



The Various Forms of Non-invasive Brain Stimulation and Their Clinical Relevance

Tom A. de Graaf, Alix Thomson, Felix Duecker, and Alexander T. Sack

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As one of the promising upcoming alternatives to traditional drug therapy in central nervous system disorders and psychiatric disease, medical devices for neuromodulation have received a lot of attention. In addition to the invasive neural implant technologies used for deep-brain stimulation, a range of non-invasive brain stimulation (NIBS) techniques have recently been at the center of interest in research and therapy. Here, we provide an overview of the ever-growing family of NIBS methodologies, their clinical applications, and mechanisms of action involved. We suggest that NIBS technologies can be classified based on (1) the underlying technique (magnetic: transcranial magnetic stimulation, or electrical: transcranial electrical stimulation), (2) the targeted neurobiological process (ongoing processing, excitability/plasticity, oscillatory entrainment), or (3) the clinical domain of application (treatment, diagnosis, or prognosis). The current overview should prove valuable in understanding along which dimensions NIBS can be compared with traditional or alternative upcoming CNS modulation technologies.

Learning Objectives

- Gain an overview of the most commonly used NIBS techniques and protocols, including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES).
- Understand the physical and physiological mechanisms of action of TMS and TES.
- Understand NIBS through three different classification schemes: (1) mechanisms of action, (2) targeted brain process, and (3) clinical application.

7.1 Introduction

We are now two decades from the “decade of the brain” (1990–2000), but progress in neuroscience has continued unabated. With no end in sight as of yet, the numbers of

meaningful breakthroughs and neuroscience publications have only grown. In the wake of these developments, the last decade has seen an increase in more applied research as well as commercialization of brain-based treatment and products. For instance, treatment of depression with commercially available brain stimulation devices is now established, and the question is no longer whether such treatment is effective, but rather whether it should be considered as a first-line or even first-choice treatment. Such rapid progress was perhaps no surprise, as better understanding of the central nervous system (CNS) naturally led to developments of a range of techniques and tools that allow CNS interventions/modulation. Developments aiming both to facilitate ever more sophisticated research, and to measure (diagnosis, prognosis) and directly modulate (treatment) CNS activity in clinical applications.

Besides the invasive neural implant technologies used for deep-brain-stimulation, “non-invasive brain stimulation” (NIBS) has been referred to as one of the most promising families of devices/techniques. These tools have been around for a few decades now, but some of their recent incarnations and applications have exploded onto the clinical and research landscape only recently. Some of the newer applications are outlined in the companion chapter 8, where we also critically discuss limitations and unknowns. But roughly speaking, NIBS has in recent years demonstrated equivalent or even superior effects relative to alternative (e.g., drug) treatments of certain brain-based disorders, such as major depression disorder, with only minimal side effects. So, it seems useful to provide an overview of the NIBS toolkit in this chapter and then discuss the applications and limitations in the next chapter.

NIBS differs from other neuromodulation techniques in several key aspects. Firstly, it is *non-invasive*, in the sense that it does not penetrate (the skin remains intact) or introduce external substances into (e.g., drugs, neural implants, or electrodes) the body.

Definition

Non-invasive brain stimulation (NIBS): Altering neural activity through the (concurrent or preceding) application of a stimulus, such as electrical or magnetic, non-invasively through the intact skull.

This sets it apart from otherwise conceptually overlapping techniques such as deep brain stimulation (Aum and Tierney 2018), electroconvulsive therapy (ECT) (Lisanby 2007), optogenetics (Kim et al. 2017; Henderson et al. 2009), or chemical neuromodulation (Robbins 2000). Secondly, NIBS is considered a local (*brain*) neuromodulation approach, for instance able to target a cortical site of around a centimeter squared (Deng et al. 2013), as opposed to neuromodulation with chemicals that flood the system or system-level approaches such as neurofeedback (Sitaram et al. 2017). Thirdly, NIBS involves direct neuromodulation (*stimulation*), in the sense that it actively induces action potentials or modulates membrane potentials (Romero et al. 2019; Jackson et al. 2016). As such, NIBS directly affects activity in the building blocks of the CNS: neuronal firing.

Yet, even if NIBS is a more restrictive term than “neuromodulation,” it still encompasses a wide, and rapidly growing, family of techniques and approaches. In fact, the range of NIBS techniques and applications has grown to the point where it is not trivial to decide what sort of taxonomy (classification scheme) makes most sense. At the same time, it is crucial to maintain a meaningful overview and to allow evaluations and comparisons of NIBS techniques relative to other options for both research and clinical application within the dynamic landscape of CNS medical devices and approaches. Depending on one’s question, it might be useful to classify NIBS techniques according to the underlying physical mechanisms. This is a good starting point and perhaps the classical approach to categorizing the various techniques. Alternatively, it might actually be more valuable to classify NIBS techniques according to the biological mechanism they target/modulate. Indeed, it

turns out that very different NIBS approaches might be interchangeable for certain interventions, at least conceptually (Dunlop et al. 2017; Blumberger et al. 2013). Lastly, it makes sense to evaluate the contributions of NIBS in different clinical settings, discussing NIBS approaches in the context of diagnosis, prognosis, or treatment. All three of these taxonomy schemes have merit, they are largely orthogonal, and together they offer a complete picture of the physical mechanisms underlying the modulation, the biological mechanisms modulated, and the range of resulting applications of NIBS in the lab and the clinic.

7.1.1 NIBS Techniques (Table 7.1)

From the perspective of mechanisms of action, NIBS can be divided into magnetic and electrical techniques. *Transcranial magnetic stimulation (TMS)* allows magnetic stimulation (Barker et al. 1985).

Definition

TMS: transcranial magnetic stimulation. TMS involves the non-invasive delivery of a magnetic pulse to a brain region. This pulse can induce electric field/current that, if sufficiently strong, can depolarize neurons to induce action potentials.

TMS hardware includes a generally non-portable stimulation device positioned on a table or trolley, with a port to which different TMS coils can be connected. Inside the device, a large capacitor can charge up to high voltage, leading to a strong electrical current if a TMS coil is connected and an internal switch is flipped to close the circuit. The current flows through the TMS coil, which consists of one (circular coil) or two neighboring (butterfly or figure-8 coil) windings, housed in a synthetic protective casing which is placed on the skull of the patient (or over peripheral nervous system). Due to well-established physical principles of electromagnetic induction, the following sequence of events occurs: (1) the electric cur-

Table 7.1 NIBS techniques (simplified)

Technique	Protocol	Stimulation parameters	Effects	Applications (conceptual)
Repetitive transcranial magnetic stimulation (rTMS)	1 Hz	1 pulse per second	Inhibitory (LTD-like)	“Virtual lesion”; research clinical treatment
	10 Hz	10 pulses per second	Excitatory (LTP-like)	“Neuro-enhancement”; research clinical treatment
	cTBS	3 pulses at 50 Hz, repeated at 5 Hz. Continuous for 600 pulses	Inhibitory (LTD-like)	Same as 1 Hz rTMS
	iTBS	3 pulses at 50 Hz, repeated at 5 Hz for 2 seconds on, 8 seconds off 600 pulses	Excitatory (LTP-like)	Same as 10 Hz rTMS
Transcranial magnetic stimulation (TMS)	Single pulse	1 pulse, delivered manually every 5–7 seconds	Excitation	Diagnosis/prognosis
	Paired pulse	2 pulses, different inter-pulse intervals	CNS interactions	Diagnosis/prognosis
Transcranial electrical stimulation (TES)	Anodal tDCS	Continuous, direct current stimulation	Depolarize membrane potential (also, LTP-like)	Increase regional excitability, similar as 10 Hz rTMS
	Cathodal tDCS	Continuous, direct current stimulation	Hyperpolarize membrane potential (also, LTD-like)	Decrease regional excitability, similar as 1 Hz rTMS
	tACS	User-defined frequency. Polarity alternates between electrodes	Sinusoidally affects membrane potentials	Align/amplify/impose neuronal oscillations
	tRNS	Random high-frequency, polarity alternates between electrodes	May increase neuronal excitability	May increase regional excitability

rent through the TMS coil gives rise to a perpendicular magnetic field. Since the electric current is rapidly changing, the magnetic field is rapidly changing in proportion, becoming a magnetic “pulse.” (2) The magnetic pulse crosses the scalp and skull unhindered, noninvasively. (3) In the conductive neuronal tissue reached by the magnetic field, electrical activity is again induced (Polson et al. 1982; Walsh and Rushworth 1999; Jalinous 1991; Hallett 2007; Rossini et al. 2015; Kammer et al. 2001).

The strength of the induced electric field and electric currents is proportional to the rate of change of the magnetic field, rather than the strength of the magnetic field directly (which, incidentally, is why an MRI scan does not stimulate the neurons) (Jalinous 1991; Barker 1991). This is also why different “waveforms” of the electric currents through the TMS coil can have different effects on the affected neurons (Kammer et al. 2001; Groppa et al. 2012). Irrespectively, the mechanism of TMS is that

the magnetic pulse and associated induced electric field are sufficient to depolarize (most likely the axons of cortico-cortical inter-) neurons to achieve action potentials with each TMS pulse (Romero et al. 2019; Pashut et al. 2011).

- ▶ Single suprathreshold TMS pulse and associated electric field are sufficient to depolarize neurons.

As outlined below, even such single TMS pulses can be used both in research and clinically. However, much of the excitement surrounding TMS as a research and treatment tool is based on repetitive application of single pulses. Repetitive TMS (rTMS) involves multiple pulses applied rhythmically in patterns of single or even multiple frequencies. Classical rTMS protocols such as 1 Hz rTMS and 10 Hz rTMS were soon found to affect targeted brain regions even beyond the period of stimulation (Pascual-Leone et al. 1994; Muellbacher et al. 2000). Recent patterned protocols, such as the 40-second continuous theta burst stimulation (cTBS) and the 3-minute intermittent theta burst stimulation (iTBS) protocols, were shown to have much longer after-effects on cortical excitability than the protocol duration; for cTBS up to an hour after the end of the stimulation (Huang et al. 2005). The cTBS protocol involves triplets of single pulses at 50 Hz, which themselves are presented in a 5 Hz rhythm, until 600 pulses are delivered. The iTBS protocol adds another pattern, that is, 2 seconds of such theta burst stimulation followed by 8 seconds of rest, until again 600 pulses are administered in total. Importantly, effects on excitability are (on average) inhibitory (1 Hz rTMS, cTBS) or excitatory (10 Hz rTMS, iTBS), depending on the precise parameters of the rTMS protocols. It has been suggested that both classical and patterned rTMS protocols engage synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD), to achieve these impressive modulations of neuronal activity (Huang et al. 2007; Teo et al. 2007; Cirillo et al. 2017). However, the precise mechanisms involved remain unclear and may differ between rTMS protocols.

- ▶ rTMS protocols are capable of affecting targeted brain regions beyond the period of stimulation. Depending on stimulation parameters, effects on excitability can be (on average) inhibitory (1 Hz rTMS, cTBS) or excitatory (10 Hz rTMS, iTBS).

The second family of NIBS applications involves transcranial electrical stimulation (TES).

Definition

TES: Transcranial electrical stimulation. Also referred to as low-intensity transcranial current stimulation, among other labels. Low-intensity current is administered to a brain region, not sufficiently strong to cause pain or to induce action potentials, yet sufficiently strong to modulate membrane potentials to change excitability. It can also have after-effects on excitability.

TES requires a, usually portable, stimulation device that primarily includes a battery and contact points for two connected electrodes. The latter come in different shapes and sizes, which directly affect the spatial configuration and intensity of stimulation in the brain (Woods et al. 2016). Low-intensity electric current flows between both electrodes, from the “anodal” electrode to the “cathodal” electrode (Paulus 2011). If continuous, these are referred to as anodal or cathodal transcranial direct current stimulation (tDCS) (Nitsche et al. 2008). Electric current can also be directed back and forth between both electrodes, which rhythmically switch polarity at a user-defined frequency, in transcranial alternating current stimulation (tACS) (Paulus 2011). A different setting on these machines causes current to switch direction much more often and at differing frequencies, which is called “transcranial random noise stimulation” (tRNS) (Terney et al. 2008). No matter which of these protocols are applied, in contrast to TMS (and also to electroconvulsive therapy (ECT), for example), TES primarily does not actually excite neurons to the point

of action potentials. Instead, it achieves neuromodulation by changing the resting membrane potentials of affected neurons (Jackson et al. 2016; Radman et al. 2009). For instance, anodal tDCS depolarizes neurons slightly, bringing them “closer to threshold,” which means fewer excitatory inputs will be required to induce action potentials (Liebetanz et al. 2002). Cathodal tDCS instead hyperpolarizes, achieving the opposite effect on excitability. tRNS may increase excitability, but by less straightforward mechanisms (Antal and Herrmann 2016). tACS sinusoidally changes membrane potentials, mimicking naturally occurring neuronal oscillations (Krause et al. 2019). Interestingly, all of these modulations of cortical excitability seem to last beyond the period of stimulation, just as in rTMS (Bindman et al. 1964).

➤ **TES primarily does not actually excite neurons to the point of action potentials. Instead, it achieves neuromodulation by changing the resting membrane potentials of affected neurons.**

There are ongoing developments in both these families of NIBS methodologies. For instance, TES is becoming more sophisticated by the use of more focal electrode montages (e.g., a small center electrode surrounded by a ring electrode or several small surrounding electrodes) (Sehm et al. 2013) and research in computational modeling to better understand the achieved distributions of induced electric fields for different electrode montages (Saturnino et al. 2018; Thielscher et al. 2015). In TMS, research to better understand the precise biological mechanisms affected by different protocols; how to tailor rTMS protocols to individual physiology; and how best to design coils and waveforms to achieve reliable or deeper (subcortical) modulation is underway (Deng et al. 2013; Romero et al. 2019; Cirillo et al. 2017; Cuyppers et al. 2014; Banerjee et al. 2017; Medaglia et al. 2019). Fundamentally different tools that do not involve TMS or TES are arising as well. Still under investigation is “static magnetic stimulation” which involves a strong local static magnet (Oliviero et al. 2011), and recently

“focused ultrasound” stimulation (Legon et al. 2014) has been receiving attention as a new alternative to TMS/TES with similar potential applications and a new set of pros and cons. Here, ultrasound at particular frequencies is directed toward particular brain regions, possibly mechanically causing neurites to “vibrate” and depolarize through entirely different mechanisms as compared to TMS (Krasovitski et al. 2011). While not yet as mainstream as TMS or TES, this ultrasound approach is an interesting avenue to follow going forward. We will restrict our further discussion to TMS and TES technologies.

7.1.2 The Biological Mechanisms in the CNS Targeted by NIBS

We provided an overview of NIBS approaches, mainly TMS and TES with various specifications, based on how these techniques work: the underlying physics. A very different perspective, and indeed different classification scheme, arises when we focus on their effects in the brain. In other words, we can also classify NIBS technologies according to the biological mechanism affected. We find it useful to delineate three targeted biological mechanisms, or three neuromodulation targets, to capture most NIBS applications.

Non-repetitive TMS is often referred to as “single-pulse TMS” or “event-related TMS,” but this seems a bit restrictive. The point is that NIBS is used to excite neurons briefly. Every such administration of NIBS is momentary and delivers a datapoint. In research, event-related TMS can be used for “chronometric studies” for example, where a particular event (e.g., the presentation of a visual image on screen) is time-locked to TMS pulses (e.g., a single pulse 100 milliseconds after image presentation) to evaluate the causal role of the targeted cortical region (e.g., occipital cortex) for a particular function (e.g., image discrimination: an occipital pulse around 100 ms will impair discrimination or even make the image invisible) (de Graaf et al. 2011). Clinically, single TMS pulses can be applied to motor cortex to elicit motor-evoked potentials (MEPs)

that can be measured with electromyography (EMG) (Rothwell et al. 1999). The amplitude of the MEP, which is simply a quantification of a TMS-induced motor twitch, has clinical implications. As we discuss below, this can be in diagnosis and prognosis, in isolation or coupled with neuroimaging techniques. Also under this category, one might consider paired-pulse TMS, which involves two TMS pulses administered in quick succession (Valls-Sole et al. 1992). When applied to the motor cortex, a subthreshold TMS pulse preceding a suprathreshold TMS pulse by around 2–7 milliseconds will reduce the MEP elicited by the latter pulse (Valls-Sole et al. 1992; Kujirai et al. 1993). This reduction is called short-interval cortical inhibition (SICI) and has clinical implications, as do long-interval cortical inhibition (LICI) and intracortical facilitation (ICF), all of which involve paired TMS pulses applied to motor cortex in different configurations of TMS intensity and inter-pulse intervals (Berardelli et al. 2008; McClintock et al. 2011; Rossini et al. 1994). By using two TMS coils, one over motor cortex and the other over anatomically/functionally connected regions, it is possible to quantify similar modulations of MEP by prior excitation of other motor network nodes (Hampson and Hoffman 2010). Interesting work has taken similar approaches beyond the motor system to understand cortical information flows (Pascual-Leone and Walsh 2001). Ultimately, these are all instances of momentary NIBS excitation of neurons to achieve different goals.

Plasticity targeted NIBS refers to the collection of NIBS tools and protocols that likely engage either LTD or LTP to transiently decrease or increase cortical excitability, respectively. To decrease cortical excitability, there are cathodal tDCS, classical inhibitory rTMS (1 Hz), and cTBS. To increase excitability, there are anodal tDCS, tRNS, classical excitatory rTMS (10 Hz), and iTBS (Rossini et al. 2015). It is not unequivocally established that all these protocols indeed similarly engage LTD and LTP, or that they rely on the same mechanisms of action in the brain, but that is not what is relevant here. What is relevant is that they all can serve the same

functional purpose. If one wishes to increase excitability beyond the period of stimulation, or decrease it, there are these various – in many ways very different – options. One can weigh the pros and cons according to the use case, or the patient. In research, temporarily changing cortical excitability in a local brain region allows assessment of the causal contribution that region makes to various tasks (e.g., decreasing excitability might induce a task impairment). In clinical applications, treatment with NIBS builds on this foundation, though an additional mechanism of plasticity is somehow involved which remains imperfectly understood. After all, the effects of these NIBS protocols are in the range of minutes to hours, not weeks to years (Cirillo et al. 2017). Yet, the clinical efficacy of repeating such protocols over weeks has indeed been reported to last for such extended periods of time (Dunlop et al. 2017; Sonmez et al. 2019; Blumberger et al. 2018).

Entrainment is the final NIBS application to mention here. The human brain operates in large part by means of naturally occurring oscillations. The power and phase of these oscillations, in different frequency bands, have been related to various sorts of motor, cognitive, and perceptual functions (Ward 2003). In turn, neuromodulation of these oscillations is possible. Especially for research, short bursts of TMS pulses can briefly increase the power of oscillations in a particular frequency band in a particular region to evaluate the causal contribution of these oscillations to a task of interest (Thut et al. 2011). tACS can achieve the same for a longer period of time (Polania et al. 2012; Pogosyan et al. 2009). In fact, alpha power was increased even beyond the period of alpha-frequency tACS (Helfrich et al. 2014). Both methods allow the investigation and modulation of both oscillatory power and phase. Since many psychiatric disorders have been related to oscillatory/connectivity dysfunction, the direct NIBS-targeting of oscillations has the potential to make unique neuromodulatory contributions not only to the lab but also to the clinic (Hong et al. 2010; Michelini et al. 2018; Schnitzler and Gross 2005).

7.1.3 Clinical Applications of NIBS

In our companion Chapter 8, we place NIBS in the context of traditional clinical tools. Here, we would like to delineate the three core clinical applications of NIBS, providing a classification scheme along a third, more applied, dimension. These applications are diagnosis, prognosis, and treatment.

Diagnosis and *prognosis* currently primarily involve non-repetitive TMS, that is, either single-pulse TMS or paired-pulse paradigms as outlined above. In all cases, the principal idea is to assess responses to TMS pulses to obtain information about the current brain state (diagnosis) which may also have predictive value regarding the further development of a disorder/disease (prognosis). To illustrate, single-pulse TMS applied over primary motor cortex can typically elicit muscle twitches (motor-evoked potentials; MEP). However, damage to the corticospinal tract can cause subtle changes of MEP amplitudes and latencies, or even a complete absence of motor responses (Kobayashi and Pascual-Leone 2003). TMS thus allows probing the integrity of the motor system, which is a critical diagnostic step in the acute phase after stroke, a useful tool for monitoring changes during stroke rehabilitation, and even of prognostic value as the presence/absence of MEPs is indicative of the potential for long-term functional recovery (Di Pino et al. 2014).

Similarly, the minimum intensity required to observe a TMS-induced motor response (motor threshold) is an established measure of cortical excitability. While inter-individual variability of cortical excitability currently poses some limits in terms of specificity, there are promising applications of TMS as a diagnostic marker in epilepsy (Kimiskidis et al. 2014), and monitoring excitability changes over time can help in determining which particular antiepileptic drug effectively decreases cortical excitability without relying on the occurrence of seizures as a marker of treatment success (Badawy et al. 2012).

Lastly, the vast majority of studies have focused on diagnostic and prognostic applica-

tions of TMS in the motor system because of the simplicity of MEP recordings. However, the potential of TMS dramatically increases when combined with neuroimaging. In recent years, EEG has become very popular to assess brain responses to TMS pulses outside the motor system. In a pioneering research line, the simultaneous combination of TMS and EEG has been used to reveal how TMS-induced activity spreads throughout the brain in various disorders of consciousness. Strikingly, the complexity of the brain network response was sufficient to allow researchers to accurately classify individual patients as being in unresponsive wakefulness syndrome, a minimally conscious state, or locked-in syndrome (Sarasso et al. 2014). Admittedly, the technical complexities of such multimodal approaches currently constrain their application in clinical practice, but fully integrated systems to record TMS-induced changes in EEG activity are already emerging on the market.

Not only can NIBS be used to help establish a diagnosis, or inform a prognosis, it is perhaps most well-known for its application as actual brain-based *treatment*, in neurorehabilitation but especially also for psychiatric disorders. This application relies on the lasting effects on plasticity described above. In its currently most widespread clinical application, NIBS is applied to either increase cortical excitability in left frontal cortex or decrease cortical excitability in right frontal cortex to treat depression (Santre et al. 1995; O'Reardon et al. 2007; Hoppner et al. 2003). The evidence for efficacy is strongest for high-frequency left frontal rTMS (O'Reardon et al. 2007). As discussed above, anodal tDCS may have similar effects, since it should achieve the same thing: an increase in excitability (Brennan et al. 2017). This particular example at the same time exemplifies that things are never as straightforward as they seem: left frontal rTMS works well for treatment-resistant depression patients, while left frontal anodal tDCS actually receives more evidence for efficacy in non-treatment-resistant patients (Blumberger et al. 2013). This, as well as NIBS treatment efficacy in

a range of other disorders, is under intense investigation. It seems NIBS might be helpful in the treatment of not only mood disorders but also neuropathic pain, motor disorders, anxiety disorders, and a range of other brain-based malfunctions (Chen et al. 2017; Chalah and Ayache 2019). Excellent, and at the same time exhaustive, reviews on the precise level of evidence for both rTMS and tDCS can be found in overview articles by Lefaucheur et al. (Lefaucheur et al. 2017; Lefaucheur et al. 2014) for rTMS and by O'Reardon et al. (2007) for tDCS. In fact, as elaborated in the companion chapter, an updated overview was recently published by an overlapping group of experts (Lefaucheur et al. 2020).

➤ Conclusion

Non-invasive brain stimulation (NIBS) is an umbrella term for a wide and growing range of techniques and applications. There are so many techniques, and in fact we have presented three different classification schemes to create an overview of NIBS. NIBS applications were classified according to their physical principles, the biological mechanisms they targeted, and clinical applications. The value of NIBS in research is established. Its value in clinical applications is becoming increasingly clear and has received sufficient empirical support that implementation is widespread. But such rapid growth and acknowledgment come with a risk. NIBS to “improve” the healthy human brain (neuroenhancement) and as a sort of mental panacea (to cure all brain problems) has captured the public imagination, while at least some clinicians remain more wary. NIBS is a technique with such wide applications, at low cost, with minimal side effects, with minimal risks involved – does it not sound too good to be true? We address this question in the companion Chapter 8.

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