glutamatergic dysfunction as playing a key role in the development of schizophrenia, bipolar disorder, and major depressive disorder [31–33]. Moreover, changes in glutamatergic and GABAergic activity can be easily evaluated and monitored over time by using paired-pulse Transcranial Magnetic Stimulation (TMS) protocols [34–38].

Pharmacological studies have demonstrated that blockade of NMDA receptors prevents tDCS-induced excitability changes, for anodal as well as cathodal polarization, whereas NMDAR agonists improve anodal aftereffects [39, 40]. In particular, NMDARs regulate the influx of calcium ions (Ca^{2+}) into the neuron, a critical step to modulate the induction of both LTD and LTP plasticity [41, 42].

Regarding GABA modulation, a hierarchical model has been recently proposed: anodal tDCS also decreases GABA, thus leading to an increase in neuronal firing rates, which in turn enhances both local gamma-band oscillatory activity and functional connectivity among highly connected areas [43–45]. The possibility to modulate gamma-band, through a reduction in GABA release, is intriguing because this oscillatory activity seems to be selectively impaired in schizophrenia, although the exact relationship with disease mechanisms is not completely understood [46, 47].

3.5 New Frontiers in the tDCS Effects in Neuropsychiatric Diseases

In recent years, novel potential mechanisms have been explored, including a putative action on the inflammatory response. In particular, animal studies have proved that tDCS has a polarity-specific migratory effect on neural stem cells (NSC) in vivo, thus influencing the development and the distribution of microglia in the adult brain [48]. In addition, tDCS seems to directly modulate inflammatory response by downregulating pro-inflammatory cytokines [49].

Although not yet confirmed in humans, these results are intriguing for the use of tDCS in the treatment of neuropsychiatric disorders. In fact, recent evidence strengthens the role of inflammation in the pathophysiology of schizophrenia and other neurodegenerative diseases; in particular, the role of microglia in psychosis

has been suggested, as the immune system plays not only an essential role in inflammatory processes but also in neurodevelopment and synapse refinement [50–53].

Further studies are needed to better understand the putative role of tDCS in modulating inflammatory responses, both in health and disease.

3.6 Contribution of Neurophysiology in the Study of tDCS Aftereffects

3.6.1 Transcranial Magnetic Stimulation (TMS)

Plastic changes induced by tDCS could be objectively assessed and monitored over time by using neurophysiological techniques, such as Transcranial Magnetic Stimulation (TMS). Single-pulse TMS has been used in the past to evaluate the effects of anodal and cathodal polarization of Motor Evoked Potentials (MEPs) in humans [10, 54], whereas paired-pulse TMS specifically investigates intracortical synaptic changes induced by tDCS [35–37]. Moreover, other TMS parameters can predict the response to tDCS modulation: in particular, the latency and duration of transcallosal inhibition (TI), as measured by single-pulse TMS, are significantly correlated to the extent of tDCS modulation [55]. That is of critical importance in the selection of patients who may benefit from early noninvasive neuromodulation strategies.

3.6.2 Electroencephalography (EEG) and Event-Related Potentials (ERPs)

EEG has been used to provide valuable information on the tDCS mechanisms of action. In particular, anodal tDCS has proved to increase alpha and beta power during and after stimulation, thus leading to a widespread activation of functionally connected brain areas [56]. This finding supports the use of tDCS for modulating the "resting state" of the brain, especially in cognitive and neurodegenerative disorders. Similarly, combined TMS-EEG studies have suggested that anodal tDCS specifically affects task-related functional networks, and the boost of specific circuits correlates with the observed clinical cognitive enhancement [57, 58]. Also, the endogenous event-related potentials (P3-ERPs) seem to be valuable markers for monitoring tDCS aftereffects on specific pathways involved in cognition; for instance, tDCS applied over the dorsolateral prefrontal cortex (DLPC) increases P3 amplitudes, supporting the role of DLPC both in preattentive and attentive functions [59–61]. In another study, Radman and co-workers have proved that tDCS applied over the DLPC also modulates language processing, without facilitating overt second language word production [62]. Similarly, Baptista and colleagues have shown that the stimulation of the medial prefrontal cortex modulates ironic information at the initial stage of irony comprehension [63], a phenomenon impaired in several neuropsychiatric disorders, such as autism [64, 65] and schizophrenia [66].