An Introduction to the Basic Principles of TMS and rTMS

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1.1 Introduction

Transcranial magnetic stimulation (TMS) is a unique experimental tool that allows researchers to non-invasively stimulate and study the cortex in healthy and diseased states [1] (Fig. 1.1). It has been used both 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 transcranial magnetic stimulation (rTMS) and the neuronal structures activated by the techniques.

1.2 Overview of TMS Technology

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. If this current induced in the brain is of sufficient strength, it will produce depolarisation 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 depolarised. An action potential is initiated when this depolarisation is of significant magnitude. Electrical fields experience resistance because of scalp and skull and other intermediary tissue. Magnetic fields,

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_1,

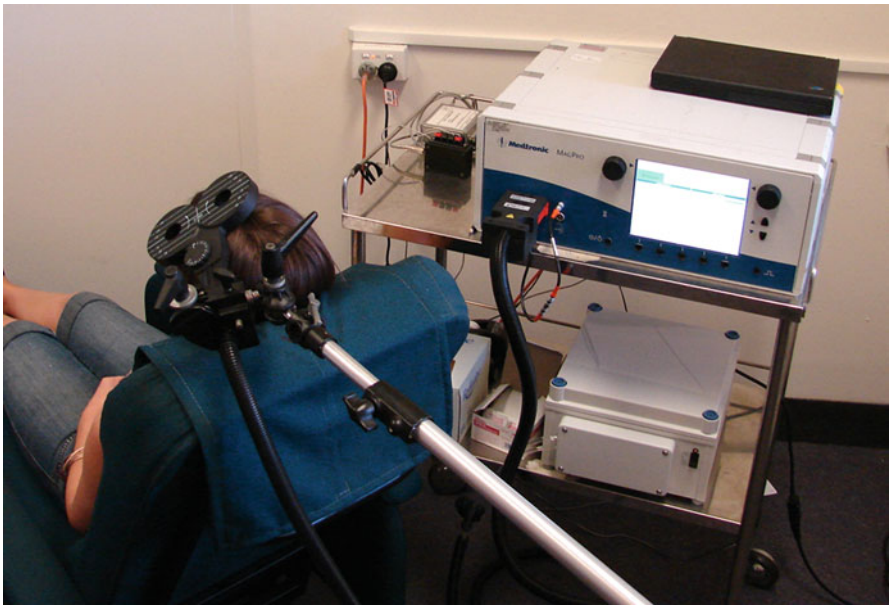

Fig. 1.1 A figure-of-8 Magstim coil held over the head in a custom-built stand. Electromyography (EMG) electrodes are placed to record muscle activity induced by stimulation of the motor cortex

by contrast, experience absolutely no resistance from the above-mentioned structures. The magnetic field strength, however, is significantly reduced in relationship to the distance between the stimulation target and the magnetic source. The circuit involved in TMS includes a capacitor, a thyristor switch and a coil. Charge and discharge of the capacitor are coordinated by the thyristor switch which acts as a 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. In commercially available stimulators, several types of coils are typically used. These include circular and figure-of-eight-shaped coils. In general, figure-of-eight-shaped coils produce a stronger 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 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 many commercially available stimulators are indeed air-cooled.

One drawback to air cooling is the loud noise of the air compressor. 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. The H-coil is a much newer type of coil with multiple coil windings developed to generate greater depth of penetration. For example, whilst 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 structures (e.g. the dorsal anterior cingulate and subgenual cingulate) in the pathophysiology of depression.

By and large, in small figure-of-eight-shaped coils, 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 45º 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 is 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 conceptualised as a cellular substrate of learning and memory. As theorised 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 depolarise 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 by 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 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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