rTMS Treatment for Depression

A Practical Guide

Paul B. Fitzgerald
Z. Jeff Daskalakis

Second Edition

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An Introduction to the Basic Principles of TMS and rTMS

1

Abstract

Transcranial magnetic stimulation (TMS) is a technique for stimulating brain activity that is dependent on several basic physical principles. When a substantial electrical current is induced in a stimulating coil, this is able to produce a transient time variable magnetic field. When a magnetic field of this sort and of sufficient strength is applied to the brain, it can induce an electrical current in the brain producing firing of groups of nerve cells. When TMS is applied repeatedly, it will progressively change brain activity. Low-frequency stimulation is able to reduce activity in underlying brain tissue, but high-frequency stimulation increases the activity. The discovery and practical application of these basic techniques has led to the widespread use of rTMS in neuroscientific and clinical applications.

1.1 Introduction

Transcranial magnetic stimulation (TMS) is a unique experimental and therapeutic tool that allows researchers to noninvasively stimulate and study the cortex in healthy and diseased states [1] (Fig. 1.1). It has been used as an investigational tool to measure a variety of cortical phenomena including cortical inhibition and plasticity [2, 3], as a probe to explore cognitive mechanisms [4], and as a treatment tool in illnesses such as depression and schizophrenia [5, 6]. This chapter will review the physical principles of TMS and repetitive and the neuronal structures activated by the techniques (Box 1.1).

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Box 1.1 A Note on Terminology

TMS refers to the general process of transcranial magnetic stimulation, using a time variable magnetic field to induce the firing of cortical neurons. This will encompass the use single or paired TMS pulses in experimental paradigms as well as other applications of the technology.

rTMS, or repetitive transcranial magnetic stimulation, refers to the application of repeated TMS pulses, usually at a set frequency, with the intention to make a transient or longer lasting change to local and potentially distributed brain activity.

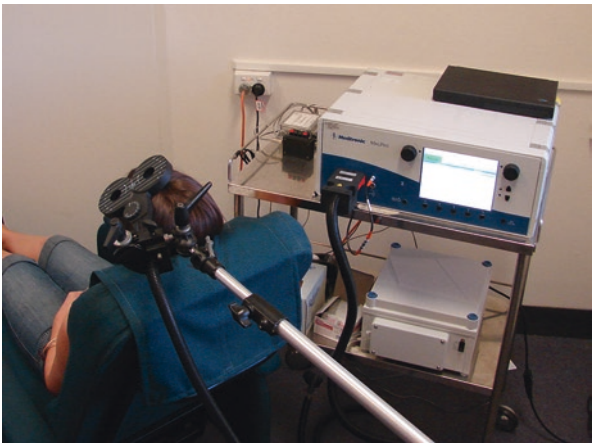

Fig. 1.1 A figure-of-eight MagVenture coil held over the head in a custom-built stand connected to a MagPro R30 device

1.2 Overview of TMS Technology

The use of TMS is dependent on some basic physical principles, first described in the nineteenth century. In 1831 Michael Faraday demonstrated that a current was induced in a secondary circuit when it was brought in close proximity to the primary circuit in which a time-varying current was flowing. Here, a changing electrical field produces a changing magnetic field that, consistent with Faraday's law, causes current to flow in a nearby conducting material. With TMS, electrical charge is stored in capacitors. Periodic discharge of this stored energy from the capacitors and through a conducting coil produces a time-varying electrical field. This electrical field produces a transient magnetic field that will cause current to flow in an appropriately located secondary conducting material, such as neurons in superficial layers of the cortex. If this current induced in the brain is of sufficient strength, it will produce depolarization of the conducting neural tissue located just under the coil.

As described electrical fields that are applied to neurons can excite these cells. The electrical field will produce a current in the intracellular and extracellular space.

This causes cell membranes to become depolarized. An action potential is initiated when this depolarization is of significant magnitude. Electrical fields experienced resistance because of scalp and skull and other intermediary tissue. Magnetic fields, by contrast, experience absolutely no resistance from the abovementioned structures. The magnetic field strength, however, is significantly reduced in relationship to the distance between the stimulating target and the magnetic source.

In regard to the generation of the TMS pulse, the requisite circuit includes a capacitor, a thyristor switch, and a coil. Charge and discharge of the capacitor are coordinated by the thyristor switch which acts as gate for conduction of the electrical field through the coil. The field that is subsequently produced is either monophasic or biphasic. This difference depends on the properties of the circuit that is used.

Commercially available stimulators produce two pulse types: a biphasic pulse or a monophasic pulse. A biphasic pulse is sinusoidal and is generally of shorter duration than a monophasic pulse, which involves a rapid rise from zero, followed by a slow decay back to zero. Monophasic pulses were typically used in the initial investigative applications of TMS, whereas biphasic pulses have been used in the vast majority of applications of rTMS as biphasic pulses can be produced more efficiently when applied repetitively at short intervals.

In commercially available stimulators, multiple types of coils are typically used. These include circular and figure-of-eight shaped coil. In general, figure-of-eight shaped coils produce a stronger and more focused magnetic field with better spatial resolution of activation compared to circular coils [7]. In contrast, circular coils tend to produce larger and deeper fields. This may be preferred when the neuroanatomic target is not precise. Iron-core coils, as used in the Neuronetics rTMS system (see Chap. 17), are advantageous in that they tend to require less power to produce strong magnetic fields and, as a corollary, generate less heat [8]. By contrast, more traditional round or figure-of-eight copper coils generate significant heat that increases as more pulses are delivered. Two methods are used to dissipate this heat. Air can be used to effectively dissipate heat and some commercially available stimulators are indeed air-cooled. One drawback to air cooling is the loud noise of the air compressor or additional weight of a fan if this is placed directly on the coil itself.

Liquid cooling can also be used. In this method the liquid helps dissipate the heat by surrounding the coil allowing for rapid heat exchange from the copper wiring to the liquid which is contiguous but not in direct contact with the coil. H-coils are a newer class of coils with multiple coil windings developed to generate greater depth of penetration (see Chap. 17). For example, while conventional figure-of-eight coils lose 50% of their magnetic field strength when the target is more than 2 cm from the stimulator, the H-coil is able to generate sufficient field strength at 6 cm [9]. This may be advantageous given the role of deeper cortical structure (e.g., the dorsal anterior cingulate and subgenual cingulate) in the pathophysiology of depression.

By and large, in small figure-of-eight shaped coil types most commonly used in rTMS treatment of depression, neurons are activated in a cortical area of approximately 2–3 cm^2 and to a depth of approximately 2 cm [10]. In most studies, figure-of-eight coils are held over the cortex flat and at about 45° from the midline position, perpendicular to the central sulcus. This induces a current from posterior to anterior

direction, perpendicular to descending pyramidal neurons and parallel to interneurons, which modulate pyramidal cell firing [11]. It is the orientation between the coil and underlying neural tissue that allows researchers to selectively activate different groups of neurons providing useful information regarding neuronal inhibition, excitation, and connectivity.

1.3 Overview of Repetitive TMS (rTMS) Technology

Repetitive transcranial magnetic stimulation (rTMS) involves stimulation of the cortex by a train of magnetic pulses at frequencies between 1 and 50 Hz in contrast to single pulse TMS in which the frequency of stimulation is <1 Hz [12]. Higher frequencies can be achieved because the bipolar stimulus, as opposed to a unipolar stimulus, is shorter and requires less energy to produce neuronal excitability. Thus, capacitors can charge and discharge rapidly, thereby achieving high stimulation rates. It is the ability to achieve such high stimulation rates that has made rTMS a valuable tool in investigation and treatment of many neuropsychiatric disorders.

Repetitive TMS can either activate or inhibit cortical activity depending on stimulation frequency [13]. Low-frequency (~1 Hz) stimulation for a period of approximately 15 min induces a transient inhibition, or a decrease in activity, of the cortex [14]. The mechanisms behind such inhibition are unclear although there are similarities to long-term depression, a cellular experimental phenomena where repeated low-frequency stimulation reduces activity in individual synapses [14]. In contrast, stimulation at frequencies above 1 Hz has been shown to induce increased cortical activation [15]. The mechanisms by which such activation occurs are also unclear although some authors suggest that it may be due to a transient increase in the efficacy of excitatory synapses [16]. It has also been argued that the orientation between the coil and underlying neural tissue that allows researchers to selectively activate different groups of neurons may be key to understanding the principles mediating its therapeutic efficacy. That is, by virtue of the fact that TMS activates neurons transsynaptically [17] (i.e., activation of interneurons), neuronal stimulation can selectively activate or inhibit the cortex.

Stimulating at high frequencies has been shown to produce transient "functional" lesions in cortical areas receiving stimulation [4, 18]. Therefore, rTMS may be used as a neurophysiological probe to test the functional integrity of different cortical regions by either activating these regions or inhibiting them. It has been postulated that stimulation at high frequencies can also facilitate plasticity: the way in which the brain adapts to stimulation or environmental change. Potentiation of plasticity may also represent a mechanism through which rTMS exerts its therapeutic effects in depression. Plasticity in the cortex involves an adaptive rewiring of neurons in response to environmental change. Synaptic plasticity has long been conceptualized as a cellular substrate of learning and memory. As theorized by Hebb in 1949 [19], synaptic plasticity is represented by changes in synaptic strength in response to coincident activation of coactive cells, which manifest as long-term potentiation (LTP) or long-term depression (LTD). LTP depends, in part, on activation of a double-gated NMDA receptor that serves as a "molecular" coincidence detector.

These calcium-permeable glutamatergic receptors are able to provide a long-term augmentation of postsynaptic signal once activated by an input sufficient to depolarize postsynaptic membrane and relieve tonic Mg^{2+} inhibition [20, 21]. rTMS can cause neurons in the cortex to generate repeated and consistent firing of coactive cells, thereby producing plasticity in the cortex. Modifying plasticity has been regarded as a downstream mechanism through which serotonin reuptake inhibitors result in depression treatment [22]. rTMS therefore may exert its antidepressant effects by potentiating plasticity in the cortex.

1.4 Sham Stimulation

Double-blind placebo or sham-controlled rTMS trials are the best methods through which the clinical effects of rTMS can be optimally derived. Sham stimulation can involve lifting the coil off the person's head, thereby generating sound but no tactile sensation. It may be hard to ensure the adequacy of blinding with this form of sham control which is now rarely used. Another method through which sham rTMS can be applied is by tilting the coil at either 45° or 90° or stimulating with material between the coil and surface of the head. These methods may produce noise and some scalp sensation without generating sufficient field strength to activate the cortex. A criticism that has been levied with this approach is that the scalp sensation is very weak and, therefore, also easy to differentiate from active TMS despite the fact that subjects who participate in these trials are, for the most part, rTMS naïve. George et al. [23] reported on a novel and very effective method to which to generate sham stimulation. In this method, "active" sham stimulation is produced through an electrical field being generated by a peripheral nerve stimulator to produce scalp sensation at the stimulation site. Through these methods, the ability to predict active versus sham stimulation was reduced to chance [23].

1.5 Noise

A loud clicking noise is heard when the stimulator is discharged. This clicking noise is generated by internal stress that is caused by the rapid alternating electrical field that is produced in the capacitor, cables, and the stimulating coil. The clicking sound that is generated is between 120 and 300 dB. As such, it is always advised that both operators and subjects wear hearing projection throughout the treatment.

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The History of TMS and rTMS Treatment of Depression

2

Abstract

The use of electrical and magnetic devices to alter brain activity has been periodically suggested for many years. The actual concept of transcranial magnetic stimulation (TMS) was proposed in the late 1900s, but technology did not exist at that time to produce sufficiently strong magnetic fields to stimulate brain activity. This technology, first developed in the 1980s, is now widely used in TMS and *repetitive* transcranial magnetic stimulation (rTMS) applications including in the treatment of depression. rTMS refers to the use of repeated TMS pulses, at a specific frequency, usually with an intent to change brain activity, rather than just to produce a response to a single pulse. Initial studies investigating the capacity of rTMS to modify mood were conducted in the early to mid-1990s. Modern applications of rTMS were first enacted in studies when high-frequency rTMS was applied to the left DLPFC with these studies published in 1995 and 1996. Since that time, the field has progressed substantially with a large body of research establishing the use of rTMS and many studies exploring alternative methods of application.

2.1 Introduction

The application of electricity and magnetic fields in medicine has a long but not always distinguished history. Reports of the use of electrical techniques in medicine date back at least to the Roman Empire where in 46 AD Scribonius Largus, physician of the emperor Tiberius, described the use of torpedoes (aquatic animals capable of electrical discharge) for medical applications [1, 2].

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The live black torpedo when applied to the painful area relieves and permanently cures some chronic and intolerable protracted headaches … carries off pain of arthritis … and eases other chronic pains of the body.

For any type of gout a live black torpedo should, when the pain begins, be placed under the feet. The patient must stand on a moist shore washed by the sea and he should stay like this until his whole foot and leg up to the knee is numb. This takes away present pain and prevents pain from coming on if it has not already arisen. In this way Anteros, a freedman of Tiberius, was cured. (Compositiones Medicae, 46 AD)

The notion that electricity could be used for therapeutic purposes was carried through the Middle Ages and during the Renaissance gained particular attraction. In the 1600s in England, William Gilbert, physician to Queen Elizabeth, published *De Magnete*, in which he described the use of electricity in medicine. Gilbert described that when certain materials are rubbed, they will attract light objects. He coined the name "electricity" from the Greek "electron" for amber [3].

During the 1700s the use of electricity for the treatment of paralysis was suggested by Krueger, a Professor of Medicine in Germany, and Kratzenstein published a book on electrotherapy. Kratzenstein described a method of treatment which consists of seating the patient on a wooden stool, electrifying him by means of a large revolving frictional glass globe, and then drawing sparks from him through the affected body parts.

The development of the field diverged in several significant directions in the coming centuries, in parallel with the expansion of knowledge in the physical sciences. These will be briefly described in turn.

First, heralding the development of the science of electrophysiology, in 1780 in Italy, Luigi Galvani, Professor of Anatomy at the University of Bologna, first observed the twitching of muscles under the influence of electricity (prepared from the leg of a frog) [4]. Alessandro Volta subsequently demonstrated that the "galvanic" effect did not require contact with the animal (and also contributed to the development of the battery) [4]. Another Italian, Carlo Matteucci, was able to show that injured tissue generates electric current [4].

During the same time the notion of magnetism, in particular that of "animal magnetism," became widely known due to the work of Anton Mesmer. The concept was first described by Paracelsus (1530) but considerably popularized by Mesmer through his various works including the *Propositions Concerning Animal Magnetism* in 1779 and his doctoral thesis 'De influxu planetarum in corpus humanum' produced in 1766 [4]. Mesmer's concept, however, is related to magnetic properties only by analogy as he described the response of the human body to heavenly bodies and the bodies' reciprocal interaction with the environment as analogous with the properties of a physical magnet. Mesmer initially constructed physical apparatus (the *baquet*) that was used to effect the animal magnetism of a subject but latter disposed of the use of metallic objects altogether. Mesmer's ideas became very popular in certain European countries (especially Germany, Russia, and Denmark) but were progressively discredited, and Mesmer eventually closed his Paris clinic. Although Mesmer's ideas were widely disproved, especially through a series of scientific commissions in Paris, the notion that imagination (rather than magnetism) could have physical effects took hold and substantially contributed to the development of the field of hypnosis [4].

In a different direction, the notion of "magnet therapy" became widely popular through several centuries. This was based upon the presumption that electrical or magnetic stimulation could be a "nutrient" to the body that was thought of as electric. Examples of this movement include the establishment of an "electrical therapy" department which was established in the mid-1880s at Guy's Hospital in London under Dr. Golding Bird. Various "therapeutic" devices, including "electrical belts," were widely popular through the early part of the twentieth century.

2.2 Early Attempts to Develop TMS-Like Approaches

The modern concept of TMS could not be envisioned prior to the early 1800s due to lack of knowledge until that time of the properties of magnetic fields and their relationship to electrical currents. It was Michael Faraday who first outlined the principle of mutual induction in 1831 (e.g., as later described in his *Lectures on the Forces of Matter*, given at The Royal Institution of Great Britain, December 1859) [5]. This principle states that a current can be induced in a secondary circuit when its relationship to a primary circuit is altered in several specific ways, including that the primary current is turned on or off or the primary current is moved relative to the secondary current. Faraday described that this effect was mediated through the magnetic flux created by the changing circuit and that alterations in the magnetic flux would induce an electrical field [5]. The line integral of this electric field is referred to as the electromotive force and this force is responsible for the induced current flow. The magnitude of this effect can be quantified and mathematically described. Importantly, the magnitude of the force is proportional to the rate of change in the magnetic flux.

Nikola Tesla in the USA in the latter part of the nineteenth century was experimenting with the physiological effects of high-frequency currents [5]. He constructed a variety of flat-, cone-, and helix-shaped coils that were used to produce physiological effects. Tesla coils or Oudin resonators consisted of primary and secondary large coils used to produce an ionization of the air between the coils. A patient would sit between the coils and experience a sensation described by Tesla as like the "bombardment of miniature hail stones." These coils formed the basis for the latter development of diathermy that was propagated by Tesla and the Frenchman d'Arsonval. Tesla also contributed significantly to the development of X-ray [5].

D'Arsonval was also the first person to develop ideas that could be considered equivalent to modern TMS technology. He reported the effects of cranial stimulation with a large magnetic coil producing a 110 V current at 42 Hz. The coils utilized by d'Arsonval were similar to those developed by Tesla but without the secondary coil [4]. He described numerous physiological responses to his coil including the development of dilation of blood vessels, vertigo, syncope, and phosphenes. Phosphenes, or visual flashes of light, are produced with modern TMS stimulation of the occipital visual cortex, and it is possible that this was the source of the experiences produced in the experiments of D'Arsonval, although from knowledge of the capacity of technology of the day it seems more likely that they were the result of direct retinal stimulation.

As these reports were published in French, they were not widely read in the English- and German-speaking scientific communities. Independent reports of a similar nature were made by Beer in 1902 [6], and a device designed for use in the treatment of depression and other neuroses was actually patented by Pollacsek and Beer in Vienna. Widespread use of this device did not follow and one can reasonably assume that the induced fields would have been insufficient to have likely therapeutic effects. The report of Beer inspired several other investigators. Thompson produced a large 32 turn coil in which a subject's head was to be placed which produced some sight and taste sensations [7]. Dunlap reported a controlled experiment designed to test the veracity of the reports of the sensations produced with these devices "controlling" for the noise produced [8]. Visual sensations were associated with the alternating current but he was unable to confirm other sensations. Magnusson and Stevens produced two elliptical coils, which were used to produce visual sensations including flickering and a luminous horizontal bar [9].

For several decades after, little research was published in this area. In 1947 Barlow described the use of a small coil to produce visual sensations through stimulation at the temple but not the occiput. The conclusion was drawn that the site of this stimulation was retinal [10].

The field of magnetic stimulation of brain tissue did not significantly advance for the greater part of the twentieth century. Through this time, variations on electrical therapies continued to remain popular. For example, Lakhovsky working in Paris in the 1920s developed his "multiple wave oscillator," a device designed to produce a broad-spectrum electromagnetic field between two large circular electrodes [11]. The patient would sit between two of these coils and have disturbances of cellular function corrected. The therapeutic properties of devices generating fields of this type have not been established although this marginal field of medicine still has its proponents to this day. In recent years there has been a resurgence of interest in the role of pulsed weak electromagnetic fields in the treatment of disease states including multiple sclerosis, although controlled trials are lacking [12].

The direct electrical stimulation of the unexposed cortex was first attempted in the 1950s [13] but this proved too painful for its routine use. The field was further developed in the early 1980s with attempts to alter the electrical stimulation to enhance the effect and lessen discomfort, but additional problems with painful jaw contraction were encountered [14, 15]. Electrical stimulation has gained some use in experimental electrophysiology but has been largely, but not completely [16], replaced by magnetic stimulation.

2.3 The Development of Modern TMS

Modern TMS has a relatively brief history. Barker first started investigating the use of short pulsed magnetic fields to stimulate human peripheral nerves in the 1970s [17]. The first device capable of generating cortical activity was developed by Barker and others in Sheffield, England, and first described in 1985 [18]. Stimulators first attracted the attention of neurologists and neurophysiologists due to their capacity to be applied in the testing of nerve activity from the cortex to the

periphery. The first therapeutic reports of the use of TMS were in the treatment of mood disorders, which emerged around the same time as reports of the capacity of TMS to alter the mood of healthy control subjects. The initial studies in healthy controls suggested that rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) could induce a mild increase in self-reported sadness. rTMS applied to the right DLPFC could improve self-rated positive mood [19, 20]. Mood effects across these and other studies were relatively inconsistent and produced with differing TMS parameters. Later studies did not necessarily confirm that mood changes could be produce reliably in healthy control subjects. However, initial studies in depressed patients were also being undertaken around the same time. The very first studies utilized stimulation over the vertex and in general reported inconclusive results, especially as they were usually open-label studies in small samples [21–23]. In 1994 it was proposed that the prefrontal cortex (PFC) might be a more effective target for TMS [24]. This idea was based upon the evidence of a link between the response to electroconvulsive therapy (ECT) and changes in PFC function [25] as well as imaging studies reporting abnormalities in the PFC in depressed patients [26].

The first published studies using focal stimulation of the prefrontal context followed and appeared in 1995 and 1996. In the first of these studies, George et al. reported the treatment of six medication nonresponsive patients with 20 Hz TMS applied to the left PFC [27]. This was followed with a double-blind study of 2 weeks of treatment applied with a sham control in a crossover design [28]. Around the same time Pascual-Leone et al. reported a sham-controlled crossover study with 5 days of 10 Hz treatment [29]. The results of these two studies were sufficient to arouse the interest of researchers around the world in the use of high-frequency rTMS applied to the left DLPFC. Studies since that time have substantially extended the dose of stimulation applied, both in regard to the number of treatment sessions and to the number of pulses applied per session. However, many of the basic aspects of treatment used in these initial studies, for example, the methodology for coil placement, have not really advanced substantially since the mid-1990s. Some researchers have developed new, alternate ways to utilize rTMS. For example, Klein et al. in the late 1990s developed the approach of using low-frequency rTMS applied to the right DLPFC [30], an approach which has subsequently proven to be of similar efficacy to standard high-frequency left-sided rTMS.

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