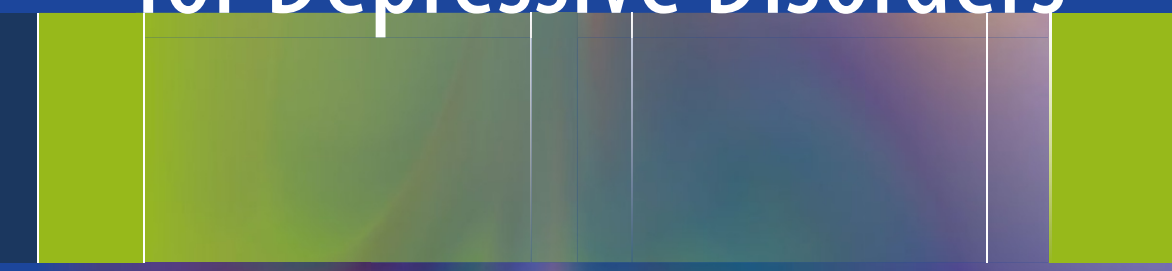
Paul B. Fitzgerald
Z. Jeff Daskalakis

Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders



A Practical Guide

Springer

Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders

Paul B. Fitzgerald • Z. Jeff Daskalakis

Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders

A Practical Guide

Springer

Paul B. Fitzgerald
Professor of Psychiatry
Monash Alfred Psychiatry Research Centre
Monash University Central Clinical School
and The Alfred
Melbourne
Victoria
Australia

Z. Jeff Daskalakis
Centre for Addiction
and Mental Health (CAMH)
University of Toronto
Toronto
Ontario
Canada

ISBN 978-3-642-36466-2 ISBN 978-3-642-36467-9 (eBook)
DOI 10.1007/978-3-642-36467-9
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013936440

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Depression is widely recognised as a common and significant problem that has a major impact on patients, their families, the health-care system and society in general. It is also widely recognised that the treatments available to date for depression have been insufficient to meet the needs of a considerable percentage of patients with this problem.

In this context, repetitive transcranial magnetic stimulation (rTMS) has been developed as a further treatment option. Considerable research efforts, undertaken by academic psychiatrists around the world for over 15 years, have clearly established the therapeutic efficacy of this treatment. Although considerable questions still need to be addressed in regard to the mechanism of action of rTMS and how best it should be applied, it clearly is able to substantially relieve depression for many patients who undergo this therapy.

In recent years, rTMS has progressively been approved for use in the treatment of depression in a substantial number of countries, and its use in clinical practice is now dramatically escalating. Clinicians throughout Europe, the USA, Canada and a number of other countries are increasingly utilising rTMS treatment in clinical practice across a variety of settings. However, only limited resources are currently available to support the widespread clinical utilisation of rTMS. There is a large and substantive academic literature exploring the use of this treatment, but this is not necessarily accessible in a timely manner to busy clinicians wishing to offer rTMS, or who, when using this treatment, are faced with new clinical problems.

This book is designed to address this gap. We aim to provide an accessible guide for clinicians in the use of rTMS treatment in clinical practice. The book aims to both summarise the scientific literature supporting the questions addressed, but also to provide succinct, accessible and clinically relevant information. The initial chapters provide background to aid the reader in understanding the science underpinning the use of rTMS treatment. We then consider in some depth specific aspects to do with the application of rTMS treatment of depression, including the safety of treatment and its potential side effects. We then describe both the evidence base for its use in the treatment of depression and the clinical considerations relevant to the selection of treatment parameters and identification of appropriate patients. In the final chapters, we address practical issues in treatment provision in the application of rTMS in other disorders.

This book is primarily written for clinicians who are considering providing rTMS treatment in clinical practice, or who are already doing so. However, we hope it will also provide a useful primer for researchers considering undertaking academic study in this area. As is illustrated in the pages of this book, considerable questions still need to be addressed as regards the optimisation of rTMS treatment in clinical practice. We are hopeful that academic exploration of this therapy will continue to address this important area.

We would like to thank Sally Herring for her invaluable assistance with editing and putting together this book. Paul Fitzgerald would like to acknowledge the support of an NHMRC Practitioner Fellowship and Jeff Daskalakis would like to thank CIHR for their Clinician Scientist Award. We would both very much like to thank our families for their support and encouragement: Elle, Jake, Sian, Stella, Taso and Elly!

Melbourne, VIC, Australia Paul B. Fitzgerald
Toronto, ON, Canada Z. Jeff Daskalakis

Contents

An Introduction to the Basic Principles of TMS and rTMS

1

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,

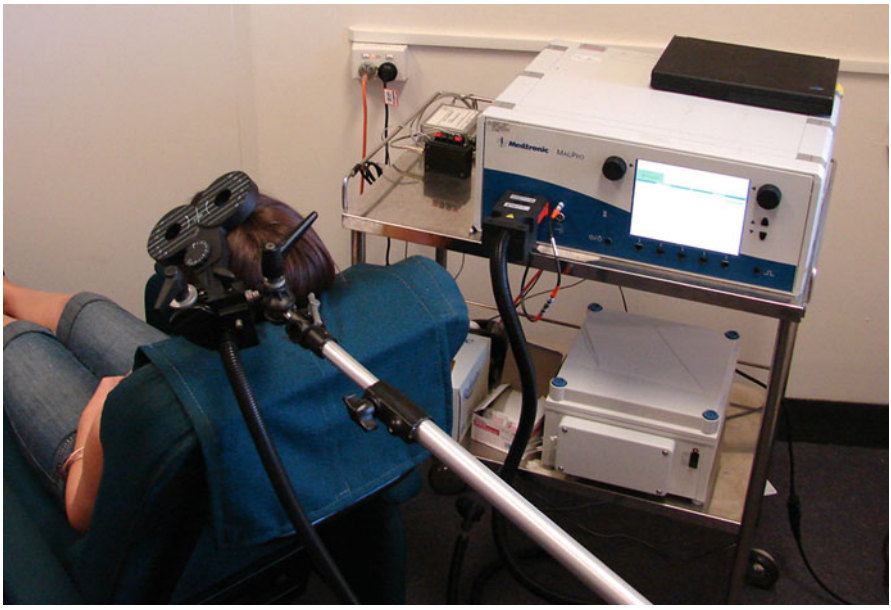


Fig. 1.1 A figure-of-8 Magstim coil held over the head in a custom-built stand. Electromyography (EMG) electrodes are placed to record muscle activity induced by stimulation of the motor cortex

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.

References

1. Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1(8437):1106–1107, Epub 1985 May 11
2. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A et al (1993) Corticocortical inhibition in human motor cortex. J Physiol (Lond) 471:501–519
3. Classen J, Liepert J, Wise SP, Hallett M, Cohen LG (1998) Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 79(2):1117–1123
4. Flitman SS, Grafman J, Wassermann EM, Cooper V, O'Grady J, Pascual-Leone A et al (1998) Linguistic processing during repetitive transcranial magnetic stimulation. Neurology 50(1): 175–181
5. Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996) Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348(9022): 233–237
6. Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney DS (2000) Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 355(9209):1073–1075
7. Ueno S, Tashiro T, Harada K (1988) Localized stimulation of neural tissue in the brain by means of a paired configuration of time-varying magnetic fields. J Appl Phys 64:5862–5864
8. Epstein CM, Davey KR (2002) Iron-core coils for transcranial magnetic stimulation. J Clin Neurophysiol 19(4):376–381, Epub 2002 Nov 19
9. Roth Y, Amir A, Levkovitz Y, Zangen A (2007) Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. J Clin Neurophysiol 24(1):31–38, Epub 2007 Feb 06
10. Barker AT (1999) The history and basic principles of magnetic nerve stimulation. Electroencephalogr Clin Neurophysiol Suppl 51:3–21
11. Amassian VE, Deletis V (1999) Relationships between animal and human corticospinal responses. Electroencephalogr Clin Neurophysiol Suppl 51(3):79–92
12. Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108(1):1–16
13. Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117(12):2584–2596
14. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M et al (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48(5):1398–1403
15. Siebner HR, Peller M, Willoch F, Minoshima S, Boecker H, Auer C et al (2000) Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. Neurology 54(4):956–963
16. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117(Pt 4):847–858
17. Rothwell JC (1997) Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods 74(2):113–122

18. Pascual-Leone A, Gates JR, Dhuna A (1991) Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 41(5):697–702
19. Hebb DO (1949) The organization of behavior. A neuropsychological theory. Wiley, New York
20. Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361(6407):31–39
21. Rison RA, Stanton PK (1995) Long-term potentiation and N-methyl-D-aspartate receptors: foundations of memory and neurologic disease? Neurosci Biobehav Rev 19(4):533–552
22. Branchi I (2011) The double edged sword of neural plasticity: increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. Psychoneuroendocrinology 36(3):339–351, Epub 2010 Sept 30
23. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516, Epub 2010 May 05

The History of TMS and rTMS Treatment of Depression

2

2.1 Introduction

The application of electricity and magnetic fields in medicine has a long and 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 torpedos (aquatic animals capable of electrical discharge) for medical applications [1, 2].

> 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.

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_2,

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 popularised 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, 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 ionisation 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 utilised 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 be likely to have 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 to be 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 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 produced reliably in healthy control subjects. However, initial studies in depressed patients were also being undertaken around the same time. The very first studies utilised 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 utilise 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 left-sided high-frequency rTMS.

References

1. Alexander FG, Selesnick S (1956) History of psychiatry. Allen and Unwin, London, 282p
2. Kirsch DL (2002) Electromedicine: the other side of physiology. In: Pain management: a practical guide for clinicians (the textbook of the American Academy of Pain Management). CRC Press, Boca Raton, Florida, p 749–758
3. Gilbert W (1600) De Magnete ("On the magnet"). Chiswick Press, London
4. Becker RO, Marino AA (1982) The origins of electrobiology. In: Becker RO, Marino AA (eds) Electromagnetism & life. State University of New York Press, Albany
5. Cheney M (1983) Tesla – man out of time. Twenty First Century Books, Breckenridge
6. Beer B (1902) Ueber das Auftraten einer objective Lichtempfindung in magnetischen Felde. Klin Wochenschr 15:108–109
7. Thompson SP (1910) A physiological effect of an alternating magnetic field. Proc R Soc London (Biol) B82:396–399
8. Dunlap K (1911) Visual sensations from the alternating magnetic field. Science 33:68–71
9. Magnusson CE, Stevens HC (1911) Visual sensations caused by the changes in the strength of a magnetic field. Am J Physiol 29:124–136
10. Barlow HB, Kohn HL, Walsh EG (1947) Visual sensations aroused by magnetic fields. Am J Physiol 148:372–375
11. Lakhovsky G, inventor (1934) Apparatus with circuits oscillating under multiple wave lengths. United States Patent Office patent 1,962,565. 12 June 1931
12. Sandyk R (1996) Electromagnetic fields for treatment of multiple sclerosis. Int J Neurosci 87(1–2):1–4
13. Gualiterotti T, Patterson AS (1954) Electrical stimulation of the unexposed cerebral cortex. J Physiol (Lond) 125:278–291
14. Merton PA, Hill DK, Morton HB, Marsden CD (1982) Scope of a technique for electrical stimulation of human brain, spinal cord, and muscle. Lancet 2(8298):597–600
15. Merton PA, Morton HB (1980) Stimulation of the cerebral cortex in the intact human subject. Nature 285(5762):227
16. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ et al (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91(2):79–92, Epub 1994 Aug 1

17. Barker AT (1999) The history and basic principles of magnetic nerve stimulation. Electroencephalogr Clin Neurophysiol Suppl 51:3–21, Epub 1999 Dec 11
18. Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1(8437):1106–1107, Epub 1985 May 11
19. George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P et al (1996) Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 8(2):172–180
20. Pascual-Leone A, Catala MD, Pascual-Leone A (1996) Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. Neurology 46(2):499–502
21. Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller H-J (1993) Application of transcranial magnetic stimulation in drug-resistant major depression – a report of two cases. Hum Psychopharmacol 8:361–365
22. Kolbinger HM, Holflich G, Hufnagel A, Moller H-J, Kasper S (1995) Transcranial magnetic stimulation (TMS) in the treatment of major depression – a pilot study. Hum Psychopharmacol 10:305–310
23. Grisaru N, Yaroslavsky U, Abarbanel JM, Lamberg T, Belmaker RH (1994) Transcranial magnetic stimulation in depression and schizophrenia. Eur Neuropsychopharmacol 4:287–288
24. George MS, Wassermann EM (1994) Rapid-rate transcranial magnetic stimulation (rTMS) and ECT. Convuls Ther 10:251–253
25. Nobler MS, Sackheim H (1998) Mechanisms of action of electroconvulsive therapy. Psychiatric Annals 10:23–29
26. George MS, Ketter TA, Post RM (1994) Prefrontal cortex dysfunction in clinical depression. Depression 2:59–72
27. George MS, Wassermann EM, Williams WA et al (1995) Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6:1853–1856
28. George MS, Wasserman EM, Kimbrell TA et al (1997) Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 154:1752–1756
29. Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996) Rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348:233–237
30. Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999) Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. Biol Psychiatry 46(10):1451–1454

The Mechanism of Action of rTMS

3

3.1 Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of stimulating nerve cells in cortical regions of the brain [1] which can also produce significant therapeutic effects in a number of neurological and psychiatric disorders. However, the mechanisms through which such treatment effects occur is uncertain. Generally speaking, it has been proposed that the effects of high-frequency rTMS in depression occur through an increase of activity in the left DLPFC, which is proposed to be underactive in patients with depression. Low-frequency right-sided rTMS is proposed to reduce right-sided DLPFC activity which is proposed to be overactive in patients with depression. However, rTMS has a complex series of effects on the brain, and research has not necessarily consistently demonstrated these relationships.

In this chapter, we will review the brain mechanisms postulated to be altered by TMS and how they may relate to the treatment of depression.

3.2 Effects of rTMS Assessed in the Motor Cortex

The majority of research into the effects of rTMS has occurred in the motor cortex, where there are easily available means to study alterations in cortical activity. In particular, single and paired pulses of TMS applied to the motor cortex can be utilised to index aspects of cortical excitability and inhibition, providing a ready mechanism to study the effects of repetitive rTMS stimulation. In this regard, rTMS has been shown to result in changes in several physiological parameters in the motor cortex, including in excitability, evidenced in motor threshold (MT) and motor-evoked potential (MEP) alterations; in cortical inhibition and facilitation, evidenced in silent period (SP) and paired pulse inhibition and facilitation (ppTMS) changes; and in alterations in cortical plasticity. These changes appear to be rTMS frequency and intensity dependent.

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_3,

3.2.1 Effects on Motor Cortical Excitability

Low-frequency rTMS (1 Hz or less) has been shown to decrease corticospinal excitability (see review in [2]). For example, Chen et al. [3] demonstrated that a 15-min train of suprathreshold 0.9 Hz rTMS applied to the motor cortex reduced MEP size. This reduction lasted at least 15 min after the end of the stimulation train. Siebner et al. [4] found a similar reduction in MEP size in healthy controls, but not in patients with writer's cramp when 1 Hz rTMS was applied over the left primary motor hand area. These findings have been confirmed in more recent studies. Subthreshold 1 Hz stimulation for 4 [5] or 10 [6] min both resulted in significant reduction in MEP size. Muellbacher et al. [7] found that 1 Hz suprathreshold TMS for 15 min increased the motor threshold and reduced MEP amplitude. Notably, the degree of these effects has been shown to be dependent on stimulation parameters such as intensity [8].

Effects of 1 Hz stimulation may also be seen at sites not directly targeted for stimulation. Gerschlager et al. [9] used a considerably lower stimulation intensity than previous studies (90 % active motor threshold (AMT) which approximately corresponds to 60–70 % of resting motor threshold (RMT)). They demonstrated that prolonged 1 Hz stimulation of the premotor cortex, but not the primary motor, parietal or prefrontal cortex, resulted in MEP suppression for at least 15 min. These authors suggest that the effects of premotor cortex stimulation is due to its rich connection to the primary motor cortex and that such stimulation can suppress primary motor cortex excitability even more so than stimulation of the motor cortex itself. Wassermann et al. [10] found that 1 Hz rTMS reduced the excitability of the contralateral, non-stimulated motor cortex as demonstrated by a reduction in the slope of the MEP recruitment curve. Thus, low-frequency stimulation of a cortical area may evoke cortical inhibition in interconnected areas [11]. Reduction of cortical excitability with low-frequency rTMS is clearly relevant to the treatment of depression, with low-frequency stimulation evaluated as an antidepressant strategy when applied to the right DLPFC [12].

High-frequency rTMS appears most likely to have effects opposite to that of low-frequency rTMS and to result in increased motor cortical excitability when applied to the motor cortex (see [2]). For example, Pascual-Leone et al. [13] demonstrated a pattern of facilitation of MEPs produced by a train of rTMS that varied with stimulus intensity and frequency. With 5 Hz rTMS at 150 % RMT, there was clear facilitation of MEPs. At 10 and 20 Hz rTMS with lower intensities (110 % RMT), there was also a consistent pattern of facilitation. In contrast, with 150 % RMT at 10 and 20 Hz rTMS, an alternating pattern of MEP inhibition and facilitation was demonstrated. Several other studies have also demonstrated that MEP size increases with high-frequency rTMS (>1 Hz) [14–16]. Modugno et al. [17] reported that 20 stimuli of 5, 10 and 20 Hz applied to the motor cortex at 100 % RMT resulted in brief MEP suppression that lasted for about 1 s after rTMS. This suppression in the post-train interval was prolonged with longer trains or higher frequencies. Increasing the intensity of the rTMS to 130 and 150 % of RMT resulted in facilitation rather than suppression of the MEP, consistent with previous findings [15]. Therefore, high-frequency rTMS at low intensity may cause inhibition for 1–2 s after the rTMS

train, whereas at higher-intensity, high-frequency rTMS consistently produces facilitation. The mechanisms by which altered excitability occurs in the cortex are unclear. However, it has been suggested that decreased excitability is related to the synaptic process of long-term depression [3], whereas increased excitability has been related to long-term potentiation [18].

The relevance of these studies to understanding the mechanism of action of rTMS in depression is uncertain. Clearly, individual high-frequency rTMS trains applied to the motor cortex increase excitability. However, what is less clear is an understanding of the effects of cumulative stimulation trains over a long treatment session and the accumulation of changes in cortical excitability with daily rTMS sessions over a matter of weeks as is applied in treatment protocols.

3.2.2 Effects on Motor Cortical Inhibition and Facilitation

rTMS can also induce changes in cortical inhibition and facilitation. These changes can be assessed using single- and paired pulse TMS paradigms including (1) short-interval intracortical inhibition (SICI) (i.e. paired pulse TMS (ppTMS) at inhibitory interstimulus intervals (ISIs) of <5 ms) [19], (2) long-interval intracortical inhibition (LICI) [20, 21] and (3) silent period (SP) [22] methods (see Fig. 3.1). These inhibitory paradigms may measure different subtypes of inhibitory GABAergic neurotransmission [23]. Cortical facilitation can be measured using paired pulse TMS with interstimulus intervals between 10 and 20 ms, referred to as intracortical facilitation (ICF) [19]. ICF may be mediated by glutamatergic neurotransmission [24].

3.2.2.1 Silent Period (SP)

The effects of rTMS on the SP have been investigated in several studies examining the effects of pulse number, stimulation frequency and intensity. A silent period is mostly believed to assess activity of the $GABA_B$ receptor. Berardelli et al. [25] demonstrated lengthening of the SP with 3 and 5 Hz rTMS at 110 and 120 % of the RMT. Romeo et al. [26] tested rTMS frequencies of 1, 2, 3, 5, 10 and 15 Hz at intensities just above the RMT. They found that trains delivered at ≥2 Hz resulted in a prolongation of the SP, whereas trains delivered at 1 Hz had no effect. In both studies, the authors suggested that the SP was prolonged because rTMS activated cortical inhibitory interneurons. Fierro et al. [27] explored the effects of 1 and 7 Hz rTMS at intensities of 100, 115 and 130 % of the RMT. They found that 1 Hz rTMS applied to the motor cortex near or above the motor threshold reduced the SP. This was interpreted as a decrease in cortical inhibition. In contrast, 7 Hz rTMS resulted in an inconsistent pattern of smaller and larger values for the SP. The authors concluded that rTMS applied at low 1 Hz frequency decreases the excitability of inhibitory interneurons.

Therefore, it appears the effects of rTMS on the SP are dependent on frequency and intensity of stimulation. High-frequency rTMS (>1 Hz) results in lengthening of the SP, whereas low-frequency rTMS (~1 Hz) results in shortening of the SP. Moreover, at high frequencies, increasing the stimulus intensity results in further lengthening of the SP [28]. For example, frequencies ranging from 1 Hz to priming

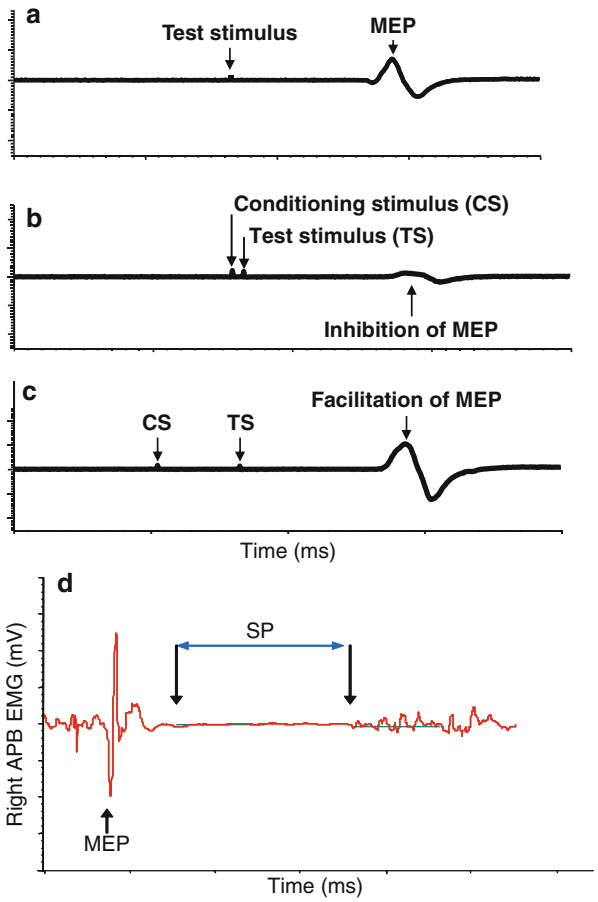


Fig. 3.1 Illustration of the assessment of the measures of short and long intracortical inhibition (SICI and LICI), cortical facilitation (*CF*) and the cortical silent period (*SP*). In the measurement of CF, SICI and LICI, the motor-evoked potential (*MEP*) response to a single test stimulus (**a**) is compared to the MEP response produced by a conditioning and test stimulus (**b**, **c**). When the conditioning stimulus is provided at a very short interval prior to the test stimulus (1–4 ms), the MEP produced is substantially reduced in size (as illustrated in **b**) which is SICI. CF is produced when the interstimulus interval is between 10 and 15 ms and the MEP size is increased over the baseline measure (**c**). LICI is produced when the interstimulus interval is extended to 100 ms (not shown). The SP measure is demonstrated in **d**. The TMS pulse is applied when the corresponding muscle in the contralateral hand is undertaking a tonic muscle contraction. A period of suppression of tonic muscle activity is produced following the MEP, and this is referred to as the silent period

(i.e. 6 Hz followed by 1 Hz), 10 and 20 Hz stimulation resulted in a prolongation of the SP. 20 Hz stimulation resulted in greatest prolongation of the SP. As the silent period was reported to be shortened in depression [29], this finding could help to identify the stimulation parameters needed to optimally treat depression. In fact, treatment with ECT in depression was associated with significant lengthening of the

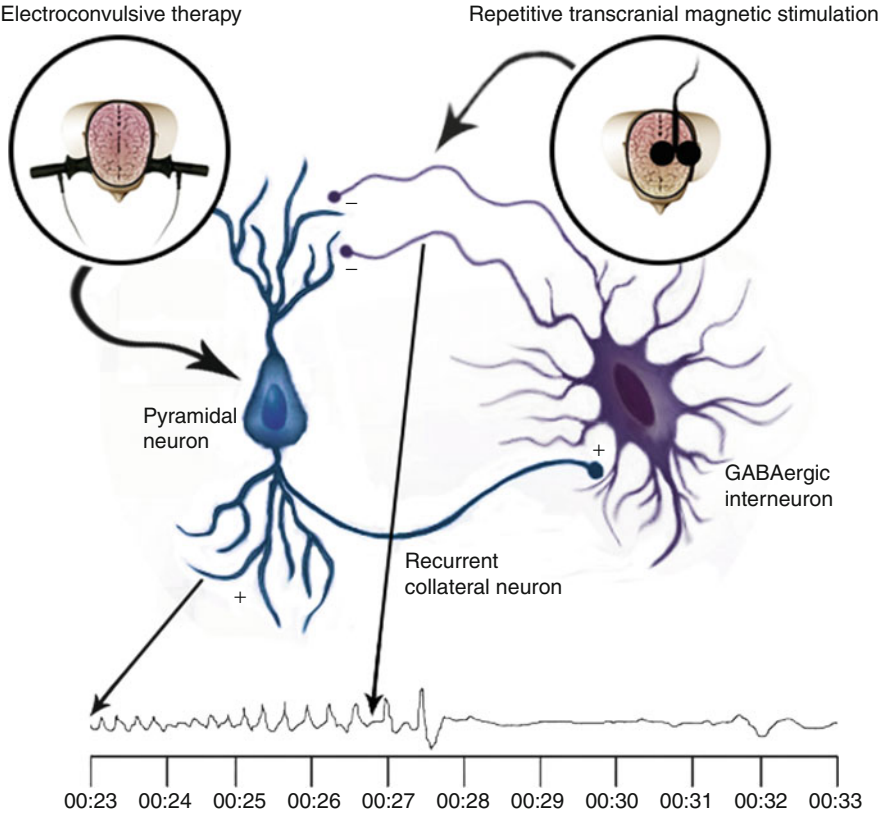


Fig. 3.2 Proposed mechanism for the role of GABAergic potentiation in the treatment of MDD. Cortical stimulation through treatments such as electroconvulsive therapy (ECT) results in rhythmic activation of pyramidal neurons with concurrent spike and wave complexes on electroencephalography (EEG). Subsequently, GABA interneurons are activated via feedback loops which attenuate cortical seizure activity, suppress EEG activity and potentiate GABA inhibitory neurotransmission. Repetitive transcranial magnetic stimulation (rTMS) may exert therapeutic effects by transsynaptic facilitation of GABAergic neurotransmission in an analogous manner

SP [30]. It is possible that both ECT and rTMS share similar mechanisms of action. For example, in Fig. 3.2 we illustrate how ECT induces seizures through direct activation of pyramidal neurons. Seizures terminate, in part, through activation of recurrent collaterals which activate GABAergic interneurons which could account for the SP prolongation seen with ECT. By contrast, rTMS activates interneurons transsynaptically [31], and this could result in a direct effect on GABAergic interneurons without causing a seizure.

3.2.2.2 Paired Pulse Inhibition and Facilitation (ppTMS)

The effects of rTMS on cortical inhibition and facilitation have also been evaluated through ppTMS. SICI assessed with ppTMS is widely believed to assess activity at the $GABA_A$ receptor. Pascual-Leone et al. [32] demonstrated SICI was significantly

reduced with 1,600 subthreshold rTMS stimuli applied at 10 Hz to the motor cortex. In contrast, the same number of subthreshold stimuli applied at 1 Hz had no effect on SICI. Similarly, Peinemann et al. [33] demonstrated that 5 Hz TMS applied to the motor cortex at 90 % RMT caused a significant reduction in SICI but no change in ICF. SICI was significantly reduced after only 30 stimuli of 120 % RMT at 5 Hz [34]. Similarly, SICI was reduced at a stimulation frequency of 15 Hz, whereas ICF was increased. Romero et al. [6] found that subthreshold stimulation with 1 Hz for 10 min significantly decreased ICF, without a concomitant change in SICI. These authors suggest that these effects occur through cortical disfacilitation. As ICF may be associated with activity of excitatory glutamatergic circuits [24], disfacilitation may result in decreased cortical excitation. Therefore, these studies suggest that high-frequency rTMS decreases SICI and, perhaps, increases ICF. Conversely, low-frequency rTMS may decrease ICF without concomitant change in SICI.

The result of this series of studies exploring the effect of rTMS on SP and SICI suggests that rTMS modulates activity at both GABA receptor subtypes.

3.2.3 Effects of rTMS on Motor Cortical Plasticity

Repetitive TMS has also been shown to affect cortical plasticity. In this context, plasticity refers to the reorganisation of the central nervous system (CNS) through changes in internal connections, representational patterns and/or neuronal properties [35]. Ziemann et al. [35] demonstrated that the deafferented motor cortex becomes modifiable by inputs that are normally subthreshold for inducing plastic changes. Their findings suggest that rTMS can modulate plasticity and may potentially be used to enhance cortical plasticity when it is beneficial and suppress it when it is detrimental. In a subsequent study [36], lorazepam (which enhances $GABA_A$ergic neurotransmission) and lamotrigine (which blocks voltage-gated Na^+ and Ca^{2+} channels) were found to abolish the increase in MEP size and decrease in SICI associated with concurrent ischemic nerve block and rTMS to the contralateral motor cortex. Conversely, dextromethorphan (NMDA receptor antagonist) suppressed the changes in SICI but had no effect on MEP. These results provide evidence that the increase in MEP size induced by rTMS and deafferentation involve both GABA-related inhibitory circuits and voltage-gated Na^+ or Ca^{2+} channel-mediated mechanisms. Also, rTMS-induced reduction in SICI appears to involve NMDA receptor activation.

The importance of these motor plasticity findings to the understanding of the mechanisms of rTMS in the treatment of depression is not fully clear. However, depression is a disorder associated with neural mechanisms putatively associated with plasticity impairments. For example, Levinson et al. [29] demonstrated that patients with depression had SP deficits, whilst patients with treatment-resistant depression had both SICI and SP deficits. These findings imply that depression is associated with deficits in GABAergic inhibitory neurotransmission and that more treatment-resistant depression is associated with even more marked GABAergic inhibitory deficits. Further, several dimensions of depressive symptoms (e.g. memory deficits) may be associated with dysfunctional plasticity. Dysfunctional plasticity

may also be a corollary to excessive NMDA receptor activation from chronic stress [37]. Additionally, deficits in brain-derived neurotrophic factor (BDNF) in depression may result in plasticity deficits, as BDNF serves to facilitate plasticity in the brain [38]. It may be possible that one of the mechanisms through which rTMS results in enhanced plasticity is the repetitive stimulation of neurons resulting in synchronous firing and long-term potentiation. That is, by repetitively stimulating neurons, neuronal output is strengthened and, over time, may translate into meaningful and more functional patterns of activity in depression.

3.3 Effects of rTMS Assessed with EEG

Assessment of immediate and direct rTMS-induced alterations in cortical activity cannot only be assessed by electromyography (EMG) methods as described in previous chapters, but also by electroencephalography (EEG). The use of the combination of TMS and EEG methods in the investigation of TMS mechanisms is particularly relevant for studies of working memory (WM) in depression. Abnormalities of WM have been repeatedly found in patients with MDD as well as a range of other psychiatric disorders. As discussed, rTMS over the motor cortex has been shown to enhance Gamma (γ)-aminobutyric acid (GABA)-mediated inhibitory neurotransmission in healthy individuals [28]. Gamma oscillatory activity during higher cognitive tasks is an area of great interest and has recently been shown as a key neurophysiological mechanism underlying WM.

Commonly defined as the ability to maintain and manipulate information over short periods of time [39], WM is often argued as the essence of all prefrontal functions due to its importance in everyday complex cognitive tasks such as language, comprehension, learning and reasoning [40, 41]. Moreover, the dorsolateral prefrontal cortex (DLPFC) is consistently reported to mediate WM processes, revealed through enhanced blood oxygen level-dependent (BOLD) activity in functional magnetic resonance imaging (fMRI) studies [42, 43]. It has been proposed that GABA inhibitory interneurons in the DLPFC contribute to the generation and synchronisation of pyramidal neurons necessary for optimal WM performance [44, 45].

Investigating this issue, we previously conducted a study measuring the effect of 20 Hz rTMS applied to the DLPFC on γ-oscillatory activity across WM load (i.e. 0-, 1- and 2-back conditions) in healthy controls. Active rTMS significantly increased γ-oscillatory activity compared to baseline (pre) and sham stimulation. Moreover, active rTMS caused the greatest change in γ-oscillatory activity in the *n*-back conditions with the greatest cognitive demand, an effect that was limited to frontal brain regions. Finally, active rTMS had no effect on other frequency ranges (i.e. δ, θ, α, β), suggesting a selective effect to oscillatory activity in the γ-frequency range. Collectively, these results suggest that active rTMS applied to DLPFC significantly increased frontal γ-oscillatory activity which was most pronounced at *n*-back conditions of greatest difficulty. Therefore, it is possible that the effects of rTMS on

DLPFC activity in depression may occur through modulation of high-frequency oscillations, and modulation of these oscillations may occur through alterations in the GABAergic neurotransmitter system.

3.4 Neuroimaging Studies of the Effect of rTMS

Part of the allure for studying the motor cortex is that outcome variables can be easily assessed with surface EMG. Exploring non-motor regions, however, requires the combining TMS with other methods of measurement (e.g. EEG, positron emission tomography (PET), near-infrared spectroscopy (NIR) or magnetic resonance imaging (MRI)). A substantial series of studies have utilised brain imaging methods to study either the direct effects of rTMS stimulation (in a variety of cortical regions) or the effects of rTMS treatment in patients with depression.

3.4.1 Imaging of rTMS Effects

Studies directly imaging the effects of rTMS on brain regions have demonstrated that local activation of the cortex results in changes in distributed brain regions. For example, Paus et al. [46] stimulated the frontal eye fields with 10 Hz rTMS at an intensity of 70 % of the maximum stimulator output, whilst PET scans were acquired. They found significant positive correlation with regional cerebral blood flow (rCBF), as measured with ^{15}O-labeled H_2O PET over the same cortical regions, as well as concomitant excitation in the visual cortex of the superior parietal and medial parieto-occipital regions. In an alternative approach, Nahas et al. [47] used 1 Hz rTMS to stimulate the prefrontal cortex, whilst functional MRI (fMRI) scans were conducted. This was done in an effort to measure connectivity and clarify the intensities that are required to produce activation in this cortical region. Previous studies measuring activation in non-motor cortical areas based intensities on those required to produce activation to the motor cortex [48]. Given the cytoarchitectural differences between these regions [49] however, such parameters may not be accurate. As such, the prefrontal cortex was stimulated with a range of intensities (e.g. 80, 100 and 120 % of RMT). Nahas et al.'s results can be summarised into four main findings: (1) greater intensities produced greater local and contralateral activation, (2) stimulation of the left prefrontal cortex resulted in bilateral effects, (3) rTMS of the left prefrontal cortex produced greater activation on the right side than the left side, and (4) stimulating at 80 % of the RMT for 20 s failed to produce significant prefrontal activation.

An additional imaging approach used to study rTMS effects has utilised metabolic imaging with PET. With this method, Strafella et al. [50] demonstrated that rTMS applied to mid-dorsolateral prefrontal cortex resulted in dopamine release in the striatum of the human brain, indicating that rTMS applied to the cortex can induce neurochemical change in subcortical brain regions.

The most relevant conclusions from direct neuroimaging studies of rTMS to understanding the mechanism of action of rTMS treatment of depression are clearly that rTMS produces changes locally and at distant brain sites within connected circuitry. This suggests the possibility that rTMS treatment may work through local effects, distal effects or a combination of both. It is also quite plausible that the mechanism of action of rTMS may involve changing the strength of connections between areas in these brain circuits.

3.4.2 Imaging of rTMS Effects in Depression

Of more direct relevance to understanding the mechanism of action of rTMS treatment in depression are a series of studies that have examined brain activity pre- and post-rTMS treatment. Several existing lines of evidence suggest that MDD is more commonly associated with hypoexcitability over the left prefrontal cortex and/or hyperexcitability over the right prefrontal cortex. The strongest evidence in support of this relates to the much higher rates of depression in patients with left-sided strokes (the anatomic equivalent of hypoexcitability) than in the general population. Moreover, patients with right-sided strokes (the anatomic equivalent of hyperexcitability) experience manic symptoms at much higher rates than in the general population [51].

Imaging studies have also demonstrated that MDD may involve dysregulation of cortical activity, with lower activity in the left dorsolateral prefrontal cortex and higher activity in the right dorsolateral prefrontal cortex [52, 53]. Further, rTMS treatment in MDD has been directly shown to be associated with a normalisation of hypoexcitability over the left prefrontal cortex and normalisation of hyperexcitability over the right hemisphere [54]. This is consistent with the finding that rTMS applied at high frequencies (e.g. 10 Hz) increases excitability in the cortex [55], whilst rTMS applied at low frequencies (e.g. 1 Hz) decreases excitability in the cortex [3]. Specifically, Kimbrell et al. [54] reported that 13 patients with depression responded differently to 1 Hz versus 20 Hz rTMS. There was a significant negative correlation between change in HAMD scores and each frequency they were treated with. That is, responders to one frequency (i.e. 1 or 20 Hz) tended to deteriorate when the other frequency was applied (i.e. 20 or 1 Hz). Overall, however, there was a greater response to 1 Hz rTMS compared to 20 Hz rTMS. Additionally, in 11 patients who received PET scans, change in HAMD scores in response to rTMS was related to baseline glucose metabolism measures. Two weeks of 20 Hz rTMS was correlated with baseline global metabolism, with improved response associated with greater baseline global hypometabolism. Conversely, baseline global hypermetabolism was more closely associated with greater HAMD change scores following 1 Hz rTMS. The results suggest that brain metabolic biomarkers may be an effective way of optimising or personalising rTMS treatment response.

In addition to this initial PET research, studies have used a number of other methods to explore brain activity pre- and posttreatment. Research using functional magnetic resonance imaging (MRI) has indicated that high-frequency left-sided rTMS produces a bilateral prefrontal increase in task-related activation [56].

Interestingly, in the same study, successful response to low-frequency right-sided stimulation was associated with bilateral reductions in prefrontal activity. These bilateral changes suggest that successful response to rTMS treatment is not related to a simple rebalancing of left–right activity and that response to treatment may involve alternative mechanisms. Interestingly in this context, recent studies have suggested that response to rTMS may be related to changes in white matter pathways in prefrontal–subcortical circuitry [57]. This research suggests that rTMS response does not necessarily relate to local changes in cortical activity but arises through strengthening of cortical–subcortical circuitry. Strengthening of these connections could potentially allow executive prefrontal cortical regions to exert greater regulatory control over abnormally active subcortical mood circuitry.

3.4.3 Studying Brain Effects of rTMS with Near-Infrared Spectroscopy

An alternative mechanism of exploring the effects of rTMS stimulation on brain activity is through the use of near-infrared spectroscopy (NIRS). NIRS is a technique for measuring blood oxygenation (HbO) that can be used in combination with rTMS and repeatedly over time. Initial research using NIRS to study the effects of single-pulse TMS demonstrated quite consistently that higher-intensity TMS results in a drop in HbO, both at primary motor cortex (M1) and at prefrontal cortex (PFC) (e.g. [58, 59]). Subthreshold single-pulse TMS results in a more recognisable increase in HbO than would be expected to be seen during normal brain activation. More recent studies have found that the decrease in HbO that results from high-intensity TMS stimulation can also be seen with paired TMS pulses [59] and rTMS [60]. For example, we recently demonstrated that prolonged trains of 1 Hz rTMS at suprathreshold intensities produced a prolonged and sustained reduction in HbO not seen with subthreshold stimulation [61]. This pattern of substantial HbO reduction appears to be an ‘unnatural’ pattern of brain activation, differing from what would be expected for normal brain activation or engagement in a cognitive task [58, 59, 61, 62]. Speculatively, it is possible that the brain’s response to this unnatural pattern of brain activation, such as a change in vasomotor activity, may in some way underlie the therapeutic action of rTMS.

3.5 Studying Brain Effects of rTMS with Electroencephalography

EEG methods have been used relatively extensively to study aspects of rTMS treatment of depression. Initially EEG was used to investigate whether there were safety-related issues with rTMS treatment. More recently, a series of studies have investigated whether EEG markers can be used to predict successful response to rTMS treatment (e.g. [63, 64]). Of most relevance, however, are studies that have

investigated changes in EEG activity associated with successful antidepressant treatment. For example, Spronk et al. evaluated the effects of rTMS applied over the DLFPC on quantitative EEG (QEEG) and the oddball ERP in patients with depression [65]. They reported that QEEG measures did not change with treatment, with the exception of an indirect right frontal increase in delta power. By contrast, rTMS resulted in an increased positivity in ERPs over the left frontal cortex. Specifically, the P2 amplitude was significantly increased in left frontal regions. There was also a treatment-related increase in N1 and N2 ERP components. These results suggest that rTMS can alter conventional neurophysiological markers of plasticity in the cortex. Such measures may ultimately serve as biomarkers of treatment response and help tailor or personalise rTMS treatment.

3.6 Effects of rTMS on BDNF

Given the postulated role of neurotrophic factors, including BDNF, in the aetiology of depression and the mechanism of action of antidepressant medication, studies have increasingly explored whether the antidepressant effects of rTMS are modulated through rTMS-induced changes in BDNF. These studies have occurred both in animal models and in human experimental settings.

For example, high-frequency rTMS was shown to produce a substantial increase in BDNF levels in rats when stimulation was applied in awake animals, an effect not seen with low-frequency stimulation [66]. In a second study, three weeks of high-frequency stimulation was also shown to produce increases in BDNF levels along with changes in hippocampal cell proliferation [67]. In humans, Bocchio-Chiavetto et al. [68] reported that 5 daily sessions of rTMS administered to 16 patients with MDD resulted in significantly improved depression (average improvement by HAMD of 23.60 %; $p = 0.0003$) with a concomitant increase in serum BDNF levels (baseline 29.73 ± 8.02 ng/mL; posttreatment 32.63 ± 7.59 ng/mL; $p = 0.022$). However, the clinical relevance of these findings is uncertain as the authors reported the increment in the neurotrophin levels was not associated with rTMS efficacy. Additional evidence from Lang et al. [69] also failed to detect an association of BDNF with clinical improvement following 10 rTMS treatments of 14 patients suffering from treatment-resistant major depression.

The relationship of the BDNF system to rTMS response has also been explored in human subjects by considering the relationship between clinical response to treatment and BDNF genotype, specifically the effect of the val66met BDNF polymorphism. In a study of 36 patients where 31 had a diagnosis of major depression and the remainder five of bipolar disorder (depressive phase), five daily sessions of rTMS improved patient HAMD scores (baseline 23.19 ± 5.12; post-rTMS 17.50 ± 6.91; average = 25.29 %). The val/val homozygotes (32.36 ± 21.23 % improvement in HAMD) experienced a much greater improvement than met carriers (16.45 ± 19.90), indicating a role for this polymorphism in the improvement of depressive symptoms with rTMS treatment [68].

Conclusions

In summary, this chapter focused on rTMS mechanisms potentially associated with therapeutic improvement in depression. Treatment effects may relate to potentiation of excitatory and inhibitory cortical mechanisms. It is possible that rTMS responses relate to local changes in cortical activity but also that response relates to an alteration of connections between prefrontal and subcortical brain regions relevant to depression. In addition, evidence suggests that rTMS may modulate plasticity in the cortex. Finally, both BDNF and dopaminergic increases have been reported, both of which have been related to the therapeutic mechanisms of rTMS. Future studies aiming to closely associate changes in these brain mechanisms to changes in symptomatic response may help clarify the physiological basis for the therapeutic effects of rTMS and potentially lead to optimised treatments.

References

1. Barker AT (1991) An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysiol 8(1):26–37
2. Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117(12):2584–2596
3. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M et al (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48(5): 1398–1403
4. Siebner HR, Auer C, Conrad B (1999) Abnormal increase in the corticomotor output to the affected hand during repetitive transcranial magnetic stimulation of the primary motor cortex in patients with writer's cramp. Neurosci Lett 262(2):133–136
5. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000) Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 111(5):800–805
6. Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A (2002) Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 113(1):101–107
7. Muellbacher W, Ziemann U, Boroojerdi B, Hallett M (2000) Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clin Neurophysiol 111(6):1002–1007
8. Fitzgerald PB, Brown T, Daskalakis ZJ, Chen R, Kulkarni J (2002) Intensity – dependent effects of 1 Hz rTMS on human corticospinal excitability. Clin Neurophysiol 113:1136–1141
9. Gerschlager W, Siebner HR, Rothwell JC (2001) Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 57(3):449–455
10. Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R (1998) Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. Neurosci Lett 250(3):141–144
11. Chen R, Seitz RJ (2001) Changing cortical excitability with low-frequency magnetic stimulation. Neurology 57(3):379–380
12. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S et al (1999) Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch Gen Psychiatry 56(4):315–320
13. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117(Pt 4):847–858
14. Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler D et al (1997) Rapid rate transcranial magnetic stimulation – a safety study. Electroencephalogr Clin Neurophysiol 105(6):422–429

15. Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Curra A, Gilio F et al (1998) Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 122(1): 79–84
16. Maeda F, Keenan JP, Pascual-Leone A (2000) Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. Br J Psychiatry 177:169–173
17. Modugno N, Nakamura Y, MacKinnon CD, Filipovic SR, Bestmann S, Berardelli A et al (2001) Motor cortex excitability following short trains of repetitive magnetic stimuli. Exp Brain Res 140(4):453–459
18. Wang H, Wang X, Scheich H (1996) LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. Neuroreport 7(2):521–525
19. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A et al (1993) Corticocortical inhibition in human motor cortex. J Physiol (Lond) 471:501–519
20. Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol 85(6):355–364
21. Wassermann EM, Samii A, Mercuri B, Ikoma K, Oddo D, Grill SE et al (1996) Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. Exp Brain Res 109(1):158–163
22. Cantello R, Gianelli M, Civardi C, Mutani R (1992) Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42(10):1951–1959
23. Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. J Physiol 530(Pt 2):307–317
24. Ziemann U, Chen R, Cohen LG, Hallett M (1998) Dextromethorphan decreases the excitability of the human motor cortex. Neurology 51(5):1320–1324
25. Berardelli A, Inghilleri M, Gilio F, Romeo S, Pedace F, Curra A et al (1999) Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. Exp Brain Res 125(1):82–86
26. Romeo S, Gilio F, Pedace F, Ozkaynak S, Inghilleri M, Manfredi M et al (2000) Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas. Exp Brain Res 135(4):504–510
27. Fierro B, Piazza A, Brighina F, La Bua V, Buffa D, Oliveri M (2001) Modulation of intracortical inhibition induced by low- and high-frequency repetitive transcranial magnetic stimulation. Exp Brain Res 138(4):452–457
28. Daskalakis ZJ, Moller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R (2006) The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. Exp Brain Res 174(3):403–412
29. Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, Daskalakis ZJ (2010) Evidence of cortical inhibitory deficits in major depressive disorder. Biol Psychiatry 67(5): 458–464
30. Bajbouj M, Lang UE, Niehaus L, Hellen FE, Heuser I, Neu P (2006) Effects of right unilateral electroconvulsive therapy on motor cortical excitability in depressive patients. J Psychiatr Res 40(4):322–327
31. Rothwell JC (1997) Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods 74(2):113–122
32. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD (1998) Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 15(4):333–343
33. Peinemann A, Lehner C, Mentschel C, Munchau A, Conrad B, Siebner HR (2000) Subthreshold 5-Hz repetitive transcranial magnetic stimulation of the human primary motor cortex reduces intracortical paired-pulse inhibition. Neurosci Lett 296(1):21–24
34. Wu T, Sommer M, Tergau F, Paulus W (2000) Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. Neurosci Lett 287(1): 37–40

35. Ziemann U, Corwell B, Cohen LG (1998) Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 18(3):1115–1123
36. Ziemann U, Hallett M, Cohen LG (1998) Mechanisms of deafferentation-induced plasticity in human motor cortex. J Neurosci 18(17):7000–7007
37. Pittenger C, Duman RS (2008) Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33(1):88–109
38. Brunoni AR, Boggio PS, Fregni F (2008) Can the 'yin and yang' BDNF hypothesis be used to predict the effects of rTMS treatment in neuropsychiatry? Med Hypotheses 71(2):279–282
39. Baddeley A (1986) Working memory. Claredon Press, Oxford
40. Baddeley A (1992) Working memory. Science 255(5044):556–559
41. Baddeley A (2000) The episodic buffer: a new component of working memory? Trends Cogn Sci 4(11):417–423
42. Rasmussen KG, Knapp RG, Biggs MM, Smith GE, Rummans TA, Petrides G et al (2007) Data management and design issues in an unmasked randomized trial of electroconvulsive therapy for relapse prevention of severe depression: the consortium for research in electroconvulsive therapy trial. J ECT 23(4):244–250
43. Owens DS, Parker PY, Benton D (1997) Blood glucose and subjective energy following cognitive demand. Physiol Behav 62(3):471–478
44. Wang XJ, Buzsaki G (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. J Neurosci 16(20):6402–6413
45. Traub RD, Michelson-Law H, Bibbig AE, Buhl EH, Whittington MA (2004) Gap junctions, fast oscillations and the initiation of seizures. Adv Exp Med Biol 548:110–122
46. Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 17(9):3178–3184
47. Nahas Z, Lomarev M, Roberts DR, Shastri A, Lorberbaum JP, Teneback C et al (2001) Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry 50(9):712–720
48. Bohning DE, Shastri A, Nahas Z, Lorberbaum JP, Andersen SW, Dannels WR et al (1998) Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Invest Radiol 33(6):336–340
49. Christensen BK, Bilder RM (2000) Dual cytoarchitectonic trends: an evolutionary model of frontal lobe functioning and its application to psychopathology. Can J Psychiatry 45(3):247–256
50. Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 21(15):RC157
51. Huffman JC, Stern TA (2003) Poststroke neuropsychiatric symptoms and pseudoseizures: a discussion. Prim Care Companion J Clin Psychiatry 5(2):85–88
52. Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE et al (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 46(3):243–250
53. Abou-Saleh MT, Al Suhaili AR, Karim L, Prais V, Hamdi E (1999) Single photon emission tomography with 99m Tc-HMPAO in Arab patients with depression. J Affect Disord 55(2–3): 115–123
54. Kimbrell TA, Little JT, Dunn RT et al (1999) Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 46:1603–1613
55. Pascual-Leone A, Valls-Sole J, Wasserman E, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117:847–858
56. Fitzgerald PB, Sritharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G (2007) A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. J Clin Psychopharmacol 27(5): 488–492

57. Peng H, Zheng H, Li L, Liu J, Zhang Y, Shan B et al (2012) High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. J Affect Disord 136(3):249–257
58. Thomson RH, Maller JJ, Daskalakis ZJ, Fitzgerald PB (2011) Blood oxygenation changes resulting from suprathreshold transcranial magnetic stimulation. Brain Stimul 4(3):165–168
59. Thomson RH, Daskalakis ZJ, Fitzgerald PB (2011) A near infra-red spectroscopy study of the effects of pre-frontal single and paired pulse transcranial magnetic stimulation. Clin Neurophysiol 122(2):378–382
60. Kozel FA, Johnson KA, Nahas Z, Nakonezny PA, Morgan PS, Anderson BS et al (2011) Fractional anisotropy changes after several weeks of daily left high-frequency repetitive transcranial magnetic stimulation of the prefrontal cortex to treat major depression. J ECT 27(1):5–10
61. Thomson RH, Rogasch NC, Maller JJ, Daskalakis ZJ, Fitzgerald PB (2012) Intensity dependent repetitive transcranial magnetic stimulation modulation of blood oxygenation. J Affect Disord 136(3):1243–1246
62. Mochizuki H, Ugawa Y, Terao Y, Sakai KL (2006) Cortical hemoglobin-concentration changes under the coil induced by single-pulse TMS in humans: a simultaneous recording with near-infrared spectroscopy. Exp Brain Res 169(3):302–310
63. Arns M, Drinkenburg WH, Fitzgerald PB, Kenemans JL (2012) Neurophysiological predictors of non-response to rTMS in depression. Brain Stimul 5(4):569–576
64. Narushima K, McCormick LM, Yamada T, Thatcher RW, Robinson RG (2010) Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular depression. J Neuropsychiatry Clin Neurosci 22(1):75–84
65. Spronk D, Arns M, Bootsma A, van Ruth R, Fitzgerald PB (2008) Long-term effects of left frontal rTMS on EEG and ERPs in patients with depression. Clin EEG Neurosci 39(3): 118–124
66. Gersner R, Kravetz E, Feil J, Pell G, Zangen A (2011) Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: differential outcomes in anesthetized and awake animals. J Neurosci 31(20):7521–7526
67. Feng SF, Shi TY, Fan Y, Wang WN, Chen YC, Tan QR (2012) Long-lasting effects of chronic rTMS to treat chronic rodent model of depression. Behav Brain Res 232(1):245–251
68. Bocchio-Chiavetto L, Miniussi C, Zanardini R, Gazzoli A, Bignotti S, Specchia C et al (2008) 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug resistant depression. Neurosci Lett 437(2):130–134
69. Lang UE, Bajbouj M, Gallinat J, Hellweg R (2006) Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. Psychopharmacology (Berl) 187(1):56–59

Acute rTMS Treatment for Depression

4

4.1 rTMS in Depression: High-Frequency Stimulation

When TMS was first used in the treatment of depression, single pulses were applied, often to the vertex, with minimal therapeutic benefit (e.g. [1]). However, it was not long before a more substantive and rational application of rTMS was developed. This application, which involved the stimulation of left dorsolateral prefrontal cortex (DLPFC) with high-frequency rTMS pulses (Fig. 4.1), has persisted until current times.

The rationale for high-frequency stimulation to the left DLPFC arose from the observation that patients with MDD exhibit a reduction in resting activity in the left DLPFC on positron emission tomography (PET) imaging [2]. A reduction in left prefrontal activity was also proposed to underlie the increased risk of depression following left anterior strokes, and there was also a suggestion of left right anterior cerebral imbalance in electroencephalography studies. Early neurophysiological studies where rTMS was applied to the motor cortex had demonstrated that high-frequency stimulation would increase local cortical activity, usually assessed as an increase in the evoked motor activity. Therefore, initial rTMS research was proposed that high-frequency stimulation applied to the left DLPFC could increase local cortical activity and therefore ameliorate depression.

Initial studies using this technique in the mid-1990s produced considerable therapeutic benefit, despite the brief nature of the trials and relatively low dose of stimulation applied (e.g. [3, 4]). Subsequently, a very large number of open-label and sham-controlled trials have been conducted to explore the efficacy of left prefrontal rTMS (see Table 4.1). At least 30 trials have been sham controlled. Over time, there has been a progressive increase in the dose of rTMS stimulation applied during treatment research. This has manifested in changes in a number of stimulation parameters. First, the intensity of stimulation has progressively increased. Initial trials frequently applied stimulation at 90 or 100 % of the resting motor threshold (RMT), whereas recent trials have used up to 120 % of the RMT. The RMT is a measure of motor cortical excitability (see Fig. 4.2 and Sect. 6.2). Second, the number of stimulation trains applied in each treatment session has progressively increased. Initial studies provided 10 or 20 stimulation trains per session. Recent studies have applied

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_4,

Fig. 4.1 A fluid cooled MagVenture A/S coil localised over the prefrontal cortex in the custom built stand

75 trains per session with some trials even exceeding this. Finally, the total number of stimulation sessions has also progressively increased. Treatment was initially provided over 1 or 2 weeks. In recent years, treatment trials of 6 weeks duration have been conducted, with some studies exceeding even this period [23]. However, this has not been completely consistent, with some recent studies using stimulation characteristics most commonly applied in the early 2000s.

Few studies have systematically addressed whether dose is directly related to clinical response. An inference has been made that the progressive increase in dose over time has been associated with an increase in efficacy reflected by greater effect sizes in later clinical trials [24]. However, it is possible that this increase has resulted from other factors, including changes in selection criteria for patients in clinical trials. Until systematic research that randomises patients to different dosage conditions is conducted, it is important to note that it remains an assumption that higher doses are associated with better clinical response. It is also worthy of note that the possible range of techniques that can be utilised in the application of rTMS have evolved considerably, for example, with the development of a variety of neuronavigational strategies for more accurately targeting prefrontal cortical regions. However, the vast majority of studies have generally used similar techniques to those developed in the mid-1990s. For example, the majority of studies localised DLPFC by the measurement of 5 cm forward from the motor cortex in a sagittal plane.

Table 4.1 rTMS depression trials: a demonstration of the types of rTMS trials and representative results

Reference	Subjects	rTMS parameters	Significant difference: active versus sham	Results
Avery et al. [5]	68 patients with treatment-resistant depression	15 sessions, delivered to the left DLPFC at 110 % of the RMT (32 trains of 10 Hz repetitive TMS delivered in 5 s trains) Sham – 45° coil tilt	Y	HRSD scores showed a significantly greater decrease over time in the TMS group compared with the sham group. Response rate for the TMS group was 30.6 % greater than the 6.1 % rate in the sham group
Berman et al. [6]	20 patients with treatment-resistant depression	10 sessions, twenty 2 s trains of 20 Hz stimulation with 58 s intervals; delivered at 80 % RMT Sham – 45° coil tilt	Y	1 of 10 subjects receiving active treatment demonstrated a robust response (i.e. HRSD decreased from 47 to 7 points); three other patients demonstrated 40–45 % decreases in HRSD scores. No patients receiving sham demonstrated partial or full responses
Cohen et al. [7]	10 patients with treatment-resistant depression	9 sessions over 2 weeks, 20 trains at 1.5 s at 20 Hz and 100 % of RMT over left DLPFC followed by 2 trains of 60 s at 1 Hz and 100 % of RMT over right DLPFC	n/a	4 of 10 subjects showed a ≥50 % decline on the HRSD, with a strong trend for those under age 50
Conca et al. [8]	36 medicated depressed inpatients	Group 1: 110 % of RMT at 10 Hz over the left DLPFC, followed by 1 Hz stimulation of the right DLPFC at 110 % of the RMT Group 2: stimulation of the left DLPC with alternating trains of 110 % MT at 10 Hz and trains of 110 % MT at 1 Hz in the same session. Group 3: high-frequency stimulation over the left DLPC was performed as an internal control group	n/a	None of the treatment modalities was superior, but different side effects were observed

(continued)

Table 4.1 (continued)

Reference	Subjects	rTMS parameters	Significant difference: active versus sham	Results
Feinsod et al. [9]	10 patients with acute or residual schizophrenia	10 sessions, 120 stimuli daily at 1 Hz to right PFC, 9-cm round coil (100 % RMT)	n/a	Significant decrease in BPRS score but in non-specific items (anxiety, tension, restlessness)
Figiel et al. [9]	50 patients with refractory depression	5 sessions, 10 trains of 5 s with trains 30 s apart, 10 Hz stimulation at 110 % of the RMT	n/a	21 responders (42 %) based on final HRSD scores compared to baseline 56 % of patients under age 65 responded and only 23 % of those over age 65 responded
Fitzgerald et al. [10]	50 patients with treatment-resistant depression	3 trains of low-frequency rTMS to the right PFC of 140 s duration at 1 Hz were applied daily, followed immediately by 15 trains of 5 s duration of high-frequency left-side rTMS at 10 Hz for 6 weeks Sham – 45° coil tilt	Y	Significant decrease in MADRS scores for active treatment group at 2 weeks and across the full duration of the study. Those receiving active treatment met response (11 of 25 [44 %]) or remission (9 of 25 [36 %]) criteria by study end compared to the sham stimulation group (2 of 25 [8 %] and none of 25, respectively)
Fitzgerald et al. [11]	60 patients with treatment-resistant depression	Twenty 5 s HFL-TMS trains at 10 Hz and five 60 s LFR-TMS trains at 1 Hz daily Sham – 45° coil tilt	Y	Significant reduction in MADRS scores between the HFL-TMS and sham groups and between the LFR-TMS and sham groups
Geller et al. [12]	20 patients, 10 with schizophrenia and 10 with major depressive disorder	30 single pulses given in one session, 14-cm large round coil, bilateral PFC (100 % RMT)	n/a	Several patients had short-lasting non-specific improvement
George et al. [13]	12 depressed adults	20, 2 s, 20 Hz stimulations at 80 % of the RMT over the left DLPFC Sham – 45° coil tilt	Y	During the active phase, HRSD scores decreased significantly by 5.25 points

George et al. [14]	6 medication-resistant depressed inpatients	Daily left PFC rTMS over several weeks	n/a	HRSD scores improved significantly for the group as a whole decreasing from 23.8±4.2 (s.d.) at baseline to 17.5±8.4 after treatment
Grunhaus et al. [15]	40 patients with major depressive disorder assigned to rTMS or ECT	rTMS: 20 sessions, 10 Hz for either 2 or 6 s for 20 trains at 90 % of the RMT	n/a	Patients without psychosis responded similarly to both treatments and those with psychosis responded best to ECT
Hausmann et al. [16]	41 medication-free patients with major depressive disorder	10 sessions Group 1: active HFL- TMS of the DLPFC and subsequent sham LFR-TMS Group 2: simultaneous bilateral active stimulation (HFL-TMS and LFR-TMS) Group 3: bilateral sham stimulation (45° coil tilt)	N	No significant difference on the HRSD or BDI scores between groups. There was a significant effect of time on all outcome variables in all groups (patients were administered an antidepressant on the first day of stimulation)
Klein et al. [17]	79 inpatients with major depressive disorder	10 sessions, 1 Hz, 0.1-ms pulse duration, at 10 % above motor threshold (60 stimuli over 1 min) Sham – perpendicular coil tilt	Y	Significant reduction in depression scores as shown by the HRSD and MADRS after 2 weeks of active treatment
Loo et al. [18]	19 medication-resistant depressed patients	3 weeks, 15 Hz (5 s on, 25 s off) × 24 at 90 % of the RMT Sham – coils on the head were inactive and a third coil out of the subject's view was discharged for acoustic effect	N	Significant difference in HRSD and MADRS scores for each group from baseline but no changes comparing active to sham treatment
Loo et al. [19]	18 medication-resistant depressed patients	4 weeks, 10 Hz, 110 % of the RMT, 30 trains of 5 s each, 30 s apart Sham – 45° coil tilt	Y	After 4 weeks of real treatment, significant linear trends indicated improvement in the scores on the HRSD, MADRS and the BDI

(continued)

Table 4.1 (continued)

Reference	Subjects	rTMS parameters	Significant difference: active versus sham	Results
Menkes et al. [20]	8 depressed patients and 6 controls	8 sessions over 6 weeks, right frontal SF-rTMS, 0.5 Hz at RMT	n/a	Significant antidepressant effect was noted in depressed patients on the HRSD and BDI scales. No change on either scale was noted in the controls
O'Reardon et al. [21]	301 medication-free patients with major depressive disorder	5 days/week for 4–6 weeks, 10 pulses per second at 120 % of the RMT, 3,000 pulses per session over left DLPFC Sham – separate coil with embedded magnetic field	Y	Active TMS was significantly superior to sham on the MADRS at week 4 as well as HRSD at weeks 4 and 6
Padberg et al. [22]	18 patients with medication-resistant major depressive disorder	10 Hz, 0.3 Hz or sham stimulation, 250 stimuli per day for 5 days at 90 % of the RMT over the left DLPFC	N	Scores on the HRSD showed a significant time by group interaction; however, the effect was clinically marginal
Pascual-Leone et al. [4]	17 patients with medication-resistant depression	5 sessions, 20 trains of 10 s duration separated by 1-min pauses, 10 Hz at 90 % of RMT, positioned over vertex, left or right DLPFC Sham – 45° coil tilt	Y	Left DLPFC rTMS resulted in a significant decrease in scores on the HRSD and BDI

DLPFC Dorsolateral prefrontal cortex, *RMT* Resting motor threshold, *HRSD* Hamilton depression rating scale, *BPRS* Brief psychiatric rating scale, *MADRS* Montgomery asberg depression rating scale, *HFL-TMS* High-frequency left-sided TMS, *RLF-TMS* Low-frequency right-sided TMS, *ECT* Electro-convulsive therapy, *BDI* Beck depression inventory

Fig. 4.2 Assessing the resting motor threshold using a hand held coil during stimulation of the motor cortex

The vast majority of clinical trials conducted investigating the efficacy of rTMS have been independently funded and conducted by individual research groups. However, several larger-scale multisite sham-controlled trials have now been published. The first of these studies was sponsored by an equipment manufacturer who had patent protection over a modified rTMS coil design. This study involved the randomisation of over 300 medication-free patients to either active or sham stimulation [21]. Treatment was provided on a daily basis for 6 weeks which could be continued during a 3-week taper period. Seventy-five trains at 10 Hz were provided daily at a relatively high intensity. A non-identified sham stimulation coil system was used to ensure the blinding of both patients and clinicians. This trial demonstrated an antidepressant effect of active treatment compared to sham. However, this was not consistently found on all of the outcome measures, including the a priori nominated primary outcome measure. A substantial difference in antidepressant effect was seen depending on the degree of treatment resistance: patients who had not responded to only one antidepressant medication in the current episode responded to a substantially greater degree than those with a greater degree of treatment failure. Treatment was generally very well tolerated in this trial with no major adverse events. The results of this trial were used by the manufacturer, Neuronetics Ltd, to achieve device registration approval in the USA in 2008.

A second multisite US trial was funded independently by the National Institute of Mental Health [25]. One-hundred and ninety-nine patients were randomised to either active or sham stimulation which involved 3,000 10 Hz pulses applied on a daily basis for 3 weeks, with a possible 3-week extension for partial responders.

Similar methods were used to those applied in the Neuronetics Ltd-sponsored study. Active stimulation produced a greater percentage of patients who achieved remission of depressive symptoms than sham stimulation, although the overall rates of remission in both groups were low (14.1 versus 5.1 %). Treatment was also tolerated well in this study with a low dropout rate and no major adverse events.

A different approach was adopted in a third large trial conducted in Europe across multiple centres [26]. In this study, active or sham rTMS was concurrently commenced with antidepressant medication. No difference between active and sham stimulation was seen although it is possible that clinical benefits of rTMS were masked by the confounding co-administration of medication. Whilst this trial does not speak to the overall efficacy of rTMS, it does strongly suggest that there is limited value in concurrently commencing treatment with rTMS and medication.

We have been involved in the conduct of a series of large non-sham-controlled multisite trials investigating various rTMS stimulation parameters (e.g. [27, 28]). In these studies, when rTMS is applied in a relatively heterogeneous but treatment-resistant sample of patients, we have generally found a response rate of approximately 50 %.

4.1.1 Meta-Analysis

The results of a large number of studies exploring the efficacy of rTMS treatment in depression have been explored and summarised in a number of meta-analyses. The most recent of these were published in 2009 and 2010 and so have not included all of the latest research. The meta-analysis conducted by Schutter et al. [29] involved 30 trials and 1,164 patients. The authors of this study found that there was a highly significant effect of active treatment compared to placebo, indicated by the average reduction in depression severity scores ($p < 0.00001$) with a moderate effect size (0.39). Interestingly, the degree of pre-existing medication resistance and the intensity at which rTMS was applied did not affect outcomes. The authors of this study carefully evaluated the possibility of publication bias influencing analysis outcomes. There was no evidence of such a bias (non-publication of negative trials in the statistical analysis or the funnel plot). The authors concluded that approximately 270 unpublished negative studies would be required to counteract the positive results seen.

The most recent meta-analysis conducted by Slotema et al. found similar results [30]. Thirty-four studies were analysed comparing rTMS to sham stimulation (total $n = 1{,}383$). The effect size was 0.55 ($p < 0.001$) and over 18,000 unpublished negative trials would be required for these results to have been produced by publication bias. Importantly, these authors found significant differences when rTMS was applied under different medication conditions. The overall effect size when rTMS was applied as a monotherapy was substantially higher (0.96, $p < 0.001$) than when rTMS was concurrently applied with medication (0.51, $p < 0.001$). The effect size was lowest when rTMS was started simultaneously with medication treatment (0.13, $p > 0.05$).

4.1.2 rTMS Versus ECT

In addition to trials exploring the efficacy of rTMS compared to sham stimulation, a number of trials have also compared high-frequency rTMS to ECT [15, 31–35]. The majority of these studies report that rTMS has produced a similar degree of efficacy to ECT. However, these studies have not typically provided power analyses to indicate whether the studies have sufficient sample size to detect between group differences.

The first of the rTMS/ECT comparison studies did demonstrate a difference between the treatments. In this trial, patients with psychotic depression showed greater benefit with ECT [33] although no differences were seen in patients without psychosis. A second more recent study also reported greater beneficial effects of ECT [36]. The overall results of these studies have been summarised using meta-analysis. This analysis included six studies ($n=215$). It was found that ECT produced a greater clinical benefit with an effect size of 0.47 ($p=0.004$).

Interpretation of studies comparing ECT to rTMS is somewhat problematic. All of these studies have compared a fixed number of unilateral rTMS treatments to a flexible course of often uni- and bilateral ECT. The number of rTMS treatments provided has often been relatively low in number compared to recent studies. In addition, no studies have allowed patients not responding to left-sided rTMS to cross over to right-sided or bilateral treatments, potentially the equivalent of converting from unilateral to bilateral ECT.

The question has also been raised as to whether comparing rTMS to ECT is really a substantially meaningful comparison [37]. We have argued that rTMS is more likely to be a complementary treatment provided to patients who do not require an urgent clinical response, which would suggest a need for immediate ECT, or in whom ECT is considered not suitable for safety or other clinical reasons. It is likely that rTMS will most frequently be offered to patients who are at early stages of treatment resistance or who have not quite the same degree of illness severity.

4.1.3 Summary

A substantive series of single-site and multisite research trials have comprehensively established that rTMS applied at high frequency to the left DLPFC has antidepressant efficacy greater than sham. The major continuing concern about this literature is whether studies have demonstrated a clinically relevant and sufficiently substantial clinical effect. One way to address this is to compare the effect sizes seen in trials to equivalent effect sizes seen with antidepressant medication strategies. O'Reardon et al. in their pivotal industry sponsored clinical trial calculated that the number needed to treat (NNT) (number of patients needed to treat to get one responder) for rTMS was 12 at 4 weeks and 9 at 6 weeks [21], not dissimilar to the NNT for antidepressant medications [25] calculated from a large data set [38]. It is worthy of note that a considerable number of rTMS trials have been conducted in

patients with high rates of treatment resistance. Rates of remission with medication treatment in patients who have failed to respond to more than two antidepressants are very low, as demonstrated in the large STAR*D study, most likely substantially less than 20 % (e.g. [39]).

4.2 Low-Frequency Right-Sided rTMS

High-frequency rTMS applied to the left DLPFC is not the only form of rTMS that has been systematically explored. Low-frequency stimulation (usually 1 Hz) applied to the right DLPFC has also been evaluated across a series of randomised controlled trials. In the first of these, conducted back in 1999, Klein et al. applied two relatively brief trains (1 min each), 3 min apart to the right DLPFC [17]. Patients were randomised to active or sham stimulation. Active stimulation was provided with a circular coil and generated a substantially greater improvement compared to sham stimulation. Since that time, a series of mostly relatively small studies have compared low-frequency right DLPFC stimulation to sham. These have used relatively divergent methods with some trials limited to the 120 pulses applied by Klein et al. but others extending up to 1,600 and 2,000 pulses per treatment session. Most trials have utilised standard figure of eight shape coils. The majority of these studies have shown positive antidepressant effects. This finding has been confirmed in a recent meta-analysis which demonstrated an effect size of 0.634 for active compared to sham stimulation [40]. This result appears robust as approximately 120 negative studies would be required to render the effect significant. Notably, within this analysis, the author compared the effect size apparent with low-frequency right-sided stimulation to that found in a previously conducted meta-analysis of left-sided high-frequency stimulation [29]. No differences were found, suggesting similar clinical effects. This is consistent with the findings of studies directly comparing the clinical effects of these forms of stimulation (e.g. [11]). Response to one type of rTMS does not seem to exclude the possibility of response to the other [41]. It is also possible that there are differences in the patients who would respond to either type, such that treatment could be individualised, but this has not been systematically investigated.

It is worthy of note that low-frequency stimulation should be safer than high-frequency stimulation as it reduces rather than increases cortical excitability, limiting further the risk of rTMS-related seizure induction [42]. As such, this might prove to be a useful therapeutic option in patients with increased risk of rTMS-related seizures. In our experience, across the conduct of the large number of clinical trials including both low- and high-frequency stimulation, generally low-frequency stimulation is better tolerated, associated with less scalp discomfort and fewer headaches. Occasionally patients who cannot continue with high-frequency stimulation have been able to receive a successful full course of low-frequency stimulation applied to right DLPFC.

4.3 Bilateral rTMS

A third possibility that has been explored is the application of rTMS in a bilateral fashion. This has been driven both by the observation of the efficacy advantage of bilateral ECT and a motivation to take advantage of the efficacy of both right- and left-sided treatment approaches. The first study that explored bilateral rTMS applied simultaneous high-frequency stimulation to both sides of the brain [18]. No significant differences during 3 weeks of treatment were seen between active and sham stimulation in this study.

The majority of subsequent bilateral trials have utilised the combination of low-frequency right-sided rTMS with high-frequency left-sided rTMS applied in a sequential fashion (sequential bilateral rTMS). The first study of this sort compared bilateral rTMS to high-frequency left-sided rTMS and a condition with high (10 Hz)- and low (1 Hz)-frequency rTMS both applied to left DLPFC [8]. No difference was found between the groups. However, this study was small, with a short 5-day period of treatment. A second study also showed no difference in response between bilateral and left-sided rTMS, but rTMS commenced concurrently with antidepressant medication treatment [16]. In a study where sequential bilateral rTMS was directly compared to sham condition over a 6-week treatment period, a substantially greater response to active stimulation was seen compared to sham [10]. In this study, almost 50 % of patients met response criteria and 36 % met criteria for clinical remission.

However, despite the positive effects seen in this latter study, subsequent reports have not convincingly demonstrated a consistent benefit of bilateral over unilateral treatment. One sham-controlled randomised study showed a greater response to bilateral compared to sham stimulation [43] but a similar sized study had exactly the opposite outcome [44]. In a much larger but not sham-controlled comparison, we found no difference between unilateral right-sided low-frequency rTMS and bilateral rTMS [27]. A second smaller study found an advantage of right over bilateral stimulation [45].

4.4 Other Approaches

4.4.1 Priming

There are potentially a variety of other approaches to the treatment of depression, some of which have been subject to limited evaluation. For example, although low-frequency stimulation has predominately been applied to right DLPFC, several studies have suggested that low-frequency stimulation applied to the left DLPFC may have antidepressant effects [9, 22, 46]. We have also demonstrated that bilateral 1 Hz stimulation appears to have antidepressant activity [27]. One study has also investigated the effects of low-frequency stimulation applied to the right parietal cortex and suggested that this novel approach does have antidepressant effects [47].

Another approach that may have value is the use of a 'priming' stimulation sequential combination. Priming stimulation involves the administration of a number of low-intensity high-frequency rTMS trains (usually subthreshold 6 Hz stimulation) prior to standard low-frequency rTMS [48]. The 6 Hz stimulation is proposed to 'prime' the cortex and enhance the reduction in excitability produced by low-frequency stimulation. One study has shown that right-sided priming stimulation may be more effective than low-frequency right-sided stimulation applied alone [49]. Priming with 6 Hz was suggested on the basis of physiological experiments. However, there may be other and potentially more effective methods of priming stimulation that have yet to be explored.

4.4.2 Theta Burst Stimulation (TBS)

Theta burst stimulation is a form of patterned TMS. It typically involves the application of very short (e.g. 3 pulses) high-frequency bursts, usually at 50 Hz. These bursts are repeated at theta frequency (usually 5 Hz). During continuous TBS (cTBS), stimulation is continued for 40 s in a single train. During intermittent TBS (iTBS), 2 s trains are repeated with 8 s intervals for a total time of typically 190 s. These forms of stimulation have opposite effects with iTBS producing an increase, and cTBS a decrease, in cortical excitability.

Studies using TBS in the motor cortex have shown that it can produce changes in cortical excitability with much briefer stimulation periods than with traditional rTMS [50]. Preliminary data suggest that TBS may have antidepressant effects, but substantial controlled trials have not yet been conducted [51]. The very brief periods of stimulation required during TBS are very attractive in regards to clinical applications. There certainly appears to be significant capacity to produce greater effects whilst still maintaining moderate treatment times. However, it may not be possible to substantially increase clinical effects by changing stimulation doses. One study has found that doubling the duration of iTBS results in a decrease in cortical excitability rather than an increase [52]. The same study found that increasing the length of stimulation with cTBS also reversed its effects. Considerable work is required to establish optimal TBS paradigms for clinical applications and to evaluate these in patients.

4.5 Other rTMS Methodological Issues

4.5.1 Treatment Targeting

The vast majority of clinical trials conducted with rTMS have utilised a relatively simplistic method for localising DLPFC. This method involves localising the motor cortical site for hand muscles and then measuring 5 cm anterior in a parasagittal line over the scalp surface (5 cm method) (see Chap. 7) [53]. However, research has demonstrated that this is likely to be inaccurate in a significant percentage of patients

[54]: in fact, a majority of patients may not receive stimulation in true DLPFC using this approach.

Several other localisation alternatives are possible, most using various forms of neuronavigation. Neuronavigational techniques most typically require the co-registration of the location of an individual's head to some form of digitised brain scan. Several hardware approaches to this form of co-registration are available which track the location of the head in three-dimensional space using either magnetic fields, infrared or other forms of optical localisation. The procedure is undertaken whereby an individual's head in three-dimensional space is co-registered to a previously obtained brain scan, usually an MRI. The hardware is then used to localise a site on the scalp surface that corresponds to the location on the MRI scan that the operator wishes to target for rTMS treatment.

Although research has clearly indicated that the 5-cm method is suboptimal for the targeting of rTMS stimulation to DLPFC, few studies have directly investigated the value of alternative approaches. One factor that restricts this capacity is knowing exactly where in DLPFC one should actually target stimulation.

4.5.1.1 Possible Anatomical Localisation

One approach would be to base stimulation targeting on the known structural neuroanatomy of a relevant target area. In regard to structural neuroanatomy, the boundaries of DLPFC were originally described by Brodmann during the dissection of a single brain in the 1900s (areas 9 and 46). These regions are relatively expansive across the superior, middle and inferior frontal gyri. A more recent redefinition of areas 9 and 46 based on the dissection of multiple brains produced a more narrowly defined area [55]. Area 9 is predominately contained within the superior frontal gyrus across an expanse of approximately 2.5 cm. Area 46 is localised over the middle portion of the middle frontal gyrus with an anterior–posterior extension of approximately 2 cm. The total volume of DLPFC based on this definition exceeds the area that is likely to be stimulated by standard TMS coils: however, stimulation over the junction of these two regions is likely to produce stimulation of a significant proportion of DLPFC as defined in this way.

4.5.1.2 Functional Localisation

Given that DLPFC is a relatively extensive area, a second neuronavigational approach would be to target stimulation based on knowledge from functional imaging of the regions within DLPFC that are known to be abnormally active in depressive states. A considerable range of functional neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have explored brain regions involved in depression – regions that change with successful medication treatment and regions activated by various emotional and cognitive tasks. Unfortunately, these studies have produced a relatively diverse range of results that are somewhat hard to integrate. Studies have attempted to quantitatively integrate the results of these studies to better identify a target within DLPFC for rTMS treatment but have not clearly identified one unique and clearly superior target [56]. A second approach using neuroimaging is not to look for a global target

but to utilise neuroimaging scans in individual subjects to choose stimulation sites for each individual patient.

4.5.1.3 Assessment of Neuronavigational Approaches

Only one study has substantially explored the value of treatment targeting based on structural landmarks using a neuronavigational tool [57]. In this study, all subjects underwent the 5-cm localisation procedure as well as an MRI-based neuronavigational process identifying the site of the junction between Brodmann area 9 and 46 as defined by Rajkowska et al. [55]. They were then randomised to have treatment at one or other of these sites. Depression improved in both patient groups but to a significantly greater degree in the patients receiving treatment at the neuronavigational site. Notably, the neuronavigational site was more anterior and somewhat more lateral than the site identified using the 5-cm method.

In regard to functional neuroimaging, several studies have attempted to target treatment based upon areas of hypometabolism on PET scanning [58, 59]. These studies have generally not found an improved treatment response based on PET metabolism data although [59] did support the notion of targeting DLPFC based on structural neuroimaging. Finally, one study has indicated that a more anterior and lateral coil location is associated with better antidepressant response [60].

Although there is a suggestion in this research that neuronavigational approaches may improve treatment response, it is possible that enhanced outcomes may be achieved just by changing the site of stimulation, rather than having to individually identify the target with neuronavigation. A number of these neuronavigation studies have suggested that the optimal site of stimulation is likely to be more anterior and perhaps more lateral to that typically identified by the 5-cm method. The 5-cm method clearly also does not take into account variation in individual head size. These limitations may be overcome by an approach that takes head size into account and produces a more anterior stimulation target but does not require scanning of every subject. An example of this would be the use of EEG localisation sites, such as the use of specific EEG points [61, 62]. This approach would be relatively easy to adapt into clinical practice but does require specific assessment prior to its widespread use.

Neuronavigational Coil Localisation

A number of systems are commercially available for the neuronavigational localisation of TMS stimulation, although most have been predominately developed for research applications and are not necessarily set up for easy translational use in clinical practice. These systems typically map the position of the head (and hence the brain) to a reference MRI image. Once this mapping has occurred, the software will represent the relationship of a sensor, or TMS equipment the sensor is attached to, to the MRI image of the brain. This allows the user to identify accurately where the TMS coil is to be placed in reference to the brain scan rather than just the scalp surface. Some systems will then allow for the position of the coil and its orientation to be tracked during stimulation.

4.5.2 Altered Coil Design and Profile of Stimulation

Initial rTMS studies used large round coils that produced an area of stimulation that was difficult to target. The vast majority of rTMS depression clinical trials have utilised standard figure of eight coil designs that produce stimulation of approximately 1–2 cm^2 of tissue but limited cortical penetration. More recently, technology has been developed to produce substantially deeper stimulation, for example, of the more orbital medial, cingulate or insula cortical regions. This so-called deep TMS is done with a novel coil design that produces more widespread cortical stimulation with substantial penetration into deeper brain regions [63, 64]. Preliminary data appears promising [65] and controlled trials are underway. A recent paper reported an open-label study which included 4 weeks of acute treatment and 18 weeks of continuation treatment [66]. The remission rate at the end of the initial 4 weeks was only 27 %, but this had improved to over 70 % at the end of the study.

4.6 Issues with the Conduct of Clinical Trials of rTMS

One of the main issues with the conduct and interpretation of clinical rTMS trials from the outset has been the methodology of sham or placebo stimulation. All of the earlier rTMS trials used some variation of a method whereby a standard rTMS coil is placed on the head but angled away such that the majority of the produced magnetic field was not oriented in towards the brain. If the coil is angled correctly, some degree of scalp nerve stimulation may be produced mimicking in part the sensation produced with active TMS. The most common variations of this technique involved one of the two wings of the coil touching the scalp with the coil angled away from the scalp at either 45° or 90°. Studies investigating the capacity of this type of stimulation to act as an effective placebo were conducted in the early 2000s. For example, Lisanby et al. showed that tilting the coil away from the scalp from one wing would markedly attenuate the magnetic stimulation produced in the brain [67], and this method was widely adopted. They also demonstrated that tilting the coil forward across both wings did not substantially reduce the degree of intracortical stimulation; this approach should clearly be avoided.

In more recent years, a variety of new approaches have been developed and adopted. Neuronetics Ltd developed an active and sham coil system for their pivotal registration trial, which involved the use of a known active coil for the measurement of motor thresholds followed by the randomisation to either one of two coils, one of which was active and one of which was sham, for the provision of clinical trial treatment. The active and sham coils were identical in appearance in an attempt to maintain the blind of treaters as well as patients. Another approach has been the development of combined TMS and electrical stimulation systems. In this approach, electrical stimulation of the scalp would be used to produce scalp sensation during sham TMS stimulation [68, 69]. Systems utilising this approach are now commercially available, for example, from MagVenture A/S.

Variation in the quality of sham stimulation used in rTMS trials has led to some concern about interpretation of the results of many of these. Regardless of the form of sham stimulation utilised, the greatest reassurance about the quality of sham stimulation adopted can come when efforts are made to formally assess whether blinding has effectively been maintained. Studies are increasingly utilising methods to assess whether patients have successfully remained blind although future research should also include adequate assessment of the blinding of raters and potentially treaters.

Conclusions

A variety of methods utilising rTMS treatment for depression have been developed over the last 15 years. An extensive series of studies have evaluated the use of high-frequency stimulation applied to the left dorsolateral prefrontal cortex. This research clearly demonstrates the short-term efficacy of this technique. There is also good evidence for the efficacy of low-frequency stimulation applied to the right DLPFC, although this form of rTMS has not been the subject of large-scale sham-controlled multisite trials. A variety of new approaches, including theta burst stimulation, deep TMS and neuronavigationally targeted TMS, may potentially offer significant advances on standard techniques but require further evaluation.

References

1. Grisaru N, Yaroslavsky U, Abarbanel JM, Lamberg T, Belmaker RH (1994) Transcranial magnetic stimulation in depression and schizophrenia. Eur Neuropsychopharmacol 4:287–288
2. George MS, Ketter TA, Post RM (1994) Prefrontal cortex dysfunction in clinical depression. Depression 2:59–72
3. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL et al (1997) Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 154(12):1752–1756
4. Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996) Rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348:233–237
5. Avery DH, Holtzheimer PE 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL et al (2006) A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 59(2):187–194
6. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS et al (2000) A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry 47(4):332–337
7. Cohen CI, Amassian VE, Akande B, Maccabee PJ (2003) The efficacy and safety of bilateral rTMS in medication-resistant depression. J Clin Psychiatry 64(5):613–614
8. Conca A, Di Pauli J, Beraus W, Hausmann A, Peschina W, Schneider H et al (2002) Combining high and low frequencies in rTMS antidepressive treatment: preliminary results. Hum Psychopharmacol 17(7):353–356
9. Feinsod M, Kreinin B, Chistyakov A, Klein E (1998) Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. Depress Anxiety 7(2):65–68

10. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J (2006) A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 163(1):88–94
11. Fitzgerald PB, Brown T, Marston NAU, Daskalakis ZJ, Kulkarni J (2003) A double-blind placebo controlled trial of transcranial magnetic stimulation in the treatment of depression. Arch Gen Psychiatry 60:1002–1008
12. Geller V, Grisaru N, Abarbanel JM, Lemberg T, Belmaker RH (1997) Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 21(1):105–110
13. George MS, Wasserman EM, Kimbrell TA et al (1997) Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 154:1752–1756
14. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P et al (1995) Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6:1853–1856
15. Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R et al (2000) Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry 47(4):314–324
16. Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler K, Lechner T et al (2004) No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. J Neurol Neurosurg Psychiatry 75(2):320–322
17. Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999) Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. Biol Psychiatry 46(10):1451–1454
18. Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC et al (2003) Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. Psychol Med 33(1):33–40
19. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S (1999) Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry 156:946–948
20. Menkes DL, Bodnar P, Ballesteros RA, Swenson MR (1999) Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case–control pilot study of safety and efficacy. J Neurol Neurosurg Psychiatry 67:113–115
21. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216
22. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD et al (1999) Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res 88(3):163–171
23. Daskalakis ZJ, Levinson AJ, Fitzgerald PB (2008) Repetitive transcranial magnetic stimulation for major depressive disorder: a review. Can J Psychiatry 53(9):555–566
24. Gross M, Nakamura L, Pascual-Leone A, Fregni F (2007) Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 116(3):165–173
25. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516
26. Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G et al (2007) Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 191:441–448
27. Fitzgerald PB, Hoy K, Gunewardene R, Slack C, Ibrahim S, Bailey M et al (2010) A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. Psychol Med 7:1–10

28. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ (2006) A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol 9(6):655–666
29. Schutter DJ (2009) Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 39(1):65–75
30. Slotema CW, Blom JD, Hoek HW, Sommer IE (2010) Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? a meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 71(7):873–884
31. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M (2000) Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. Int J Neuropsychopharmacol 3(2):129–134
32. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J et al (2002) Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry 51(8):659–667
33. Grunhaus L, Dannon P, Schreiber S (1998) Effects of transcranial magnetic stimulation on severe depression. Similarities with ECT. Biol Psychiatry 43:76S
34. Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG et al (2007) A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry 164(1):73–81
35. Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO et al (2006) Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar nonpsychotic refractory depression: a randomized, single-blind study. Int J Neuropsychopharmacol 9(6):667–676
36. McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D et al (2007) The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. Health Technol Assess 11(24):1–54
37. Fitzgerald P (2004) Repetitive transcranial magnetic stimulation and electroconvulsive therapy: complementary or competitive therapeutic options in depression? Australas Psychiatry 12(3): 234–238
38. Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG et al (2005) Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry 66(8):974–981
39. Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE, McGrath PJ et al (2006) A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. Am J Psychiatry 163(7):1161–1172
40. Schutter DJ (2010) Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Psychol Med 40(11):1789–1795
41. Fitzgerald PB, McQueen S, Herring S, Hoy K, Segrave R, Kulkarni J et al (2009) A study of the effectiveness of high-frequency left prefrontal cortex transcranial magnetic stimulation in major depression in patients who have not responded to right-sided stimulation. Psychiatry Res 169(1):12–15
42. Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117(12):2584–2596
43. Blumberger DM, Mulsant BH, Fitzgerald PB, Rajji TK, Ravindran AV, Young LT et al (2012) A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. World J Biol Psychiatry 13(6):423–435
44. Fitzgerald PB, Hoy KE, Herring SE, McQueen S, Peachey AV, Segrave RA et al (2012) A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. J Affect Disord 139(2):193–198

45. Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L (2010) Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? Neuroscience 167(2):323–328
46. Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P et al (2009) Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. J Affect Disord 115(3):386–394
47. Schutter DJ, Laman DM, van Honk J, Vergouwen AC, Koerselman GF (2009) Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. Int J Neuropsychopharmacol 12(5):643–650
48. Iyer MB, Schleper N, Wassermann EM (2003) Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23(34):10867–10872
49. Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G et al (2008) Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. J Clin Psychopharmacol 28(1):52–58
50. Paulus W (2005) Toward establishing a therapeutic window for rTMS by theta burst stimulation. Neuron 45(2):181–183
51. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E (2010) Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int J Neuropsychopharmacol 13(3):387–393
52. Gamboa OL, Antal A, Moliadze V, Paulus W (2010) Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204(2):181–187
53. Schonfeldt-Lecuona C, Lefaucheur JP, Cardenas-Morales L, Wolf RC, Kammer T, Herwig U (2010) The value of neuronavigated rTMS for the treatment of depression. Neurophysiol Clin 40(1):37–43
54. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C (2001) Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 50(1):58–61
55. Rajkowska G, Goldman-Rakic PS (1995) Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. Cereb Cortex 5(4):323–337
56. Fitzgerald PB, Oxley TJ, Laird AR, Kulkarni J, Egan GF, Daskalakis ZJ (2006) An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res 148(1):33–45
57. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R et al (2009) A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 34(5):1255–1262
58. Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M et al (2003) Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. J Psychiatr Res 37(4):267–275
59. Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F et al (2010) Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. Int J Neuropsychopharmacol 13(1):45–59
60. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F et al (2009) More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. Biol Psychiatry 66(5):509–515
61. Fitzgerald PB, Maller JJ, Hoy KE, Thompson R, Daskalakis ZJ (2009) Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul 2:234–237
62. Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ (2009) Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul 2(4):234–237
63. Deng ZD, Peterchev AV, Lisanby SH (2008) Coil design considerations for deep-brain transcranial magnetic stimulation (dTMS). Conf Proc IEEE Eng Med Biol Soc 2008:5675–5679

64. Salvador R, Miranda PC, Roth Y, Zangen A (2007) High-permeability core coils for transcranial magnetic stimulation of deep brain regions. Conf Proc IEEE Eng Med Biol Soc 2007: 6653–6656
65. Rosenberg O, Shoenfeld N, Kotler M, Dannon PN (2010) Deep TMS in a resistant major depressive disorder: a brief report. Depress Anxiety 27(5):465–469
66. Harel EV, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y (2012) H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: an 18-week continuation safety and feasibility study. World J Biol Psychiatry. Epub 2012/02/07
67. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA (2001) Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry 49(5):460–463
68. Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H et al (2008) Development and evaluation of a portable sham TMS system. Brain Stimul 1(1):52–59
69. Mennemeier M, Triggs W, Chelette K, Woods A, Kimbrell T, Dornhoffer J (2009) Sham transcranial magnetic stimulation using electrical stimulation of the scalp. Brain Stimul 2(3):168–173

Clinical Indications and Patient Selection 5

5.1 Stage of Illness and Treatment Resistance

There are a variety of times during the evolution of depressive illness when patients may potentially present for rTMS treatment. This could include during the initial episode of depression, during depressive relapse, during a period of persistent treatment-resistant depression or possibly when well, in regards to maintenance therapy. There is varying depth in the data that informs the use of rTMS across differing illness stages. It is reasonable to extrapolate potential efficacy across these stages, but sensible decisions about the likelihood of response should be based upon the balanced judgement of the accumulated experience of rTMS treatment in the stage of illness being considered.

There are a variety of established treatment options for patients with depressive disorders. Approximately 40 % of patients with an index episode of depression will respond to a single course of an antidepressant treatment, an additional 30 % to multiple antidepressants and augmentation strategies [1]. Systematic, equivalent data on response rates to psychological treatments is not available. However, it is reasonable to assume that a substantial proportion of individuals will not be suitable for these approaches or will continue to experience depressive symptoms despite adequate therapy. These groups of patients are typically regarded as having treatment-resistant depression (TRD).

Patients with treatment-resistant depression have been the focus of a substantial bulk of the rTMS antidepressant research. However, there is considerable variation in methods used to define TRD [2] and this has affected the consistency and clarity of the definition of patient populations across treatment trials. Some trials have considered treatment-resistant patients as those who have failed as few as two antidepressant medication trials. Stricter definitions expand the number of failed trials and/or require these to have come from at least two separate medication classes. Tools such as the Antidepressant Treatment History Form (ATHF), the Thase and Rush staging model (TRSM) and the Massachusetts General Hospital staging model (MGH-S) have been developed to assist in the characterisation of individuals as treatment resistant but have differing psychometric properties [3]. However, any of

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_5,

these are likely to provide assistance in the process of the assessment of patients for rTMS treatment. It is important to gain information on a series of clinical features of past treatment failure as part of this process (see Box 5.1).

Box 5.1. Characteristics of Previous Biological Treatment Trials

1. Number of medication trials in current episode
2. Number of lifetime failed trials
3. Duration of each trial
4. Degree of clinical response (absent/partial/complete)
5. Maximal dose of medication prescribed in relation to therapeutic and maximally recommended doses
6. Number of drug classes covered by medication trials
7. Number of augmentation strategies utilised
8. Characteristics of ECT courses: laterality, stimulation location, pulse parameters, number of treatments, seizure characteristics

Despite a large number of rTMS trials having been conducted in patients who have failed a substantial number of medication trials, registration for rTMS in the USA was based on data from a comparison of antidepressant response between TMS and sham stimulation in patients who had failed to respond to only one antidepressant medication. There is certainly a suggestion in the literature that a lesser number of failed medication trials are a positive predictor of likely antidepressant response (e.g. [4, 5]). However, several large studies have failed to confirm this relationship (e.g. [6]). On the basis of this literature, although it would seem to be favourable to make rTMS treatment available relatively early in the course of a treatment history, patients should not be excluded or dissuaded from treatment when they have failed a greater number of treatment episodes. In our experience, we have seen patients who have failed large numbers of medication trials respond to rTMS. We have also seen patients respond following a failed course of ECT, something that we thought initially was unlikely to be the case. The mechanisms of action of rTMS and ECT are likely to vary significantly, and at this stage, there is no indication of any degree of overlap in the patients likely to respond to either. Therefore, a course of rTMS should still be considered, especially as once patients have failed ECT, they have few other treatment options.

It is also inevitable that as rTMS becomes increasingly available questions will arise as to whether it should be presented as a first-line treatment option. Clearly no comparative data has been obtained as to the relative efficacy, or the efficacy compared to sham, in this early population. rTMS is a more involved, time-consuming and most likely more expensive procedure than antidepressant medication, and as such the market for it as first-line treatment is likely to be limited. However, there is a significant percentage of the population who are resistant to the idea of taking medication for the treatment of depression, and for some of these patients, rTMS

may be an attractive option. In addition, it is possible to speculate that early intervention with a non-medication treatment such as rTMS may avoid medication-related complications and enhance brain plasticity in a way that ultimately improves long-term outcomes for patients with depression.

5.1.1 Clinical Recommendations

It appears reasonable for rTMS to be available as an option to patients with varying degrees of failure to respond to antidepressant strategies. However, response rates are likely to be higher in patients with lesser degrees of treatment resistance. It is possible that earlier intervention with rTMS may enhance longer-term outcomes, but further research, particularly focused on medication naive subjects, is required to establish this.

5.2 Illness Type: Unipolar and Bipolar Depression

Most clinical trials investigating the effectiveness of rTMS have predominately or exclusively enrolled patients with unipolar major depressive disorder. For example, the two largest multisite sham-controlled rTMS studies conducted to date excluded patients with bipolar disorder [7, 8]. Some studies, however, have included both patients in the depressive phase of bipolar disorder and those with unipolar depression. Within these trials, no analyses have suggested that a bipolar diagnosis is a negative predictor of the likelihood of clinical response. In one study of low-frequency stimulation applied to the right prefrontal cortex, patients with bipolar disorder had a substantially higher response rate (almost 70 %) than the overall group (51 %) [6]. However, most studies do not provide this sort of separate analysis to allow sufficient inferences to be made about the relative efficacy of rTMS subtypes in bipolar disorder. There is also a considerable lack of studies that have directly explored the antidepressant efficacy of rTMS in bipolar disorder alone.

In the first of these few studies, 20 patients were randomised to active or sham stimulation provided over 20 treatment sessions [9]. There was a significant improvement in depression with active but not sham stimulation. A second small study enrolled 23 patients and provided 5 Hz stimulation to the left DLPFC but failed to find a significant benefit of active stimulation over sham [10]. A third study, this time open label, provided low-frequency stimulation applied to the right DLPFC [11]. Six of 11 patients responded and four achieved remission. A number of the patients with a greater degree of response remained well over a 12-month follow-up [12]. A more recent study included 19 patients with bipolar disorder who received open-label active rTMS using a novel coil providing deeper brain stimulation [13]. A significant improvement in depression was seen with a response rate greater than 60 %. Of note, one patient experienced a generalised seizure during this trial.

A number of reports have described switching to mania in patients receiving rTMS treatment for bipolar depression (e.g. [14–17]). However, the overall risk of

this appears to be low, and potentially no higher than that seen with sham stimulation [18]. No studies have systematically investigated whether the co-prescription of mood stabilisers reduces the possibility of a manic switch. However, in the absence of evidence that these medications can affect the efficacy of rTMS treatment, provision of mood-stabilising medication would be sensible in any patients who have previously experienced substantial manic symptoms. This would particularly include patients whose past symptoms required hospitalisation or resulted in significant risks to the individual or others. The degree to which the patient can be monitored throughout the treatment course should also be taken into consideration. rTMS treatment should be withheld when manic symptoms are first evident during a course of treatment or when there is a dramatic shift in the level of mood symptoms.

Early research did investigate the possible treatment of mania with rTMS. In a small early study, manic symptoms appeared to be preferentially reduced with the provision of high-frequency rTMS to the right DLPFC compared to the left DLPFC [19]. Two subsequent case series showed promising results with right-sided high-frequency stimulation [20, 21], but when right DLPFC rTMS was compared to sham stimulation, no differences were seen [22]. More recently and in contrast to this earlier research, a larger sham-controlled study of 41 patients has shown a substantial anti-manic effect of right-sided high-frequency stimulation [23].

5.2.1 Clinical Recommendations

The vast majority of rTMS research has focused on the treatment of unipolar major depression. However, there is reasonable support at this stage for the use of rTMS in the treatment of patients with bipolar depression, especially given the clinical challenges with the management of this condition. The use of concurrent mood stabiliser medication should be carefully considered in patients with a history of substantial manic episodes and all patients monitored for the emergence of manic symptoms during treatment. The use of rTMS to treat mania is an area that requires further research before conclusions can be drawn on its clinical utility.

5.3 Elderly Patients with Depression

Depression, and especially treatment resistance, is clearly an important issue in the elderly [24]. Treatment resistance is more common in elderly patients with depression, and there are increasing complications with the use of other antidepressant modalities, including drug-to-drug interactions [25]. However, this importance has not been reflected in rTMS research, with only a minimal body of work investigating the usefulness of rTMS in this patient population. Studies conducted to date consist only of several open case series and several small underpowered and probably ‘underdosed’ clinical trials. In the former category, 49 elderly patients (mean age 69 years) received left- or right-sided rTMS. Treatment dose was quite variable and sometimes low (in some patients at 80 % of the RMT) [26]. However, there was

a significant overall reduction in depression symptoms, and nine patients achieved response criteria. Conversely, a small randomised trial specifically conducted in elderly subjects (mean age 60 years) failed to show differences between active and sham stimulation [27]. However, treatment was only provided for 5 days and, based on pulse number and intensity, at very low dose. A second small trial provided treatment for 10 days but again at relatively low dose and in a small sample of only 24 patients. No differences between active and sham stimulation were found [28].

Based on an initial observation that elderly patients may not respond to rTMS to the same degree, it has been hypothesised that compared with younger patients, the elderly have a greater scalp-to-cortex distance in frontal areas relative to motor cortex. This would result in a lower degree of magnetic stimulus penetration. One approach to address this involves the measurement of scalp-to-cortex distance on MRI scanning in DLPFC and motor cortex. An adjustment of stimulus intensity is then made to take into account differences in motor cortex and frontal cortex scalp-to-cortex distance. Nahas et al. investigated this approach in 18 treatment-resistant elderly subjects (mean age 61 years) [29]. The applied intensities ranged up to 141 % of the RMT. Five of the 18 patients responded to the adjusted treatment, but no comparison was made with non-adjusted rTMS. In an open-label trial, 6 out of 20 patients (mean age 66.8 years) responded to 2 weeks of treatment [30].

Some information about the potential benefit of rTMS treatment in the elderly may come from the analysis of age effects in larger treatment samples. In several large studies we have conducted, there has been no relationship evident between age and a poorer response to rTMS treatment (e.g. [6, 31]). In a recent open-label study of 130 patients treated in a naturalistic setting, there was also no relationship found between clinical response and age [32]. Anecdotally, we have treated patients with depression across the elderly spectrum including patients in their late 80s and early 90s. Treatment has been well tolerated, with no substantial difference in patient experiences or response compared with younger subjects. No adjustment for scalp-to-cortex distance was made in any of these larger studies.

5.3.1 Clinical Recommendations

Treatment-resistant depression in the elderly is common and other treatment alternatives can be frequently difficult to administer. rTMS should be considered as a treatment option in this age group although efficacy is not yet supported by substantial randomised trials. Further research is required to understand whether dose adjustments based on scalp-to-cortex distance enhance clinical outcomes.

5.4 Adolescent Depression

A very limited literature has explored the potential use of rTMS in the treatment of depression in adolescents. The first published paper described the treatment of three adolescent patients and four 18-year-olds with 2 weeks of high-frequency stimulation

applied to the left DLPFC [33]. A relatively low dose of stimulation was used (1,600 pulses per session). Two of the three adolescent patients improved with treatment. A subsequent report evaluated treatment efficacy in two adolescent patients provided with a slightly higher dose of rTMS treatment (2,000 pulses per day) with clinical response seen in both patients [34]. A third case series included five subjects younger than 18 [35]. Each patient received 14 treatment sessions (400 pulses per session). Three of the five patients had a significant reduction in depressive symptoms. No major adverse events were reported in any of the patients described in this case series. However, a recent report described the development of a generalised seizure in a 16-year-old female patient during the first session of a planned course of rTMS treatment [36]. The patient had no predisposing factors for the development of a seizure but was receiving 100 mg of sertraline per day at the time. The authors of this case report do not describe a clear progression of tonic–clonic activity, and it is possible that the event was a syncopal seizure. Notably, the dose of rTMS provided in this case was quite low (4 s 10 Hz trains at 80 % of the motor threshold). It has been proposed that the seizure threshold may be lower in this age group, extrapolating from the situation with ECT [37]. However, this has not been systematically studied. Over 1,000 subjects under 18 have received single- or paired pulse TMS in investigative studies without the report of any seizures [38]. However, two adolescents receiving TMS in a stroke study were reported to have experienced a syncopal event [39], and practitioners should be aware of this possibility, especially where there is a history of syncope with other procedures such as injections.

5.4.1 Clinical Recommendations

Limited systematic research has explored the use of rTMS in the treatment of depression in adolescents. Practitioners should be aware of the possibility of syncope and potentially a lower seizure threshold. rTMS presents as a potentially promising way to avoid the early use of medications treatments but should not be adopted until evaluated adequately.

5.5 Pregnant or Breastfeeding Patients

The presentation of patients with depression in the antenatal or postnatal period often poses significant management challenges. There are frequently concerns about the potential impact of antidepressant medications during these periods, and ECT is often avoided during pregnancy due to concerns about the anaesthetic and the seizure itself. Given that the magnetic field produced with a TMS device is very localised, it is unlikely that a foetus would experience significant exposure to a substantial magnetic field if rTMS was applied during pregnancy. There are clearly no child safety issues with postnatal rTMS provision. As such, rTMS treatment appeals as an alternative option for the treatment of depression presenting in the antenatal and postnatal periods. However, limited research to date has explored the use of rTMS applied at these times, and the rTMS option should be evaluated carefully for each individual.

In regard to pregnancy, a number of case reports have been published since 1999, with no evidence of major adverse events (e.g. [40]). A more recent report described a case series of 10 patients treated during the second or third trimester [41]. These patients received low-frequency right-sided rTMS in up to 20 treatment sessions with seven experiencing clinical response. No adverse maternal or foetal outcomes emerged. One recent study has explored the potential acceptability of rTMS treatment to pregnant women [42]. Researchers surveyed 500 pregnant women and a second sample of 51 women who were exposed to an educational video providing information about rTMS treatment. rTMS was not considered acceptable in the first study but was considered acceptable by 15.7 % of the second sample after provision of the information video.

A similarly narrow range of research has explored the use of rTMS in postpartum depression. One case report described the use of rTMS in the successful postpartum management of a patient with bipolar disorder where rTMS was used for both the treatment of mania and depression [43]. One case series has described the management of nine antidepressant-free women with postpartum depression treated with high-frequency left DLPFC rTMS over 4 weeks [44]. Eight patients achieved remission of depression during acute treatment. Seven of these remained in remission after 6 months without further psychiatric treatment.

Despite these promising initial findings, rTMS treatment in pregnancy or the postpartum period should proceed cautiously. Although it is unlikely that an unborn foetus would be exposed to substantial magnetic fields, it is possible that hormonal changes induced by rTMS could have adverse effects, and this will require systematic research. rTMS could also induce changes in the hormonal profile of breast milk. In addition, provision of rTMS during pregnancy may require the more careful monitoring of motor thresholds and rTMS dose as hormonal fluctuations may affect cortical excitability over time.

5.5.1 Clinical Recommendations

Limited research has evaluated the use of rTMS in pregnancy or the postpartum period to date. However, there are strong reasons to avoid other biological treatments during these times. This is likely to lead to the consideration of the use of rTMS in spite of the limited evidence available for its use. Provision of rTMS under these circumstances should include a careful assessment of the risks and potential benefits of both rTMS and other treatment alternatives. Further research is clearly required in this area.

5.6 Concurrent Illness: Neurological Disease

A small literature has begun to explore whether rTMS is safe and has efficacy in the treatment of patients with depression in the context of substantive comorbid neurological conditions. Depression is a commonly occurring comorbidity in several neurological illnesses. For example, depression is common in the context of the development and persistence of Parkinson's disease [45]. In the first rTMS study to address this clinical

group, Dragasevic et al. provided low-frequency frontal rTMS to ten depressed subjects producing a significant reduction in depression despite a low dose of stimulation. A second open-label study also reported a significant reduction in depression, this time with high-frequency stimulation applied in 14 patients [46]. A small ($n=22$), sham-controlled study of 5 Hz prefrontal DLPFC rTMS also supported the antidepressant effects of rTMS in depression in patients with Parkinson's disease [47].

In a similar manner, open-label data has been collected on the use of rTMS in the treatment of vascular depression or depression that presented following stroke. Jorge et al. randomised 92 patients with depression and substantive vascular disease to active or sham left DLPFC rTMS [48]. Substantial antidepressant effects were seen with active treatment in two dose groups compared to sham. In the first trial in post-stroke depression, antidepressant effects greater than sham were seen in a small group of patients receiving 10 Hz stimulation to the left DLPFC [49]. These findings were confirmed in a subsequent double-blind study, which compared 1 Hz rTMS, 10 Hz rTMS and sham stimulation in patients with post-stroke depression [50]. High-frequency stimulation resulted in improved depression scores although no cognitive improvements were evident.

A third condition that is beginning to be explored is the presentation of depression subsequent to a brain injury. This appears to be a relatively common occurrence, but a history of dramatic head injury has frequently been an exclusion criterion in rTMS treatment trials. No clinical trial data has yet been published in this area, although a case report described promising early results [51].

5.6.1 Clinical Recommendations

The presence of an underlying or comorbid neurological disease such as stroke or Parkinson's disease does not appear to prevent the possibility of successful response to rTMS treatment. The use of rTMS treatment under these circumstances should be balanced against any potential increased risks of seizure induction related to the underlying disease entity with the substantial potential benefits if clinical response is achieved.

5.7 Other Factors

There are a number of other factors that may influence the likelihood of a successful course of rTMS treatment. There are clearly some individuals who for physiological or personality reasons are substantially more sensitive to pain or discomfort and will struggle to tolerate a course of rTMS treatment. Likewise, there are individuals who are more likely to experience headaches resulting from rTMS treatment and have difficulty tolerating this. These issues are probably more likely in patients with a history of significant pain problems and caution should be taken when initiating treatment in individuals with a history of substantial pre-existing headaches. In individuals like this, a slowly increasing stimulus intensity should be considered and low-frequency right-sided rTMS may be a sensible treatment option.

Pre-existing neck pain can also complicate a course of rTMS treatment. Patients are required to sit still for a significant period of time, and unless the neck is adequately supported, this may lead to significant discomfort. Under these circumstances, care should be taken to ensure that the patient is in a comfortable position at all times. The patient may need to have brief breaks during each treatment session to minimise the development of muscle spasm.

The presence of significant psychiatric comorbidity may also limit the likelihood of treatment response although this has not been systematically evaluated in many studies. In our clinical experience, comorbid anxiety symptoms may improve with the successful resolution of depression treated with rTMS, but this is not always the case. When anxiety symptoms persist this is likely to have a long-term negative impact on the patient's mood and contribute to earlier depressive relapse. In our experience, comorbid obsessive-compulsive symptoms are typically not successfully alleviated with standard rTMS depression protocols.

References

1. Fava M (2003) Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53(8):649–659
2. Ruhe HG, van Rooijen G, Spijker J, Peeters FP, Schene AH (2012) Staging methods for treatment resistant depression. A systematic review. J Affect Disord 137(1–3):35–45, Epub 2011/03/26
3. Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990) The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 10(2):96–104, Epub 1990/04/01
4. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A et al (2009) Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 34(2):522–534, Epub 2008/08/16
5. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO et al (2006) Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol 9(6):641–654, Epub 2006/08/31
6. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ (2006) A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol 9(6):655–666, Epub 2006/09/09
7. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516, Epub 2010/05/05
8. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216
9. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L (2002) Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. Bipolar Disord 4(Suppl 1):94–95
10. Nahas Z, Kozel FA, Li X, Anderson B, George MS (2003) Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. Bipolar Disord 5(1):40–47
11. Dell'Osso B, Mundo E, D'Urso N, Pozzoli S, Buoli M, Ciabatti M et al (2009) Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. Bipolar Disord 11(1):76–81, Epub 2009/01/13

12. Dell'osso B, D'Urso N, Castellano F, Ciabatti M, Altamura AC (2011) Long-term efficacy after acute augmentative repetitive transcranial magnetic stimulation in bipolar depression: a 1-year follow-up study. J ECT 27(2):141–144, Epub 2010/10/23
13. Harel EV, Zangen A, Roth Y, Reti I, Braw Y, Levkovitz Y (2011) H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study. World J Biol Psychiatry 12(2):119–126, Epub 2010/09/22
14. Garcia-Toro M (1999) Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression. Br J Psychiatry 175:491, Epub 2000/05/02
15. Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, Walpoth M, Rupp CI, Hinterhuber H et al (2004) Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? A case report. J Clin Psychiatry 65(11):1575–1576, Epub 2004/11/24
16. Huang CC, Su TP, Shan IK (2004) A case report of repetitive transcranial magnetic stimulation-induced mania. Bipolar Disord 6(5):444–445, Epub 2004/09/24
17. Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A et al (2003) Induction of mania by rTMS: report of two cases. Eur Psychiatry 18(4):196–198, Epub 2003/06/20
18. Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ et al (2008) Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol 11(1):119–130, Epub 2007/03/06
19. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH (1998) Transcranial magnetic stimulation in mania: a controlled study. Am J Psychiatry 155(11):1608–1610, Epub 1998/11/13
20. Saba G, Rocamora JF, Kalalou K, Benadhira R, Plaze M, Lipski H et al (2004) Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients. Psychiatry Res 128(2):199–202, Epub 2004/10/19
21. Michael N, Erfurth A (2004) Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. J Affect Disord 78(3):253–257, Epub 2004/03/12
22. Kaptsan A, Yaroslavsky Y, Applebaum J, Belmaker RH, Grisaru N (2003) Right prefrontal TMS versus sham treatment of mania: a controlled study. Bipolar Disord 5(1):36–39, Epub 2003/03/27
23. Praharaj SK, Ram D, Arora M (2009) Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a randomized sham controlled study. J Affect Disord 117(3):146–150, Epub 2009/01/31
24. Bonner D, Howard R (1995) Treatment-resistant depression in the elderly. Int Psychogeriatr 7(Suppl):83–94, Epub 1995/01/01
25. Baldwin RC, Simpson S (1997) Treatment resistant depression in the elderly: a review of its conceptualisation, management and relationship to organic brain disease. J Affect Disord 46(3):163–173, Epub 1998/04/18
26. Milev R, Abraham G, Hasey G, Cabaj JL (2009) Repetitive transcranial magnetic stimulation for treatment of medication-resistant depression in older adults: a case series. J ECT 25(1): 44–49, Epub 2008/07/31
27. Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG (2001) A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. Int Psychogeriatr 13(2):225–231, Epub 2001/08/10
28. Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Muri RM, Berkhoff M et al (2004) Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. Psychiatry Res 126(2):123–133, Epub 2004/05/05
29. Nahas Z, Li X, Kozel FA, Mirzki D, Memon M, Miller K et al (2004) Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55–75 years of age: a pilot study. Depress Anxiety 19(4):249–256, Epub 2004/07/27
30. Abraham G, Milev R, Lazowski L, Jokic R, du Toit R, Lowe A (2007) Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression - an open label trial. Neuropsychiatr Dis Treat 3(6):919–924, Epub 2007/12/01
31. Fitzgerald PB, Hoy K, Gunewardene R, Slack C, Ibrahim S, Bailey M et al (2010) A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. Psychol Med 1–10. Epub 2010/10/12

32. Frank E, Eichhammer P, Burger J, Zowe M, Landgrebe M, Hajak G et al (2011) Transcranial magnetic stimulation for the treatment of depression: feasibility and results under naturalistic conditions: a retrospective analysis. Eur Arch Psychiatry Clin Neurosci 261(4):261–266, Epub 2010/08/26
33. Walter G, Tormos JM, Israel JA, Pascual-Leone A (2001) Transcranial magnetic stimulation in young persons: a review of known cases. J Child Adolesc Psychopharmacol 11(1):69–75, Epub 2001/04/27
34. Loo C, McFarquhar T, Walter G (2006) Transcranial magnetic stimulation in adolescent depression. Australas Psychiatry 14(1):81–85, Epub 2006/04/25
35. Bloch Y, Grisaru N, Harel EV, Beitler G, Faivel N, Ratzoni G et al (2008) Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. J ECT 24(2):156–159, Epub 2008/06/27
36. Hu SH, Wang SS, Zhang MM, Wang JW, Hu JB, Huang ML et al (2011) Repetitive transcranial magnetic stimulation-induced seizure of a patient with adolescent-onset depression: a case report and literature review. J Int Med Res 39(5):2039–2044, Epub 2011/11/29
37. D'Agati D, Bloch Y, Levkovitz Y, Reti I (2010) rTMS for adolescents: safety and efficacy considerations. Psychiatry Res 177(3):280–285, Epub 2010/04/13
38. Quintana H (2005) Transcranial magnetic stimulation in persons younger than the age of 18. J ECT 21(2):88–95, Epub 2005/05/21
39. Kirton A, Deveber G, Gunraj C, Chen R (2008) Neurocardiogenic syncope complicating pediatric transcranial magnetic stimulation. Pediatr Neurol 39(3):196–197, Epub 2008/08/30
40. Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS (1999) Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. J Clin Psychiatry 60(1):50–52, Epub 1999/03/13
41. Kim DR, Epperson N, Pare E, Gonzalez JM, Parry S, Thase ME et al (2011) An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. J Womens Health (Larchmt) 20(2):255–261, Epub 2011/02/15
42. Kim DR, Sockol L, Barber JP, Moseley M, Lamprou L, Rickels K et al (2011) A survey of patient acceptability of repetitive transcranial magnetic stimulation (TMS) during pregnancy. J Affect Disord 129(1–3):385–390, Epub 2010/09/25
43. Cohen RB, Ferreira MS, Ferreira MJ, Fregni F (2008) Use of repetitive transcranial magnetic stimulation for the management of bipolar disorder during the postpartum period. Brain Stimul 1(3):224–226, Epub 2008/07/01
44. Garcia KS, Flynn P, Pierce KJ, Caudle M (2010) Repetitive transcranial magnetic stimulation treats postpartum depression. Brain Stimul 3(1):36–41, Epub 2010/07/17
45. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF (2008) A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 23(2):183–189; quiz 313. Epub 2007/11/08
46. Epstein CM, Evatt ML, Funk A, Girard-Siqueira L, Lupei N, Slaughter L et al (2007) An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. Clin Neurophysiol 118(10):2189–2194, Epub 2007/08/24
47. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N (2010) The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. Mov Disord 25(14):2311–2317, Epub 2010/08/27
48. Jorge RE, Moser DJ, Acion L, Robinson RG (2008) Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry 65(3):268–276, Epub 2008/03/05
49. Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D et al (2004) Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry 55(4):398–405, Epub 2004/02/13
50. Kim BR, Kim DY, Chun MH, Yi JH, Kwon JS (2010) Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients: a double-blind, sham-controlled trial. Am J Phys Med Rehabil 89(5):362–368, Epub 2010/04/22
51. Fitzgerald PB, Holy KE, Maller JJ, Herring S, Segrave R, McQueen S et al (2010) Transcranial magnetic stimulation for depression following traumatic brain injury: a case study. J ECT 27(1):38–40

Practical Issues in Treatment Provision

6

6.1 Introduction

At the commencement of a treatment course, the prescribing practitioner is required to determine a variety of parameters for treatment provision. The choice of these should be made on an individual patient basis but may be influenced or largely determined by local policies or established protocols. Each of the following parameters must be explicitly prescribed for each patient or made clear in local protocols:

- Intensity of stimulation
- Frequency of stimulation
- Duration of each stimulation train
- Total number of stimulation trains provided in each treatment session
- Inter-train interval
- Site of stimulation
- Coil orientation

6.2 Dosing and Motor Threshold

The intensity of stimulation provided during rTMS treatment is typically defined as a percentage (usually between zero and 100 %) of the total machine output provided by the rTMS device being used. The intensity for each patient is individualised; it is typically determined relative to that individual's resting motor threshold (RMT). The RMT is an estimate of an individual's level of motor cortical excitability, established by the application of single TMS pulses to the motor cortex. The lowest stimulation intensity required to consistently induce a motor response in a peripheral muscle is determined, usually in the abductor pollicis brevis (APB) in the contralateral hand. This sets the RMT (see Boxes 6.1 and 6.2).

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_6,

Box 6.1. Assessment of the Resting Motor Threshold (RMT): Theory

Typically, the RMT is defined as the minimum machine stimulator intensity required to produce a pre-specified motor response. Most commonly, this is a defined number of motor twitches observed on a certain number of occasions (e.g. on 3 out of 5 or 5 out of 10 stimulations).

The RMT is determined by a number of factors. These include intransient factors such as the distance between the stimulation coil in the cortex and variable factors such as medication status and sleep deprivation. Critically, the resting motor threshold is also sensitively dependent on the absence of any muscle activity. If the patient has a background level of motor activity during measurement, the RMT measured is likely to be considerably lower than the true value.

The type of motor response can be assessed in one of two ways:

1. The visual observation of a muscle twitch in the contralateral hand from the site of stimulation.
2. The measurement of a motor evoked response of a specific size in the contralateral hand. This is achieved using electromyographic equipment (EMG): a significant motor response is usually defined as an EMG deviation (motor evoked potential) of greater than 50 uV peak to peak.

Assessment of the RMT with visual observation is simple and does not require the knowledge needed to set up EMG monitoring. However, EMG monitoring does give reassurance that the patient is maintaining an adequate level of muscle relaxation. In the absence of this, considerable effort should be given to ensure the patient is as relaxed as possible throughout assessment of the RMT.

It is likely that assessment based on EMG or visual observation methods generate a similar figure within individuals although studies investigating this are not completely consistent [1, 2]. The EMG is capable of detecting non-visible motor twitches but will only detect activity in a single muscle. This increase in sensitivity is typically balanced by the fact that when visualising muscle activity, it can be considered in one of a number of muscles. If RMT is measured in this way, it is likely to be of similar sensitivity to the EMG method.

The RMT can potentially be quantified in several ways. As described above, one approach is to define the RMT as a minimal intensity at which a certain number of motor evoked responses are invited out of a predetermined number of pulses: for example, the minimal intensity of which five motor responses are seen during ten stimulation pulses. However, more recently, several software algorithms have been developed that estimate the RMT from the size and presence of motor responses at varied stimulation intensities (e.g. as used in [3] and [4]), although there remains some debate about the relative advantages and disadvantages of some of these [5]. Variation in the method for measurement of RMT does further complicate the comparison of outcomes of various clinical trials. However, improvement in RMT estimation methods is likely to restrict the variability of measurements recorded rather than result in a systematically higher or lower threshold used for stimulation.

It is notable that the RMT is a measure of motor cortical excitability, not a measure of excitability of the prefrontal cortex where depression treatment is

typically applied. Methods to quantify thresholds in prefrontal regions have yet to be developed. The use of the RMT as an estimate for prefrontal treatment has support from the clinical trials of rTMS depression treatment in which few safety concerns, including only minimal incidences of seizure induction, have arisen.

Box 6.2. Assessment of Resting Motor Threshold (RMT): Techniques

A number of methods have been described for the estimation of the RMT. The basic procedure is presented here for measurement of the RMT and quantification using a simple counting method.

1. Place the coil with its centre approximately 2 cm lateral and 5 cm anterior in a parasagittal plane from the vertex. This will be approximately in line with the ears.
2. Position the coil to be on an approximately 45° angle from the midline (see Fig. 6.1).
3. Place your other hand gently yet firmly on the other side of the subject's head. Take care not to press too hard with that hand, or to press down too firmly on the coil.
4. Beginning with the intensity low (30–35 %), commence single-pulse stimulation with pulses every 3–5 s. Slowly move the coil around the estimated location of the motor cortex, applying one or two pulses at each site.
5. If no movement/twitch is observed in the contralateral hand, then the RMT for that person is higher than the current TMS output setting. Therefore, increase the output in steps of 5 %, testing the response at a number of sites at each step.
6. If a hand and/or wrist movement is observed, then the applied intensity is close to RMT. Test responses at a number of areas and mark the site on the scalp which appears to produce the greatest motor response.
7. With the intensity set at a level that produces a small but regular muscle twitch, establish the scalp location that produces the optimal response. To do this, test the response to two or three pulses over an imaginary grid of points surrounding the site which you have marked (see Fig. 6.2). Mark the optimal location.
8. Providing stimulation with pulses of approximately 0.2 Hz at the optimal location (no more frequent than one pulse every 5 s), now establish the motor threshold by your chosen method (algorithm or counting). Note, if higher frequencies of stimulation are used, this may in itself affect cortical excitability confounding RMT assessment.
9. If using a counting method, apply pulses at a slightly suprathreshold intensity: if three muscle movements are observed during five pulses (or 5 out of 10), consider this level above threshold and reduce the intensity by 1 %. Repeat this procedure until 3 (or 5) responses are not seen. The RMT is 1 % higher than this level. The same procedure can be undertaken with EMG where a 50-uV motor evoked potential response is considered above threshold.

Note: You may often see a thumb movement/twitch from the very first pulse at any given intensity level but then no observed movement following further stimulation: the response is typically greater to a first rather than subsequent pulse. A failure to get consistent responses indicates that you are below RMT.

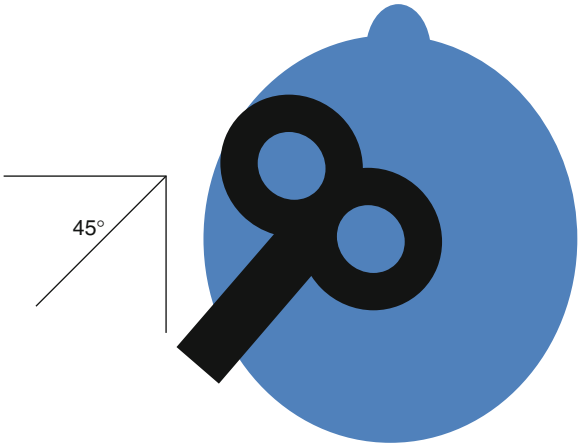


Fig. 6.1 Coil orientation at 45° to parasagittal plane

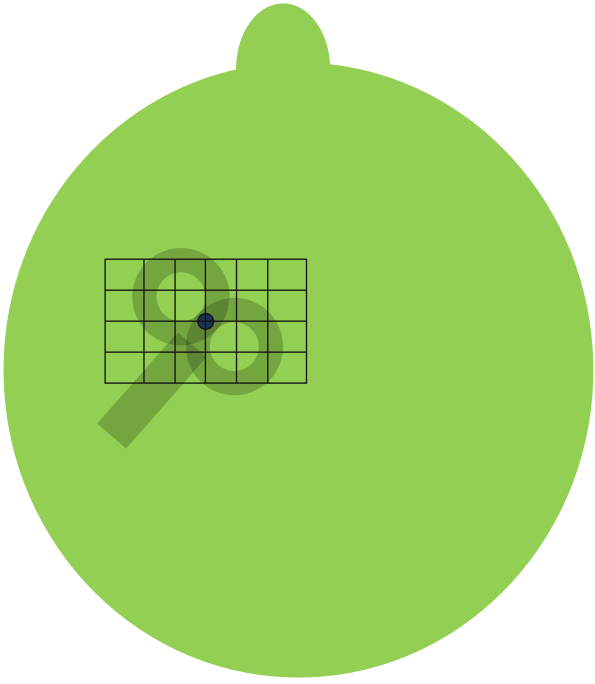


Fig. 6.2 Grid of sites: in the localisation of the optimal site for motor cortical stimulation, a series of points around the estimated optimal site should be systematically stimulated at a fixed intensity to establish the optimal site of stimulation

Across time there has been considerable variation in stimulation intensity used within rTMS treatment trials for patients with depression. Initially, trials used intensities below the RMT (80–90 %). However, in more recent years, trials have more typically used suprathreshold intensities of 110–120 %. The intensity used for stimulation has implications potentially for efficacy and definitively for safety and tolerability. In regard to efficacy, it has been proposed that the progressive increase in stimulation intensity in treatment trials over time may have contributed to greater treatment effects in more recent studies [6]. However, a substantial number of other factors have also changed over time, including the duration of treatment courses, and little direct data has evaluated the relative efficacy of treatment based on intensity relative to RMT. Higher intensities do have significant implications for safety and tolerability. Patient discomfort and pain during treatment, and the development of posttreatment headache, are certainly more common at higher treatment intensities. In addition, higher intensities are related to a greater risk of seizure induction. The risk of seizure induction is dependent on stimulation intensity, the duration of stimulation trains and the inter-train interval. According to established safety guidelines, when rTMS is applied in high-frequency trains, stimulation can safely be applied up to 120 % of the RMT if the stimulation train duration is limited to 4.2 s [7]. Little research has explored the safety implications of the interval between trains: with 10 Hz trains, some authors have proposed that the interval should be at least twice the duration of the actual train itself. At lower frequencies, the train can be extended safely to longer durations (see Table 7.1). Note, however, that the safety guidelines have only been established for stimulation in the motor cortex: no equivalent data has been obtained in regard to safety for stimulation in frontal areas used in depression treatment.

Although a specific frequency may be prescribed for a course of treatment, local practice may determine that the intensity be varied depending on factors such as patient tolerability. This may be done in one of two ways: first, the prescribed treatment intensity can be applied and the intensity lowered if this is not tolerated by the patient. Second, the patient may be commenced at a lower treatment intensity which is then progressively increased depending on tolerability. In our experience, the latter approach is preferable. If patients experience significant pain at an initial high intensity, they are more likely to be dissuaded from continuing treatment or be hypervigilant during subsequent treatment trains. Hypervigilance may increase scalp muscle contraction, further increasing the unpleasant experience of treatment. In contrast, if a positive experience of treatment is established on a low treatment intensity, intensity may be gradually increased to levels that may not otherwise have been well tolerated. Some idea of the individual patient's tolerance to treatment may be estimated during measurement of the RMT. In more sensitive patients, we would recommend commencing treatment between 40 and 50 % of the RMT and progressively increasing depending on tolerability. Although it would seem desirable to achieve maximal prescribed intensities (e.g. 120 % of the RMT), brain effects of rTMS are clearly apparent at much lower levels (e.g. 90 % of the RMT). It may be preferable to have a patient receive a treatment course at a lower intensity than to drop out of treatment altogether due to lack of tolerability of high-intensity stimulation.

This is certainly the case given that the existing clinical data does not strongly suggest a linear relationship between stimulation dose and efficacy.

As indicated previously, the RMT can be influenced by a number of patient specific factors such as medication status. Medications that suppress cortical excitability, such as benzodiazepines, are likely to increase the RMT. Importantly, withdrawal of benzodiazepines, or withdrawal of other CNS depressant medications such as alcohol, is likely to increase cortical excitability and substantially lower the RMT. If patients change CNS active medications or drug use during a course of treatment, the RMT should be reassessed and the intensity of stimulation adjusted if it is considered safe to continue with treatment.

There is also individual variation in the RMT across hemispheres. Although one study found no significant group average differences between left and right RMT in depressed patients [8], for individual patients, RMT levels can vary by up to 10 % across hemispheres. Therefore, measurement of the RMT in the hemisphere in which treatment stimulation is to be provided is recommended.

It is also possible that the RMT varies significantly across time even in the absence of changes in external factors such as medication dose. A small number of patients in a 2-week trial of rTMS experienced a significant shift in RMT level that could justify recalibration of treatment dose, although no significant group variation was found [8]. A decision to remeasure RMT over time should be influenced by considerations as to whether the patient is close to safety thresholds in the baseline dose applied. The baseline RMT level does not appear to influence the outcome of treatment [9].

Note: The intensity of stimulation will vary substantially between different brands of rTMS equipment and between different TMS coil types. It is also possible that it will vary significantly when the same machine but different coils are being used. If an individual patient is to be treated with more than one device or coil, it should be established prior to treatment if there is any variation. The easiest way to do this is to measure the resting motor threshold with the different device/coils on several patients to establish the consistency of the measures obtained.

6.2.1 Clinical Recommendations

Although there are limitations in the applicability of RMT measures to prefrontal areas, at this stage, rTMS dosing should be based on individual measurement of the RMT. There are a variety of methods for RMT assessment, a number of which are likely to be equivalent in practical implementation. The most important consideration is that each prescribing clinician is trained in and familiar with the method that he or she is able to apply consistently. RMT should be assessed at the start of each acute course of treatment to determine dosing based on safety and efficacy considerations in the hemisphere to which stimulation will be applied. The RMT should be reassessed when patients alter their consumption of CNS active drugs. The RMT should also be periodically reassessed when patients have extended treatment courses or maintenance rTMS over time.

6.3 Selection of Treatment Type and Parameters

As discussed in Chapter 4, a considerable body of research has evaluated a variety of methods of rTMS application including high-frequency stimulation applied to the left DLPFC, low-frequency stimulation applied to the right DLPFC and variations of bilateral stimulation. Clearly, the vast majority of research has established the efficacy of high-frequency stimulation applied to the left DLPFC, most commonly at 10 Hz. This data includes the pivotal Neuronetics Ltd-sponsored clinical trial that led to device registration in the USA. As such, it is likely that high-frequency stimulation applied to the left DLPFC is likely to be the initial rTMS treatment option selected for most patients.

6.3.1 Considerations with Left-Sided High-Frequency rTMS

6.3.1.1 Frequency

Although there are antidepressant studies of the effect of frequencies such as 5 and 20 Hz, the vast majority of studies have been conducted with 10 Hz stimulation. This includes the two main large randomised multisite rTMS trials [3, 10]. There are no studies showing any particular advantage of stimulation at other frequencies. Given the depth of research that has focused on this particular frequency, unless evidence emerges to the contrary, most treatment should be provided at 10 Hz.

6.3.1.2 Train Duration and Intensity

As discussed previously, there is a relationship between train duration and intensity in regard to the safety of rTMS administration. If trains are to be provided at an intensity of 120 % of the RMT, train duration should be limited to 4.2 s. Longer trains, most commonly 5 s in duration, can be safely administered at lower intensity, for example, 110 % of the RMT.

6.3.1.3 Train Number

Seventy-five trains of 10 Hz stimulation were applied in the two large multisite rTMS trials conducted to date [3, 10]. This was considerably in excess of the number of trains used in most trials until that time, with previous studies often applying only 20–30 trains. Given that the remission rates in both of these trials were fairly modest, it is not clear whether this increase in train number resulted in substantially greater efficacy than had been seen previously. Specific research is urgently required to determine whether there is a direct relationship between treatment dose (pulse number) and clinical response. In the absence of this data, the provision of 75 trains per treatment session is becoming a de facto standard treatment approach.

6.3.2 Use of Right-Sided Low-Frequency rTMS

There are a number of potential advantages of low-frequency right-sided rTMS that could lead to its potential consideration as first-line treatment or alternatively as an approach in circumstances where high-frequency stimulation cannot be tolerated or may be considered potentially unsafe. Low-frequency stimulation, especially as it is known to reduce cortical excitability rather than increase cortical excitability, is likely to be associated with a substantially lowered risk of seizure induction. Therefore, there may be circumstances in which the risks associated with a trial of low-frequency stimulation may be considered appropriate where high-frequency stimulation raises too high a risk of seizure induction. This could be because an individual patient has a risk factor for seizure induction or heightened cortical excitability. It could also be because the risk of actually experiencing a seizure may be considered too high, for example, in somebody with compromised cardiac function. It should be noted, however, that the risk of seizure induction with low-frequency stimulation is not zero but is likely to be less than with high-frequency stimulation.

Another circumstance in which low-frequency right-sided stimulation may be considered as an alternative is where high-frequency stimulation is not tolerated by individual subjects. The vast majority of patients will find low-frequency stimulation more tolerable than the intense bursts of high-frequency stimulation although this is not universal.

Finally, right-sided stimulation may be considered as a treatment option in patients who have failed to respond to high-frequency left-sided rTMS. Studies which have compared the two approaches have generally found equivalent efficacy. Little research has explored rates of response to one treatment in the event of failure of the other. We previously found that a minority of patients will respond to a trial of high-frequency left-sided rTMS if they had failed to respond to low-frequency right-sided rTMS. However, no systematic research has explored crossover in the opposite direction. However, given the low risks associated with right-sided low-frequency stimulation, this could be considered a treatment alternative in some patients.

6.3.2.1 Dosing of Right-Sided Low-Frequency rTMS

Early studies of right-sided low-frequency rTMS applied a small number of 60 s trains, usually with a 30 or 60 s inter-train interval. More recent studies have commonly used a single 15 min train (900 pulses) in each treatment session. This dosing remains much lower than the common dosing with 10 Hz stimulation (3,750 pulses across 75 trains per session), but no studies have explored higher low-frequency doses. Based on the existing data, a single 15 min treatment session at 120 % of the RMT appears a conservative and sensible approach.

6.3.3 Sequential Bilateral rTMS

At this time, it is not clear whether bilateral rTMS has a role in clinical practice. Although some studies of sequential bilateral rTMS were promising [11] and at

least one study has found superior efficacy than unilateral treatment [12], a number of studies have found equivalent or inferior responses to bilateral compared to unilateral rTMS (e.g. [13]). Based on this research, there are no clear indications for bilateral rTMS at this time.

6.3.3.1 Clinical Recommendations

At this stage, under most circumstances, first-line rTMS treatment is likely to entail 10 Hz stimulation applied to the left DLPFC. Under most circumstances, a dose of 75 four second trains applied at up 120 % of the RMT is recommended. It is likely that many patients, especially those with a RMT of greater than 50 %, will benefit from a progressive increase in treatment intensity over the course of one or more treatment sessions until the target dose is achieved. When practitioners measuring the RMT have limited experience, dosing at 110 % of the RMT is sensible to ensure that there is a margin of safety in case of minor errors in RMT estimation. Low-frequency right-sided stimulation is a good option for patients who have trouble tolerating left-sided treatment, who have additional risk factors for seizure induction or when left-sided treatment has failed to produce therapeutic effects.

6.4 Treatment Scheduling and Duration

The vast majority of rTMS studies have provided treatment 5 days per week, Monday to Friday. Two studies have explored whether this frequency of treatment is required for adequate efficacy. In the first study, one group of patients received treatment 5 days a week for 2 weeks, and the second received three treatments in week 1 and two treatments in week 2 [14]. No significant differences between the groups were seen in outcomes although the sample size in this study was relatively small. In a more recent study, 77 patients were randomised to receive either rTMS 5 days a week for 4 weeks (20 treatments) or treatment 3 days a week for 6 weeks (18 treatments) [15]. When assessed at 4 weeks, the patients who received daily treatment had improved to a greater degree. However, similar efficacy was achieved by the two groups when end-of-treatment assessments were compared. This indicated that more widely spaced treatment resulted in a slower response, but a response of a similar degree of efficacy. We have some limited experience in the provision of treatment 7 days per week. The patients treated in this way mostly have not been noted to respond more quickly and on several occasions have actually required further treatment sessions such that the overall treatment duration remained approximately 4 weeks. Limited research has explored the use of twice-daily rTMS [16]. Although this appears as effective, we lack studies comparing twice daily to once daily rTMS. Overall effect sizes seen do not seem to be greater than that seen with standard treatment.

Trials to date have varied considerably in how they have dealt with missed treatment sessions or extended session breaks, for example, over long weekends. In our experience, treatment can successfully proceed when patients have missed individual treatment sessions, but it would seem sensible to try and provide at least three treatment sessions within each week period and to limit protracted breaks.

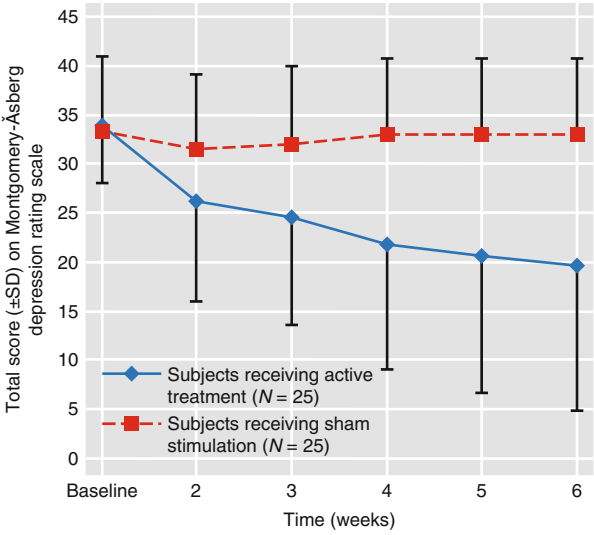


Fig. 6.3 The progressive reduction in depression scores in a clinical trial of bilateral rTMS seen in active treatment group over a 6-week period [11]

In regard to the duration of rTMS treatment courses, these have varied across time from 1 week in initial studies to 6 weeks or longer in studies published in recent years. One method of analysis has suggested that better clinical responses have been seen in more recent clinical trials than earlier studies; it is possible that the increasing duration of treatment is a factor in this improvement [6]. There does appear to be a progressive improvement in mood across time during treatment implying that longer courses of treatment are likely to result in better clinical outcomes. For example, there was a clear reduction, week by week, in depression severity across a 6-week period of time in the active treatment group in a trial of sequential bilateral rTMS conducted by our group (see Fig. 6.3) [11].

It is not clear, however, whether there is an optimal period of treatment. In a series of open-label clinical trials we have conducted, substantial response and remission rates have been achieved with 4 weeks of treatment. However, a subpopulation of patients does require a longer period of treatment to achieve substantial response. Although most patients will initially report some improvement during either week 2 or week 3 of treatment, occasionally patients do not experience mood shifts until considerably later. Four weeks seem to be a reasonably balanced minimal duration of adequate treatment. Unless patients have previously responded to a course of rTMS, we would rarely recommend continuing beyond 4 weeks if no clinical improvement has been achieved to date. A trial of right-sided treatment or another type of non-rTMS therapy should be considered under those circumstances. However, when patients have achieved partial response by the 4-week time point, extending treatment beyond this is clearly warranted and justifiable.

It can also be unclear when to cease treatment when a patient has responded clinically. Generally, patients should continue treatment whilst they are improving, but once clinical response has reached a plateau at an adequate level, we typically

recommend cessation of treatment. However, we frequently also recommend several more treatment sessions to potentially consolidate the gains achieved. It is notable that patients may continue to demonstrate some further improvement after the cessation of treatment, although it is unclear whether this is a neural/brain or psychosocial effect.

There is no evidence of the accumulation of adverse events or side effects with the extension of a course of treatment beyond 4 weeks. Patients tolerating a course of treatment will usually continue to do so. However, limited research has explored the overall safety of longer courses of rTMS treatment.

6.4.1 Clinical Recommendations

rTMS treatment should typically be provided five times per week to achieve efficacy at least equivalent to that seen in clinical trials. However, patients should not be excluded from treatment if they have missed treatment sessions: treatment at slightly reduced frequency, for example, three or four times per week, may be more acceptable to some patients and still maintain reasonable clinical results. Treatment at greater frequency, for example, twice daily or 7 days per week, cannot be justified at this stage.

A minimum duration of adequate treatment with rTMS provided on a daily basis would be 4 weeks, although some patients may require a longer course of treatment to respond. Extension of treatment beyond 4 weeks is clearly justifiable when patients have previously responded to rTMS or have had a partial improvement but continue to experience symptoms after 4 weeks.

6.5 Concurrent Treatments

There are two potential issues with the consideration of concurrent medication treatment: whether there is a possibility of an impact on treatment efficacy, either favourable or not, and whether concurrent medication treatment increases the risk of adverse events such as seizure induction.

In regard to efficacy, a large number of clinical trials of rTMS in depression have included patients receiving antidepressant and often other forms of psychotropic medication. Several of the larger multisite trials (e.g. [3]), however, have been conducted in medication-free patients. When patients on medication have been enrolled in trials, it has been common to include only those who have failed to adequately respond to medication and where the dose of medication has been unchanged for a significant period of time prior to rTMS treatment, often 4 weeks. From the results of these trials, it appears that rTMS is effective in both medication-free and concurrently medicated patients.

The situation is not as clear, however, when we consider the concurrent *commencement* of medication and rTMS treatment. Trials investigating this approach have generally found little difference between active and sham treatment, perhaps

because the possible effects are more limited when concurrent treatment is commenced (e.g. [17]). Concurrently commencing treatment also raises a simple practical clinical issue: if a patient responds under these circumstances, it is not possible to know whether it was the medication, rTMS or the combination, which resulted in clinical improvement. This uncertainty is likely to have implications for future recommendations regarding treatment options if the patient experiences a relapse.

One trial in another disorder did suggest that medication could potentially undermine rTMS response. This early study of the effect of rTMS treatment for auditory hallucinations in patients with schizophrenia found that patients responded more poorly when receiving rTMS concurrent with a mood stabiliser [18]. However, this has not been replicated in other hallucination studies, and analyses in substantial depression samples have not found this effect. In fact, analyses in depression samples have not found a moderating effect of any of the medication classes investigated.

In regard to safety considerations, the main concern is that concurrent medications may alter cortical excitability and contribute to a greater risk of seizure induction (Table 6.1). However, if medication is present at the time of the measurement of the RMT and the dose does not change over time, the effect on cortical excitability is likely to be at least partially controlled for in this initial measurement. However, changes in medication dose during treatment may result in an uncontrolled alteration of excitability increasing risk. Therefore, if substantial changes in medication doses are made, RMT levels should be remeasured and the prescribed rTMS intensity adjusted accordingly.

Of note, the greatest concerns in regard to safety of medication during rTMS treatment are likely to arise with medications known to predispose to seizures or alter excitability. Caution is warranted with clozapine, bupropion, tricyclic antidepressants and stimulants such as amphetamine derivatives. However, a number of studies have included clozapine-treated patients in trials without complication, and we have treated depressed patients concurrently taking medication from all antidepressant classes. We have also treated without incident a number of patients receiving stimulants. However, given the short duration of action of many of the medications in this class, we will often treat at a time of trough plasma levels. We also typically ensure that the measurement of the RMT and the provision of treatment occur at approximately the same time following medication dosing, for example, between 4 and 5 h after the morning or most recent dose.

6.5.1 Clinical Recommendations

There do not appear to be any adverse implications for the commencement of rTMS treatment in patients who are receiving a stable dose of psychotropic medication. Patients who have experienced a partial response to medication should not be weaned off this medication to undergo rTMS treatment unless for other specific reasons. There is no sensible rationale for the concurrent commencement of rTMS treatment and antidepressant medication, and this should be avoided. Careful monitoring

Table 6.1 Seizure risk associated with psychotropic medications

	Drug class	Drug name	Risk	Notes
Antidepressants	Tricyclic antidepressants (TCA)	Imipramine	Majority of TCA medications pose low risk at therapeutic doses	Risk may be higher in genetic slow metabolisers, significantly increased risk at high dose/in overdose
		Amitriptyline		
		Desipramine		
		Nortriptyline		
		Dothiepin		
		Clomipramine	Higher risk	
	Tetracyclic antidepressants	Maprotiline	Higher risk	
		Amoxapine		
	Selective serotonin reuptake inhibitors (SSRIs)	All in class	Low risk	SSRIs can produce hyponatremia which can precipitate seizures
	Bupropion		Risk appears low to moderate in divided doses that total <400mg/day and in slow release form	
	Phenylpiperazines	Trazodone	Low risk	
		Nefazodone		
	Selective serotonin–noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine	Low risk	Possibly higher risk at higher doses
	Mirtazapine		Low risk	
	Monoamine oxidase inhibitors (irreversible)	Phenelzine	Low risk	
		Tranylcypromine		
	Monoamine oxidase inhibitors (reversible)	Moclobemide	Low risk	
	Noradrenaline reuptake inhibitors (NRIs)	Reboxetine	Low risk	

(continued)

Table 6.1 (continued)

	Drug class	Drug name	Risk	Notes
Antipsychotics	Phenothiazines	Chlorpromazine	Higher risk	
	High-potency typical antipsychotics	Haloperidol	Low risk	
	Atypical antipsychotics	Clozapine	Higher risk	Risk is significantly dose dependent
		Olanzapine	Possibly higher risk	
		Quetiapine	Possibly higher risk	
		Risperidone	Low risk	
		Ziprasidone	Low risk	
Mood stabilisers		Lithium	Possibly higher risk	Risk substantially increased at toxic plasma levels
Benzodiazepines		All in class	Low risk	High risk in withdrawal

Data partially summarised from review in [25]

of the RMT and adjustment of treatment dose is required if medication is altered during treatment, especially when patients are receiving medications known to effect cortical excitability or the RMT.

6.6 Coil Positioning and Location

The vast majority of studies that have evaluated the efficacy of rTMS treatment in depression have utilised the standard '5-cm method' for coil localisation (see Box 6.3). This method is dependent on the accurate localisation of the optimal site for stimulation of muscles in the hand contralateral to the site of stimulation. This typically occurs during the measurement of the RMT allowing a smooth transition to the measurement of the site of stimulation after this task has been undertaken. Although it was originally proposed that the 5-cm method would result in localisation of the stimulation coil over the dorsolateral prefrontal cortex (DLPFC), considerable doubt has been raised as to whether this occurs in most patients. DLPFC is typically defined by areas 9 and 46 in the Brodmann classification system. Some time ago, research demonstrated that the 5-cm technique would result in localisation of stimulation in DLPFC in only a minority of subjects [19]. In the majority of subjects, localisation was more posterior and occasionally more medial than the DLPFC. It is possible that DLPFC stimulation would result from the extension of the stimulation field into DLPFC from the more posteriorly located sites, but the intensity of this stimulation would be quite limited. Despite these concerns, clearly stimulation using the 5-cm technique has resulted in clinical efficacy in previous clinical trials. However, it may be possible to achieve greater clinical efficacy by modification of this technique.

In planning an approach that would potentially result in enhanced efficacy, the first consideration must be to define the area most likely to achieve beneficial clinical outcomes. The original target, DLPFC defined as Brodmann areas 9 and 46, is a quite large area of lateral prefrontal cortex overlapping superior, middle and parts of inferior frontal gyri. These Brodmann regions were characterised from analysis of a single post-mortem brain, and as such there is likely to be considerable error if directly applied to a broader range of subjects. A modern post-mortem study remeasured the site of areas 9 and 46 on multiple brains, producing a significantly more constrained area focused mainly on the superior frontal gyrus (area 9) in the middle frontal gyrus (area 46) [20]. One possibility is to try and anatomically target these regions. Another approach is to try and target a region based upon an identification of DLPFC abnormalities in the neuroimaging literature. However, a quantitative meta-analysis of neuroimaging changes in DLPFC in patients with depression did not suggest a clearly uniform target [21]. Given these concerns, few clinical studies have attempted to improve on the use of the 5-cm method. One study, using MRI-based neuronavigation, compared response to treatment localised using the 5-cm method to treatment localised to the junction of areas 9 and 46 based on the multiple-brain definition of these regions [22]. Promisingly, the study found enhanced clinical response with neuronavigationally targeted treatment to this site which was considerably more anterior

Box 6.3. 5-cm Method for Location of rTMS Treatment Site

1. Locate the cortical site for the optimal stimulation of hand muscles in the contralateral side (see Box 6.2 above).
2. Mark this site on the scalp.
3. Using a flexible measuring tape, measure 5 cm forward (or more as defined by protocol) from the motor site in a sagittal plane (see Fig. 6.4).
4. Mark the subsequent site.

Measuring the distance between this site and several anatomical landmarks (e.g. the preauricular and nasion points) will allow the remeasurement of this site without the localisation of the RMT on subsequent days.

and lateral than the site typically identified using the 5-cm method. However, these results have not been replicated to date.

If we do accept the results of this comparison, does it imply that neuronavigation is required to achieve enhanced treatment outcomes? It is possible that a similar improvement in outcome may be achieved with a more simple method that also results in more anterior and lateral treatment localisation and potentially also takes into account variation in head size, a clear deficiency of the 5-cm technique. One possibility that meets these criteria is the use of the system of measurement used for the 10–20 EEG system. The methods for establishing cortical sites with this system are relatively widely understood, and EEG coordinates can be reliably correlated with underlying cortical areas [23]. A site such as the F3 EEG point is known to relate to DLPFC and is likely to be more anterior than a 5-cm localised treatment point in most subjects. A simple guide for the measurement of the F3 site has been recently published [24] (see Fig. 6.5 for an overview of the standard method). It is also possible that enhanced clinical responses may be seen with a simple modification such as measuring 6 or 7 cm anterior to the motor site. Although such an approach still does not take into account individual differences in head size, it will ensure that treatment application does not differ too substantially from that used in clinical trials. This is a sensible approach until further studies establish the efficacy of more advanced methods of DLPFC localisation.

6.6.1 Clinical Recommendations

The typical approach to localise rTMS treatment is to target a point 5 cm anterior to the optimal site of stimulating hand muscles on the contralateral side. However, this does not allow for individual variability in head size. A sensible alternative is to extend this distance, possibly to 6 or 7 cm, especially in subjects with average to above average head circumference. The use of the F3 (and F4 on the right) EEG points as locations for treatment is also a sensible and conservative modification to this technique that could be adapted for clinical use.

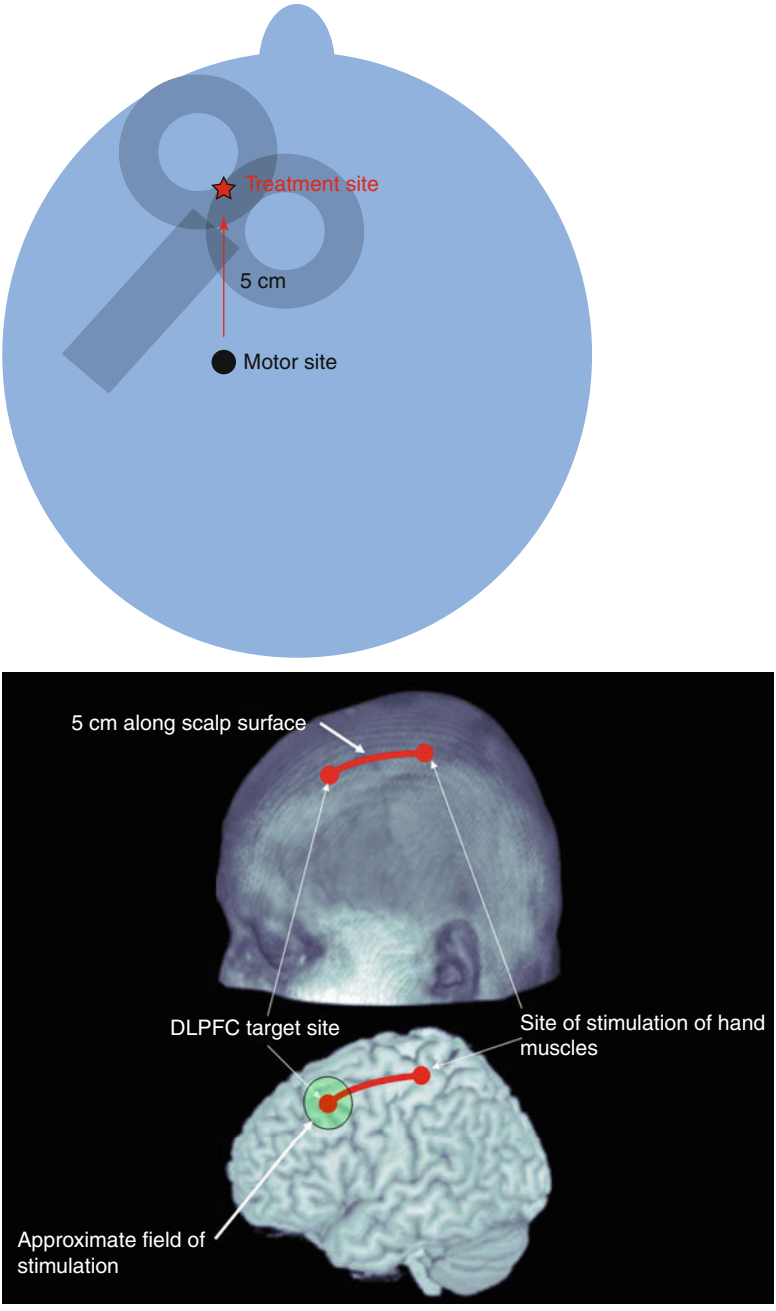


Fig. 6.4 The measurement of the 5-cm method for treatment site localisation

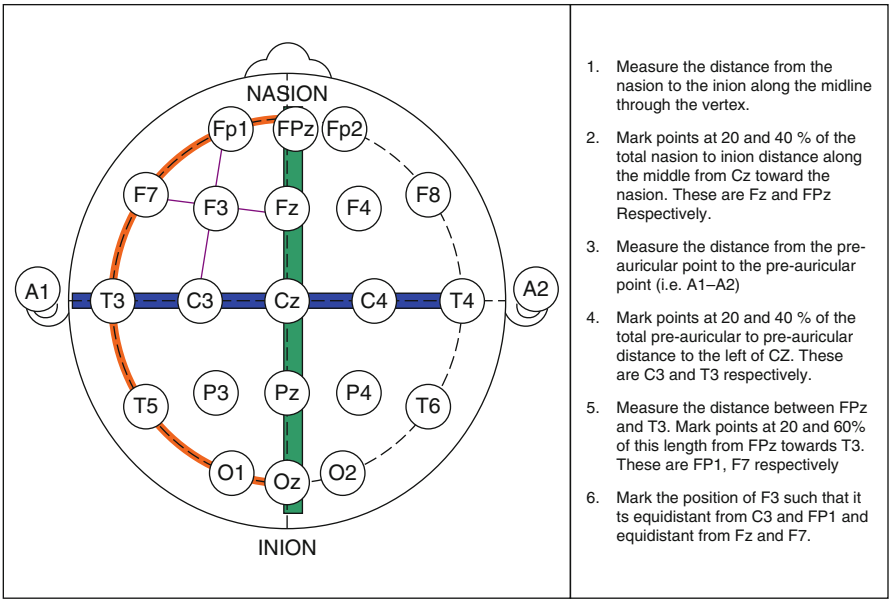


Fig. 6.5 Method for the measurement of the site of the F3 EEG point

References

1. Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS (1998) Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. J ECT 14(1):25–27
2. Hanajima R, Wang R, Nakatani-Enomoto S, Hamada M, Terao Y, Furubayashi T et al (2007) Comparison of different methods for estimating motor threshold with transcranial magnetic stimulation. Clin Neurophysiol 118(9):2120–2122, Epub 2007/07/24
3. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216
4. Qi F, Wu AD, Schweighofer N (2011) Fast estimation of transcranial magnetic stimulation motor threshold. Brain Stimul 4(1):50–57, Epub 2011/01/25
5. Awiszus F (2011) Fast estimation of transcranial magnetic stimulation motor threshold: is it safe? Brain Stimul 4(1):58–59, Epub 2011/01/25
6. Gross M, Nakamura L, Pascual-Leone A, Fregni F (2007) Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 116(3):165–173
7. Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108(1):1–16
8. Navarro R, Zarkowski P, Sporn A, Avery D (2009) Hemispheric asymmetry in resting motor threshold in major depression. J ECT 25(1):39–43, Epub 2008/06/27
9. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L (2002) Magnetic motor threshold and response to TMS in major depressive disorder. Acta Psychiatr Scand 106(3):220–223, Epub 2002/08/29

10. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516, Epub 2010/05/05
11. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J (2006) A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 163(1):88–94
12. Blumberger DM, Mulsant BH, Fitzgerald PB, Rajji TK, Ravindran AV, Young LT et al (2012) A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. World J Biol Psychiatry 13(6):423–435, Epub 2011/07/09
13. Fitzgerald PB, Hoy K, Gunewardene R, Slack C, Ibrahim S, Bailey M et al (2010) A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. Psychol Med 1–10. Epub ahead of print, 2010/10/12
14. Turnier-Shea Y, Bruno R, Pridmore S (2006) Daily and spaced treatment with transcranial magnetic stimulation in major depression: a pilot study. Aust N Z J Psychiatry 40(9):759–763, Epub 2006/08/17
15. Galletly C, Gill S, Clarke P, Burton C, Fitzgerald PB (2012) A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? Psychol Med 42(5):981–988, Epub 2011/09/14
16. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS (2007) A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med 37(3): 341–349, Epub 2006/12/21
17. Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G et al (2007) Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 191:441–448
18. Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K et al (2003) Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Arch Gen Psychiatry 60(1):49–56
19. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C (2001) Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 50(1):58–61
20. Rajkowska G, Goldman-Rakic PS (1995) Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. Cereb Cortex 5(4):323–337
21. Fitzgerald PB, Oxley TJ, Laird AR, Kulkarni J, Egan GF, Daskalakis ZJ (2006) An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res 148(1):33–45
22. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R et al (2009) A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 34(5):1255–1262, Epub 2009/01/16
23. Herwig U, Satrapi P, Schonfeldt-Lecuona C (2003) Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 16(2):95–99, Epub 2004/02/24
24. Beam W, Borckardt JJ, Reeves ST, George MS (2009) An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2(1):50–54, Epub 2009/01/01
25. Lee KC, Finley PR, Alldredge BK (2003) Risk of seizures associated with psychotropic medications: emphasis on new drugs and new findings. Expert Opin Drug Saf 2(3):233–247, Epub 2003/08/09

rTMS-Associated Adverse Events, Safety and Monitoring

7

7.1 Introduction

rTMS treatment is generally very well tolerated. It is notable that the overall discontinuation rate is markedly lower than that usually seen in depression treatment trials, especially trials of medication. For example, in the two large multisite rTMS trials, the withdrawal rate in the active groups was 12 % and <10 % [1, 2]. It is often less than 5 % in single site studies (e.g. [3]). However, there are some clear contraindications to, important safety considerations for and side effects of rTMS treatment.

7.2 Contraindications

The major contraindications to rTMS treatment fall into two categories:

1. Conditions that raise the risk of seizure induction
   These conditions include epilepsy or another seizure disorder or other forms of active brain illness such as a recent cerebral vascular accident, or a medical condition that substantially raises cortical excitability. In addition, alcohol or drug withdrawal, including withdrawal from benzodiazepines, can substantially increase seizure risk.
2. The presence of material that could interact with the induced magnetic field
   rTMS may potentially interact with implanted material through the induction of currents (especially in circular wires), through heating, through the induction of movement in magnetically active material or through changing the parameters of magnetically programmed devices.

   An implanted cochlear implant, pacemaker or other form of magnetically programmable device may be affected by the magnetic field generated with rTMS treatment. Although studies have not investigated the interaction of rTMS with a cochlear implant, these implants contain looped antenna where induced currents are likely to be substantial. rTMS stimulation has been shown outside of the body to induce only small currents in deep brain stimulation electrodes (e.g. [4, 5]). However, only local currents, not currents between the electrode and the pulse-generating case, were

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_7,

investigated; these latter currents may be greater. rTMS applied close to the pulse generator can produce substantial damage to the device [4]. Researchers have concluded that TMS may be safely applied in the presence of other forms of pulse generators (such as vagal nerve stimulation, cardiac pacemakers and spinal cord stimulators) as long as a substantial distance is maintained between the implanted wires/pulse generator and where the TMS coil is discharged [6]. Padding (such as a lifejacket) may be put in place to prevent accidental stimulation close to the pulse generator [7].

rTMS could also potentially interact with medically implanted metal components in the skull or brain. Skull plates are most commonly made from titanium which is non-ferromagnetic and has low conductivity, lessening the likelihood of significant interaction [8]. Aneurysm clips are frequently cited as a contraindication to rTMS treatment, though one study has calculated that the energy imparted on aneurysm clips would move these minimally in a manner unlikely to produce clinical problems [9].

A further area of relative contraindication to rTMS treatment is the presence of medical problems that could be destabilised if a seizure induced by rTMS was to occur. For example, the presence of substantial ischaemic cardiac disease could be a concern as a patient may not have the necessary cardiac reserve to tolerate the physiological stresses associated with a seizure. However, the potential benefit of rTMS treatment needs to be weighed against this concern, especially as the risk of seizure is quite low.

7.3 Adverse Events

7.3.1 Syncope

The major safety concern with rTMS treatment has been related to the potential for seizure induction (see below). However, syncope ('fainting') is another mechanism through which patients may lose consciousness during a medical procedure such as rTMS, and it is possible that this occurs more commonly than seizure. Syncopal reactions are relatively common following medical procedures such as blood taking, and there appears to be a group of individuals susceptible to this type of reaction.

Syncopal reactions are brief and have no long-term consequences. However, it can be difficult to distinguish these from rTMS-induced seizures. This diagnostic problem arises if patients display behavioural manifestations whilst unconscious that might be attributed to seizure activity. Seizure-like activity including muscle jerks and tonic muscle activity can occur during syncopal episodes. However, tongue biting or incontinence is infrequent during syncopal episodes and is more likely to indicate seizure activity. Syncopal episodes are frequently preceded by a patient experiencing light-headedness, a need to lie down, nausea and a sensation of heat. Notably, patients will recover consciousness fully within seconds, in a much more rapid manner than would be expected following a seizure, where full consciousness may take several minutes to re-establish. There is no definitive test to permit the

delineation of these two types of episodes: prolactin may be elevated following a generalised seizure but does not have adequate specificity to be relied on clinically.

The immediate management of a patient who has lost consciousness during TMS does not depend on whether the diagnosis of syncope or seizure is made at the time. Regardless, the patient should be assisted to lie in a prone position on one side and the airway protected as required. Movement of the subject undergoing a tonic–clonic seizure should not occur until motor activity has ceased. Evaluation following the event is likely to involve neurological review, including the possibility of the conduct of an EEG.

7.3.2 Seizure Induction

The major risk with rTMS treatment is the induction of seizure activity [10, 11]. A number of seizures were reported with TMS prior to the delineation of safety guidelines defining safe stimulation parameters [11]. Since that time, rTMS use has expanded rapidly, and large numbers of subjects have undergone stimulation protocols across a variety of psychiatric and neurological disorders. Despite this marked increase in use, there have only been sporadic published reports of seizure induction and mainly in conditions other than depression. All of the reported seizures occurring with rTMS treatment have been during or immediately after stimulation trains. There is no evidence that rTMS produces changes in brain activity that predispose individuals to experience seizures some time following the end of stimulation. In addition, where seizures have occurred, there is no evidence that individuals have developed a propensity to experience seizures in the future, or have experienced ongoing adverse consequences.

Box 7.1. Stimulation Parameters and Seizure Risk

For over 15 years, it has been recognised that the likelihood of seizure induction is related to several aspects of stimulation characteristics: stimulation frequency, train duration, intensity and the duration of time between rTMS trains. Safety guidelines have been published describing what are known to be safe combinations of these parameters. For example, when stimulation is applied at 10 Hz, 5 s is considered a safe train duration when stimulation is applied at up to 110 % of the resting motor threshold (Table 7.1). This train duration is reduced to 4.2 s at 120 % of the RMT and 2.9 s 130 % of the RMT. It should be noted that the vast majority of research that has informed these guidelines has been conducted with stimulation of the primary motor cortex. It is not clear whether the same guidelines should directly translate to other non-motor brain areas. However, providing stimulation in experimental and treatment studies within these guidelines has not resulted in a substantial rate of seizures. Therefore, in the absence of alternative data, these guidelines should be followed unless a clear rationale is provided and informed consent obtained with an awareness of the novelty of stimulation parameters.

Table 7.1 Established safe stimulation parameters for individual trains

	Intensity (% of RMT)				
Frequency	90	100	110	120	130
1	>1,800	>1,800	<1,800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

Adapted from [6]
The maximum established safe train duration for motor cortical stimulation based on varying frequencies and intensities. Stimulation in excess of the safe train duration may result in the development of seizures or seizure-like brain activity. Durations marked with a '>' are the maximal tested durations

A number of the seizures reported since the publication of safety guidelines in 1998 [11] have occurred when stimulation was provided outside of safety guidelines. For example, a generalised seizure was reported following stimulation with 10 Hz trains of 10 s duration in a patient with chronic pain (at 100 % of the RMT) [12]. A second generalised seizure occurred in a patient with major depression during 15 Hz stimulation provided via 10 s trains at 110 % of RMT [13].

However, there have been several events reported as seizures where stimulation was provided within the 1998 guidelines [11]. In one patient with bipolar disorder, a generalised seizure was induced during single-pulse TMS measurement of the RMT [14]. Notably, this patient had a family history of epilepsy and was concurrently taking chlorpromazine and lithium. A second seizure was reported during RMT assessment, but this time in a patient with multiple sclerosis [15]. A generalised seizure was reported in a patient with tinnitus receiving rTMS treatment at 1 Hz [16], although the possibility that this was syncopal has been raised [17]. A single seizure has also been reported using continuous theta burst stimulation, an experimental paradigm involving repeated application of three train pulses at 50 Hz [18].

It is notable that even in patients with a substantial risk for seizure induction, rTMS-related seizures are rare. A review of the safety of rTMS in patients with epilepsy found that less than 2 % of patients have experienced an event during rTMS (4 of 280 patients) [19].

Monitoring of EEG during rTMS treatment does not appear to provide information likely to be useful in the prevention of seizure induction. As evident in a recent review [6], multiple studies have explored the induction of transient epileptiform activity during rTMS treatment. This is occasionally detectable in patient groups but does not appear to be of use in monitoring treatment [6].

A number of conditions increase the risk of seizure induction necessitating avoidance of the rTMS procedure, or use with considerable caution. These include a past history of epilepsy or seizures or a currently active brain disorder. The presence of

unstable cardiac disease also requires caution due to the increased demands that could be placed on the cardiovascular system in the event of a seizure. A history of ongoing problematic alcohol misuse is a contraindication, especially given the increased risk of seizures during withdrawal stages of use. Patients taking benzodiazepines should be advised not to discontinue their use during treatment due to the increased risk of seizure during benzodiazepine withdrawal.

7.4 Other Potential Safety Concerns

7.4.1 Impairment of Cognition

The potential for rTMS treatment to produce cognitive impairment has been a concern since the initial development of the procedure. Given the cognitive side effects that complicate the use of ECT, it is a reasonable concern. Clearly, if rTMS is able to produce lasting brain changes sufficient to ameliorate depressive symptoms, it could potentially also produce brain changes with negative implications. Indeed, transient disruption of cognition is a well-recognised effect of stimulation at certain brain sites (e.g. [20]), though enhanced function is reported in other domains [21–23].

The main question is therefore whether deleterious effects of rTMS on cognition persist after stimulation or develop with repeated applications of rTMS during a treatment course. Fortunately, neither appear to be the case. A range of studies have investigated cognitive function in patients with depression, before and after a course of rTMS. For example, in an early study, Little et al. tested 16 cognitive measures after 1 week of 1 Hz and 1 week of 20 Hz rTMS at 80 % of the RMT in a crossover design and reported no adverse effects. No deterioration in cognitive function was also reported in an open study of 2 weeks of 20 Hz rTMS administered at 80 % of the RMT [24]. Loo et al. analysed cognitive outcomes across 39 clinical studies [10]. Although in three studies deterioration on one or more cognitive tests was reported, a substantially greater number of studies reported cognitive improvement, and no specific pattern of cognitive deterioration was apparent across the trials. An analysis of potential cognitive side effects of rTMS was also included in the pivotal Neuronetics Ltd-sponsored clinical trial [3]. In this study, up to 216,000 pulses were applied to patients, typically 3,000 pulses per day over an hour, each day, for 6–9 weeks at 120 % of the RMT. No cognitive deterioration was noted across the Mini Mental State Examination, the Autobiographical Memory Interview or the Buschke Selective Reminding Test.

The conclusion that is most appropriately drawn from these studies is that there is no current evidence that rTMS as applied in its standard clinical forms for the treatment of depression produces cognitive side effects. However, as rTMS dosing and modes of application change over time (e.g. with the introduction of theta burst stimulation), cognitive safety will require continued reappraisal. The potential capacity of rTMS to produce enduring changes in brain function should also be considered when rTMS is being used in an off-label manner.

7.4.2 Hearing Impairment

When an rTMS machine produces its magnetic field, a substantial sound is generated by the deformation of the stimulating coil. At times this sound may exceed what is considered to be safe for direct exposure to the ear, with sound levels of up to 140 dB [25]. In early studies, some changes in auditory thresholds were reported in individuals exposed to rTMS stimulation, although these reports were not of permanent changes (e.g. [26]). A persistent decrease in auditory thresholds was reported in a patient stimulated with a deep TMS (H-coil) who was not using hearing protection during the procedure [27]. A series of more recent studies have reported no changes in hearing thresholds, when rTMS is provided with appropriate hearing protection (e.g. [2]). This has led to the recommendation that therapeutic use of rTMS should be accompanied by the use of appropriate hearing protection including either earplugs or earmuffs. Hearing safety of rTMS in children has not been fully established [6].

7.4.3 Potential Histotoxicity or Other Brain Changes

It is possible that rTMS stimulation could produce damage to brain tissue either through heating effects, effects mediated through the produced magnetic field or to the effects of the induced electrical fields. In regard to the former, heating effects induced by TMS stimulation appear to be minimal and are likely to be limited by the dissemination of heat through natural brain perfusion. There are no known mechanisms through which the induced magnetic field produced during TMS stimulation could generate biological adverse effects in the absence of extraneous implanted metal in the skull or brain. Magnetic forces on ferromagnetic objects such as metallic brain implants could produce displacement of these objects. Skull plates are most commonly titanium which is non-ferromagnetic. One report has shown minimal heating of titanium skull plates with 1 Hz rTMS [8].

Studies of the effects of the induced electrical fields on brain tissue take a number of approaches. Animal studies using direct electrical stimulation have produced pathological changes in brain tissue, but only after extensive periods of stimulation at charge levels markedly in excess of that induced with rTMS stimulation [28]. Animal experiments investigating more standard TMS stimulation have failed to clearly demonstrate evidence of induced pathological changes. However, the interpretation of these studies is considerably confounded by inequities in the application of rTMS across animal and human situations [10]. One animal study reported microvacuolar changes with stimulation intensities equivalent to three times motor threshold, but this finding has not been replicated in at least four other studies that have shown no adverse changes (for review see [29]).

Studies have also looked at potential effects of rTMS on various brain parameters in human subjects. These have shown no adverse effects on the blood–brain barrier [30], no changes in gross brain structure (with MRI) [31] and no adverse effects on EEG, ECG and neurohormonal levels [32]. One human pathological study revealed

no adverse changes in the brains of two patients with epilepsy who underwent rTMS prior to surgery [33].

A further consideration is whether exposure to the magnetic field generated during rTMS has potential adverse consequences. This is especially relevant considering the ongoing debate regarding potential health and safety concerns with exposure to pulsed electromagnetic field (EMF) from mobile phones and other sources. Given the average duration of the TMS magnetic pulse and the number of pulses in treatment courses, it has been calculated that the typical treatment course would provide exposure of only short duration (e.g. 5 s) [10]. Presumably, this would increase with higher doses and longer courses of rTMS as are now currently being evaluated. However, exposure duration would still remain very short compared to other sources of EMF. The nature of the exposure also varies significantly from other sources: TMS-related exposure is high intensity and pulsed for brief duration, compared to the low-intensity but continuous exposure potentially related to other devices. The implications of this variation are unclear, but to date there has been no evidence of any safety-related concerns or complications arising in regard to EMF exposure and rTMS treatment. Although it is typically assumed that there are no direct brain effects of the magnetic field produced during TMS other than those of the secondary electrical field, it is possible that this is not the case. Neurones do contain material that is potentially magnetically manipulable [34]. However, the implications of this manipulation potential to the actions of rTMS remain completely unknown.

7.4.4 Pregnancy: Breastfeeding

As discussed in Sect. 5.5, the use of rTMS in pregnancy has only been described in a limited number of case series (e.g. [35]). No adverse events or negative foetal outcomes have been documented to date. However, the accumulated number of patients treated to date is clearly inadequate to make firm conclusions about safety. The consent of patients for treatment who are pregnant should reflect this in addition to other risk–benefit-associated issues.

A similar conclusion can be made about the use of rTMS in the treatment of patients who are postpartum and breastfeeding. Although rTMS treatment could potentially induce changes in hormonal secretion, changing breast milk composition, there is no evidence of this or associated harmful effects. In addition, hormonal fluctuations associated with breastfeeding may change cortical excitability elevating the risk of seizure induction. These risks are likely to be small.

7.4.5 Children and Adolescents

Data collected on the use of rTMS in children and adolescents has been extremely limited to date, although large numbers of subjects under 18 have participated in single-pulse and paired pulse experimental protocols. One seizure in a 16-year-old female patient has been reported with relatively low-dose stimulation parameters.

This could indicate a the possibility of a higher rate of seizure induction in this population, given that the total number of adolescent patients reported as having received treatment in the literature is very low. However, making inferences from a single case is significantly problematic. Adolescent patients may also be at a higher risk of experiencing syncopal episodes.

7.5 Safety of Operators

As rTMS becomes increasingly utilised in clinical practice, the safety of operators is likely to become the focus of increasing concern. To date, it is not an area to which substantial consideration has been addressed. One study has explored the exposure of staff applying rTMS to magnetic fields, comparing measured and extrapolated fields to European safety guidelines [36]. The authors propose that staff should maintain a distance of at least of 0.7 m from the coil whilst treatment is underway. However, testing was conducted with only one rTMS device, at a limited range of stimulation parameters.

Given that all rTMS treatment coils currently available can be held in place with a holding arm system, it seems sensible to ensure that these are always used when treatment is underway. The operator of the rTMS equipment can then be standing or seated at least 1 m from the coil during treatment, except when making brief checks of coil positioning. We would also recommend that staff administering rTMS wear appropriate ear protection due to the prolonged and repeated exposure to rTMS-related noise.

References

1. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516, Epub 2010/05/05
2. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216
3. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT et al (2008) Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 69(2):222–232, Epub 2008/02/01
4. Kumar R, Chen R, Ashby P (1999) Safety of transcranial magnetic stimulation in patients with implanted deep brain stimulators. Mov Disord 14(1):157–158, Epub 1999/01/26
5. Kofler M, Leis AA (1998) Safety of transcranial magnetic stimulation in patients with implanted electronic equipment. Electroencephalogr Clin Neurophysiol 107(3):223–225, Epub 1998/11/06
6. Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12):2008–2039, Epub 2009/10/17
7. Schrader LM, Stern JM, Fields TA, Nuwer MR, Wilson CL (2005) A lack of effect from transcranial magnetic stimulation (TMS) on the vagus nerve stimulator (VNS). Clin Neurophysiol 116(10):2501–2504, Epub 2005/08/27

8. Rotenberg A, Harrington MG, Birnbaum DS, Madsen JR, Glass IE, Jensen FE et al (2007) Minimal heating of titanium skull plates during 1Hz repetitive transcranial magnetic stimulation. Clin Neurophysiol 118(11):2536–2538, Epub 2007/09/25
9. Barker AT (1991) An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysiol 8(1):26–37, Epub 1991/01/01
10. Loo CK, McFarquhar TF, Mitchell PB (2008) A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol 11(1):131–147, Epub 2007/09/21
11. Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108(1):1–16, Epub 1998/02/25
12. Rosa MA, Picarelli H, Teixeira MJ, Rosa MO, Marcolin MA (2006) Accidental seizure with repetitive transcranial magnetic stimulation. J ECT 22(4):265–266, Epub 2006/12/05
13. Prikryl R, Kucerova H (2005) Occurrence of epileptic paroxysm during repetitive transcranial magnetic stimulation treatment. J Psychopharmacol 19(3):313, Epub 2005/05/13
14. Tharayil BS, Gangadhar BN, Thirthalli J, Anand L (2005) Seizure with single-pulse transcranial magnetic stimulation in a 35-year-old otherwise-healthy patient with bipolar disorder. J ECT 21(3):188–189
15. Haupts MR, Daum S, Ahle G, Holinka B, Gehlen W (2004) Transcranial magnetic stimulation as a provocation for epileptic seizures in multiple sclerosis. Mult Scler 10(4):475–476, Epub 2004/08/26
16. Nowak DA, Hoffmann U, Connemann BJ, Schonfeldt-Lecuona C (2006) Epileptic seizure following 1 Hz repetitive transcranial magnetic stimulation. Clin Neurophysiol 117(7): 1631–1633, Epub 2006/05/09
17. Epstein CM (2006) Seizure or convulsive syncope during 1-Hz rTMS? Clin Neurophysiol 117(11):2566–2567; author reply 7–8. Epub 2006/09/26
18. Oberman L, Pascual-Leone A (2009) Report of seizure induced by continuous theta burst stimulation. Brain Stimul 2(4):246–247
19. Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ Jr, Pascual-Leone A et al (2007) Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 10(4):521–528, Epub 2007/05/12
20. Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler D et al (1997) Rapid rate transcranial magnetic stimulation – a safety study. Electroencephalogr Clin Neurophysiol 105(6):422–429
21. Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K et al (1996) Use and safety of a new repetitive transcranial magnetic stimulator. Electroencephalogr Clin Neurophysiol 101(5):412–417
22. Foltys H, Sparing R, Boroojerdi B, Krings T, Meister IG, Mottaghy FM, Töpper R (2001) Motor control in simple bimanual movements: a transcranial magnetic stimulation and reaction time study. Clin Neurophysiol 112(2):265–274
23. Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J (2001) Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology 56(4):526–528
24. Niehaus L, Hoffmann KT, Grosse P, Röricht S, Meyer BU (2000) MRI study of human brain exposed to high-dose repetitive magnetic stimulation of visual cortex. Neurology 54(1):256–258
25. Counter SA, Borg E (1992) Analysis of the coil generated impulse noise in extracranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 85(4):280–288, Epub 1992/08/01
26. Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M et al (2001) Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. Biol Psychiatry 49(7):615–623, Epub 2001/04/12
27. Zangen A, Roth Y, Voller B, Hallett M (2005) Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin Neurophysiol 116(4):775–779, Epub 2005/03/29

28. McCreery DB, Agnew WF, Yuen TG, Bullara L (1990) Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans Biomed Eng 37(10):996–1001, Epub 1990/10/01
29. Lorberbaum JP, Wassermann E (2000) Safety concerns of TMS. In: George MS, Belmaker RH (eds) Transcranial magnetic stimulation in neuropsychiatry. American Psychiatric Press, Washington, D.C., pp 141–162
30. Niehaus L, Hoffmann KT, Grosse P, Roricht S, Meyer BU (2000) MRI study of human brain exposed to high-dose repetitive magnetic stimulation of visual cortex. Neurology 54(1):256–258
31. Nahas Z, DeBrux C, Chandler V, Lorberbaum JP et al (2000) Lack of significant changes on magnetic resonance scans before and after 2-weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. J ECT 16(4):380–390
32. Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S et al (1993) Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 89(2):120–130
33. Gates JR, Dhuna A, Pascual-Leone A (1992) Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. Epilepsia 33(3):504–508
34. Dobson J (2002) Investigation of age-related variations in biogenic magnetite levels in the human hippocampus. Exp Brain Res 144(1):122–126, Epub 2002/04/27
35. Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS (1999) Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. J Clin Psychiatry 60(1):50–52, Epub 1999/03/13
36. Karlstrom EF, Lundstrom R, Stensson O, Mild KH (2006) Therapeutic staff exposure to magnetic field pulses during TMS/rTMS treatments. Bioelectromagnetics 27(2):156–158, Epub 2005/11/24

Side Effects of rTMS Treatment

8

8.1 Introduction

rTMS is generally very well tolerated. The most commonly reported side effects of rTMS treatment are the occurrence of discomfort or pain during stimulation and the development of a headache during or after treatment. Inductions of psychiatric symptoms, muscle tension or seizure are also possible.

8.2 Site or Regional Pain

Treatment-related discomfort or pain is usually experienced directly beneath the TMS coil. However, it can also be experienced in the forehead, the region of the upper eyelid or even in the upper jaw teeth. Pain is most likely to relate to trigeminal nerve stimulation and direct muscle contraction. It is also possible that head fixation during treatment sessions will produce pain through neck discomfort.

The experience of discomfort or pain is highly variable between individuals; it may be strongly influenced by coil location or orientation as well as the intensity and frequency of stimulation. When the rates of pain and discomfort in sham controlled studies were analysed, 39 % of patients receiving active treatment reported pain or discomfort compared to 15 % with sham rTMS [1]. Despite this relatively high rate, discontinuation due to discomfort is infrequent in rTMS treatment trials.

A variety of methods have been explored to reduce treatment-related discomfort. Researchers have used topical or locally injected anaesthetic agents or inserted air-filled or foam pads between the coil and the scalp surface. A substantial beneficial effect was seen with local anaesthetic injection but not with the other techniques in a pilot study [2]. The commercially available Neuronetics Ltd-manufactured rTMS device has a single-use disposable attachment designed to reduce local discomfort. However, no systematic studies have been published exploring whether this attachment has clinical benefit.

Stimulation-related discomfort may be reduced in several practical ways. First, small modifications of coil position or orientation may lessen the sensation produced with stimulation. Given the inherent inaccuracy with standard methods of

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_8,

coil localization, although it has not been systematically assessed, there is no reason to believe that small coil modifications would substantially affect treatment efficacy. Second, a decrease in stimulation intensity will reduce discomfort in most patients. Given that there seems to be a relationship between stimulation intensity and efficacy, this decrease should be limited. However, antidepressant effects of rTMS have been seen from 90 to 120 % of the RMT and may well still be produced if intensity is decreased from the higher stimulation levels.

Anxiety also appears to be a factor determining the intensity of rTMS-related discomfort. Therefore, in most patients it is sensible to begin treatment at a low stimulation intensity that is likely be tolerable to allow patients to become comfortable with the sensation. Stimulation intensity can then be progressively increased over one or several sessions. In our experience this is a more sensible approach than starting stimulation at full intensity and reducing if required. This later approach may establish a strong negative expectation and association with treatment that may be long lasting. It is important to note that discomfort may well lessen over several treatment sessions with consistently applied intensity [3, 4]. In one study, a substantial reduction in pain occurred in the first few days with a steady progressive reduction continuing throughout 3 weeks of treatment [4].

Strategies to Minimise Scalp Discomfort and Pain

- Shift coil 0.5–1.0 cm towards the midline.
- Shift coil 0.5–1.0 cm posterior.
- Rotate handle of coil ~20° towards midline.
- Reduce stimulation intensity.

8.3 Headache

Headache is the other common side effect experienced with rTMS treatment. It has been reported in about 28 % of patients provided with active treatment compared to 16 % with sham across clinical trials [1]. Headache can be reported during stimulation or afterward treatment. On occasion this does require the use of analgesic medication.

8.4 Psychiatric Complications

The major potential psychiatric complication of rTMS treatment for patients with mood disorders is the induction of mania. This has been documented across a number of case studies (e.g. [5–7]), which include treatment even in patients with bipolar disorder. Some researchers suggested that switch rates may not substantially be greater than with sham treatment left-sided rTMS, low-frequency right-sided rTMS and bilateral stimulation. Manic induction has been reported predominately in

patients with bipolar disorder but also in several patients with unipolar depression [7, 8]. Xia et al. in 2008 summarised the literature on manic induction finding only 13 cases across over 50 randomised trials [9]. The reported rates of manic switch with active treatment were only marginally greater than that seen with sham rTMS (0.84 versus 0.73 %) and low compared to what would be expected without treatment. This suggests rTMS may not elevate manic switch rates. Whatever the relationship between rTMS treatment and mania induction, it seems sensible to warn patients undergoing treatment of this possibility, particularly those with bipolar disorder. It would be reasonable to advise patients who have experienced substantial manic episodes in the past, especially episodes compromising their well-being, to take a mood stabiliser during their course of rTMS treatment.

In one case reported by George et al. [8], manic symptoms resolved when treatment scheduling was reduced from daily to every second day. We have had similar experiences with several patients who have been able to be successfully treated by reducing the intensity of treatment scheduling, despite early emerging manic symptoms.

A second, but less well-validated, concern is the potential induction of psychotic symptoms during rTMS treatment. The development of persecutory delusions was reported in a single case study of a non-psychotically depressed subject. In this instance, a causative relationship was suggested due to a close temporal relationship with treatment [10], and the possibility that it resulted from subcortical dopamine release has been raised. Regardless, if the induction of psychotic symptoms is related to rTMS treatment, it seems a highly infrequent possibility given the large number of rTMS patients who have undergone treatment in recent years without further reports.

8.5 Seizure Risk and Other Considerations

There are no other side effects consistently reported in randomised trials as occurring at greater frequency with active stimulation compared to sham. Muscle twitching was reported in 20 % of the subjects in the Neuronetics Ltd-sponsored pivotal trial, but it was not specified whether this occurred only during stimulation or whether it was a persistent effect posttreatment [11]. Muscle twitching in the contralateral arm during rTMS treatment can occur through the inadvertent placement of one wing of a figure of eight coil close enough to the motor cortex to cause neuronal depolarisation in this brain region. When muscle twitching occurs during rTMS treatment, it is important to try and differentiate whether it is arising through direct stimulation of the motor cortex or whether it could be occurring via spreading neuronal excitation from prefrontal to motor areas. The latter may be the precursor of a seizure event.

With direct motor cortex stimulation, twitching will occur during the stimulation train and cease immediately at the end of the train. Twitching should also be substantially reduced in magnitude or cease altogether with forward movement or rotation of the coil such that the posterior wing is less adjacent to the motor cortex.

Motor cortical stimulation due to spreading excitation will result in muscle twitching that persists beyond the end of the stimulation train. If this is noted to occur, treatment should cease until review. At a minimum, the review should entail remeasurement of the motor threshold to ensure that the subject is not being treated at excessively suprathreshold intensity. If spreading excitation is noted at standard stimulation doses following remeasurement of the RMT, strong consideration should be given to stopping rTMS and looking at other treatment alternatives.

References

1. Loo CK, McFarquhar TF, Mitchell PB (2008) A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol 11(1):131–147, Epub 2007/09/21
2. Borckardt JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Anderson B et al (2006) Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT 22(4): 259–264, Epub 2006/12/05
3. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT et al (2008) Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 69(2):222–232, Epub 2008/02/01
4. Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH et al (2009) Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-label phase of a multi-site trial (OPT-TMS). Brain Stimul 2(2):88–92, Epub 2010/02/18
5. Ella R, Zwanzger P, Stampfer R, Preuss UW, Muller-Siecheneder F, Moller HJ et al (2002) Switch to mania after slow rTMS of the right prefrontal cortex. J Clin Psychiatry 63(3):249
6. Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, Walpoth M, Rupp CI, Hinterhuber H et al (2004) Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? A case report. J Clin Psychiatry 65(11):1575–1576, Epub 2004/11/24
7. Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A et al (2003) Induction of mania by rTMS: report of two cases. Eur Psychiatry 18(4):196–198
8. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P et al (1995) Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6:1853–1856
9. Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ et al (2008) Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol 11(1):119–130, Epub 2007/03/06
10. Zwanzger P, Ella R, Keck ME, Rupprecht R, Padberg F (2002) Occurrence of delusions during repetitive transcranial magnetic stimulation (rTMS) in major depression. Biol Psychiatry 51(7):602–603
11. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216

Maintenance and Continuation Treatment

9

9.1 Introduction

To date, in the significant majority of settings in which rTMS has been used in the treatment of depression, it has been applied as a time-limited treatment for a defined depressive episode. However, depression is clearly a relapsing illness, and the majority of patients who have responded to rTMS are likely to need some form of treatment to minimise the chances of experiencing relapse and/or maximise the duration of time until this occurs. In the event that relapse occurs, retreatment with rTMS may be a useful option.

9.2 Rates of Relapse Following rTMS Treatment

Unfortunately, there appears to be a relatively high relapse rate in the 6–12 months following a successful course of rTMS. This is a situation analogous to that following a successful treatment of depression with ECT, where relapse rates are known to be high and are frequently reported as up to 50 % within 6 months [1, 2].

One of the first studies to explore rTMS relapse rates compared relapse rates following successful rTMS or ECT and showed similar rates [3]: 20 % of 41 patients in the overall study relapsed over a 6-month period, 4 in each of the ECT and rTMS groups.

The largest and most substantive study of post-rTMS relapse involves the retrospective analysis of the outcomes of 204 patients who had undergone rTMS treatment. All patients had achieved remission of depression with a Hamilton Depression Rating Scale (HAMD) score of less than eight and were followed for 6 months. Relapse was defined as an increase in HAMD score above 8, a very conservative figure as patients could be defined as having relapsed with only very minor depressive symptoms. Nonetheless, approximately 25 % were categorised as having relapsed at 2 months, 40 % at 3 months and 80 % by 6 months, obviously a very high figure [4]. An additional study has reported the follow-up of patients who received rTMS treatment in a large multisite trial. Patients who had

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_9,

at least a 25 % reduction in HAMD scores during acute rTMS treatment were tapered onto antidepressant medication and followed up over 6 months. Relapse was defined as a recurrence of symptoms sufficient to meet DSM-IV criteria for major depression over two consecutive weeks. Ten of 99 (10 %) patients relapsed fully over 24 weeks and a total of 38.4 % had substantial symptom deterioration of sufficient severity to justify reintroduction of rTMS treatment (an increase of at least one point on the Clinical Global Impression-Severity (CGI-S) scale for two consecutive weeks) [5]. Fifteen patients experienced a second period of symptom recurrence following an additional course of rTMS and five patients a third period of symptom recurrence within the 6-month period all justifying further rTMS treatment.

Our centre has conducted over 700 patient treatment courses in multiple clinical trials over the past 10 years. In these trials we have observed a relapse rate of approximately 20–30 % within 3 months of treatment, increasing to a 50–60 % relapse rate during the 12 months following treatment (unpublished data). This is despite the vast majority of these patients (>95 %) being on maintenance antidepressant medication, often in conjunction with additional augmentation agents such as lithium and other mood stabilisers.

9.3 Approaches to Minimise Relapse

The first step in minimising relapse is the identification of those likely to experience it. Although there has been minimal systematic research in this area, there are likely to be clinical variables that predict the chance of early relapse. For example, the presence of persistent depressive symptoms despite a significant improvement in overall depression severity is likely to be related to early deterioration once treatment finishes. The presence of substantial ongoing life stressors, marital or work-related conflict and the presence of substantial axis II or substance related comorbidity would all seem to be potential predictors of early relapse.

Given the importance of these factors, it is critical to assess each patient towards the end of the course of rTMS treatment for factors that are likely to undermine longer-term outcomes. A direct approach to tackling comorbid issues or social stressors should commence prior to the cessation of active treatment. For example, patients with a history of comorbid substance use problems should be engaged in appropriate therapeutic programmes as early as feasible. In the context of ongoing relationship difficulties, family or marital therapy should be considered and potentially commenced prior to the end of rTMS treatment. This will allow issues that are likely to undermine progress to be identified, relevant others to be engaged and a temporary plan put in place to provide adequate support to the patient whilst longer-term changes can be undertaken.

Along with the consideration of these factors, an active maintenance plan should be instituted, involving the strategies to be adopted for each individual patient. Maintenance treatment may include antidepressant medication, psychotherapy and/or further treatment with rTMS.

9.3.1 Medication Treatment

There is clearly established efficacy for the use of antidepressant medication in the prevention of relapse following initial response to medication. However, little systematic research has investigated whether the recommencement of antidepressant treatment or continuation of antidepressants during and after rTMS treatment will reduce subsequent relapse rates. One study has addressed these issues, although unfortunately only over a very short period of time and in an atypical sample. In this trial, patients with treatment resistant vascular depression were provided acute treatment with rTMS. After rTMS patients were given 20 mg/day of citalopram and evaluated at 3, 6 and 9 weeks. Thirteen of 33 patients responded to rTMS and subsequently received 9 weeks of medication. During this 9-week period, four relapsed and nine remained well [6]. In a second study, a small group of patients with bipolar disorder whose depressive episode had responded to rTMS were followed whilst continuing antidepressant medication [7]. Of six rTMS responders, four remained well over a 12-month period of time. Of the other responders, one relapsed and another partially relapsed after 6 months.

In considering the role of antidepressant medication post-rTMS, some information may be extrapolated from trials of medication treatment post-ECT as this is also a time-limited episodic treatment. Even if patients had previously failed to respond to medication treatment, antidepressant medication may have a role in the prevention of relapse. For example, a small study showed that imipramine substantially reduced ECT relapse rates compared to placebo in medication-nonresponsive patients [8]. However, antidepressant medication alone may produce suboptimal benefits compared to combination treatment. Sackiem et al. demonstrated that lithium combined with nortriptyline, a tricyclic antidepressant, produced a substantially lower relapse rate and longer time to relapse compared to the antidepressant alone or placebo [9]. A second study has also more recently supported the notion that adding lithium to an antidepressant treatment may reduce relapse post-ECT [10]. In the context of the research, it would be sensible to suggest that where pharmacotherapy is the mainstay of maintenance treatment post-rTMS, a combination of an antidepressant and lithium should be considered. No studies have been published exploring the use of new antidepressant agents such as serotonin or serotonin noradrenaline reuptake inhibitors as maintenance therapy in conjunction with lithium. The choice of medication is likely to be influenced by factors such as previous tolerance and partial or complete nonresponse to different medication classes. Certainly in patients who relapse after rTMS with continued antidepressant treatment, the addition of lithium should be strongly considered during subsequent maintenance periods.

9.3.2 Psychotherapy

An alternative approach to the prevention of relapse post-rTMS treatment is engagement in a form of psychotherapy. Cognitive behavioural therapy (CBT) and its variations are increasingly being utilised in the treatment of depression and in the

prevention of depressive relapse. CBT is widely accepted and provided as a first-line treatment for depression and there are a number of meta-analyses supporting its efficacy (e.g. [11]). Although rates of treatment response to CBT seem to be similar to antidepressant medication, CBT appears to have distinct advantages over medication in terms of relapse prevention, with patients relapsing at a lower rate after the end of CBT treatment [12–14]. The success of CBT in maintaining treatment benefits has led to it being used as a specific relapse prevention intervention following other acute treatments. Fava et al. [15] used a sequential trial design in which the acute phase of depression was treated with antidepressant medication, with responders then tapered off medication and randomised to receive either a course of CBT or routine clinical management. After 2 years, the patients receiving CBT showed a relapse rate of 25 % compared to 80 % in the control group. After 6 years, the difference was 40 % versus 90 %, respectively [15]. Another trial found that the combination of CBT with maintenance antidepressant medication following acute episode recovery was superior to maintenance antidepressant medication alone in preventing relapse [16]. This observed advantage persisted several years later [17].

Subsequent trials have refined the delivery of CBT during the recovered phase by integrating CBT for depression [18] with mindfulness training to create an efficient 8-session course specifically targeting depressive relapse. Mindfulness training is used to develop attention control skills which help the person to more effectively recognise and disengage from patterns of depressive thinking (e.g. hopelessness, guilt, rumination) as they re-emerge, preventing them from escalating. The efficacy of MBCT in minimising relapse has been established in four randomised controlled trials which have found reduced rates of relapse in people with a history of recurrent depression (3 or more episodes), compared with routine clinical management alone [19, 20]. A meta-analysis of these four studies found an average rate of relapse over 12 months of 32 % for MBCT compared with 60 % for clinical management [21]. A further trial has found that the post-therapy relapse prevention effects of MBCT when antidepressants are withdrawn are at least as effective as continuing maintenance antidepressant medication [22]. Furthermore, there is strong evidence that the relapse-preventing effects of MBCT are mediated by changes in processes targeted by the intervention [23].

Unfortunately, no research to date has assessed the value of CBT or MBCT in the prevention of relapse post-rTMS. One small initial open-label study has explored the role of CBT in the prevention of relapse following ECT [24]. CBT post-ECT was feasible and appeared to enhance duration of persistence of response. There is no intrinsic reason why these forms of psychotherapy would not be practically useful in the prevention of relapse post-rTMS and should be actively considered.

9.4 Maintenance rTMS Treatment

The final possibility is the use of maintenance rTMS to prevent relapse. This has face validity given the response to active treatment in the individual patient. However, maintenance rTMS has only been studied in a very limited way and there

are no sham controlled studies supporting its efficacy to date. The most commonly reported maintenance model has been the provision of weekly or fortnightly single rTMS sessions, often with a progressive decrease in session frequency over time. This is often done with maintenance ECT. For example, in a small open-label follow-up study, Isserles et al. provided weekly TMS sessions to 11 patients who had remitted in a trial of a form of deep TMS [25]. Ten patients remained in the study and in remission for the 4 weeks, whilst one withdrew due to persistent insomnia. Earlier, O'Reardon et al. reported the treatment of 10 patients who received maintenance treatment once or twice a week for between 6 months and 6 years [26]. They described seven of the patients as having experienced substantial benefit, with three of the seven not requiring medication treatment. Li et al. reported the maintenance treatment of seven patients with bipolar disorder who were provided with weekly TMS for up to a year [27]. Three patients completed a full year's treatment without substantial relapse.

Another possibility is the more intensive provision of multiple sessions. Over a number of years, we have provided maintenance rTMS by administering five individual treatment sessions over a 3-day period, usually over a weekend, once per month, in patients who have had several depressive episodes successfully treated with rTMS (unpublished data). Patients enrolled in this programme had experienced a relapse within 3 months of the end of their initial course of rTMS. On response to a second course of rTMS, they were entered into maintenance treatment. In an analysis of 37 patients who were enrolled in this programme, 21 experienced a relapse after a mean treatment duration of 10.5 months. Six patients continued until study end without relapse (mean of 12 months) and eight withdrew following an average of 6.2 months maintenance treatment without having experienced relapse.

A final possibility for maintenance rTMS is the use of a targeted intermittent strategy. For example, if a patient has been noted to relapse regularly 6 months post-rTMS, initiating maintenance 5 months after acute treatment and continuing for several months may be a potentially useful approach. Similarly short periods of maintenance treatment could be used every 6 months or so. Alternatively, on demonstration of early signs of relapse, patients could be rapidly re-engaged in a maintenance treatment course of shorter duration. This strategy, however, may not be suitable for a significant proportion of patients who deteriorate rapidly.

9.5 Repeated rTMS Treatment

If patients have successfully responded to rTMS treatment and experience a relapse, they are frequently likely to be keen to engage in a further acute course of treatment. Several studies have described populations who have been engaged in retreatment during depressive relapse. The majority of these studies suggest that most patients will successfully respond to treatment when it is applied on a second or subsequent occasion [5, 28, 29]. For example, in a study by Janicak et al., 38 patients were retreated during 24 weeks of follow-up and 32 (84.2 %) subsequently improved [5]. We have previously described the treatment of 19 patients over a course of 30

episodes of depressive relapse, where the vast majority of subsequent courses resulted in treatment response [29]. This response pattern has continued into the repeat treatment of now more than 100 patients, some on more than five rTMS treatment occasions. However, we have noted that a failure to respond to treatment can occur at any subsequent treatment course.

9.6 Summary

All patients who have responded to a course of rTMS should have an individually developed maintenance treatment plan. For many patients, especially following an initial response to rTMS, this is likely to involve addressing factors that may contribute to relapse, continuing antidepressant treatment and considering psychotherapy. However, if relapse occurs despite maintenance medication and/or psychotherapy, maintenance rTMS following a subsequent treatment course may be considered. Although there is a substantial lack of systematic evidence for the use of maintenance rTMS, it is likely that a significant proportion of patients having successfully responded to rTMS but not other treatment modalities are likely to be motivated to engage in maintenance treatment. The use of maintenance rTMS under these circumstances seems clinically reasonable but should be accompanied by a systematic attempt to collect efficacy data, at least on an individual patient basis, to justify ongoing treatment.

References

1. Grunhaus L, Dolberg O, Lustig M (1995) Relapse and recurrence following a course of ECT: reasons for concern and strategies for further investigation. J Psychiatr Res 29(3):165–172, Epub 1995/05/01
2. Tew JD Jr, Mulsant BH, Haskett RF, Joan P, Begley AE, Sackeim HA (2007) Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. Ann Clin Psychiatry 19(1):1–4, Epub 2007/04/25
3. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L (2002) Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals – preliminary report. Biol Psychiatry 51(8):687–690
4. Cohen RB, Boggio PS, Fregni F (2009) Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. Depress Anxiety 26(7): 682–688
5. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM et al (2010) Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 3(4):187–199, Epub 2010/10/23
6. Robinson RG, Tenev V, Jorge RE (2009) Citalopram for continuation therapy after repetitive transcranial magnetic stimulation in vascular depression. Am J Geriatr Psychiatry 17(8): 682–687
7. Dell'osso B, D'Urso N, Castellano F, Ciabatti M, Altamura AC (2011) Long-term efficacy after acute augmentative repetitive transcranial magnetic stimulation in bipolar depression: a 1-year follow-up study. J ECT 27(2):141–144, Epub 2010/10/23

8. van den Broek WW, Birkenhager TK, Mulder PG, Bruijn JA, Moleman P (2006) Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. J Clin Psychiatry 67(2):263–268, Epub 2006/03/29
9. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM et al (2001) Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 285(10):1299–1307, Epub 2001/03/20
10. Rehor G, Conca A, Schlotter W, Vonthein R, Bork S, Bode R et al (2009) Relapse rate within 6 months after successful ECT: a naturalistic prospective peer- and self-assessment analysis. Neuropsychiatr 23(3):157–163, Epub 2009/08/26. Ruckfallraten innerhalb von 6 Monaten nach erfolgreicher EKT-Eine naturalistische prospektive Fremd- und Selbstbeurteilungsanalyse
11. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM (1998) A meta-analysis of the effects of cognitive therapy in depressed patients. J Affect Disord 49(1):59–72, Epub 1998/05/09
12. Blackburn IM, Eunson KM, Bishop S (1986) A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. J Affect Disord 10(1):67–75, Epub 1986/01/01
13. Evans MD, Hollon SD, DeRubeis RJ, Piasecki JM, Grove WM, Garvey MJ et al (1992) Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 49(10):802–808, Epub 1992/10/01
14. Simons AD, Murphy GE, Levine JL, Wetzel RD (1986) Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. Arch Gen Psychiatry 43(1):43–48, Epub 1986/01/01
15. Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S (2004) Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. Am J Psychiatry 161(10):1872–1876, Epub 2004/10/07
16. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R et al (1999) Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry 56(9):829–835, Epub 2003/07/30
17. Paykel ES, Scott J, Cornwall PL, Abbott R, Crane C, Pope M et al (2005) Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychol Med 35(1):59–68, Epub 2005/04/22
18. Beck J (1996) Cognitive therapy: basics and beyond. Guilford Press, New York
19. Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA (2000) Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol 68(4):615–623, Epub 2000/08/31
20. Ma SH, Teasdale JD (2004) Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J Consult Clin Psychol 72(1):31–40, Epub 2004/02/06
21. Chiesa A, Serretti A (2011) Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Res 187(3):441–453, Epub 2010/09/18
22. Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K et al (2008) Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol 76(6):966–978, Epub 2008/12/03
23. Kuyken W, Watkins E, Holden E, White K, Taylor RS, Byford S et al (2010) How does mindfulness-based cognitive therapy work? Behav Res Ther 48(11):1105–1112, Epub 2010/09/03
24. Fenton L, Fasula M, Ostroff R, Sanacora G (2006) Can cognitive behavioral therapy reduce relapse rates of depression after ECT? A preliminary study. J ECT 22(3):196–198, Epub 2006/09/08
25. Isserles M, Rosenberg O, Dannon P, Levkovitz Y, Kotler M, Deutsch F et al (2011) Cognitive-emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome. J Affect Disord 128(3):235–242, Epub 2010/07/29

26. O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC (2005) Long-term maintenance therapy for major depressive disorder with rTMS. J Clin Psychiatry 66(12):1524–1528
27. Li X, Nahas Z, Anderson B, Kozel FA, George MS (2004) Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? Depress Anxiety 20(2):98–100
28. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, Pearlman C, Stern WM, Thall M et al (2008) An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. J Clin Psychiatry 69(6):930–934
29. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J (2006) Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. Aust N Z J Psychiatry 40(9):764–768, Epub 2006/08/17

The Use of rTMS in Other Psychiatric Disorders

10

10.1 Introduction

As has been described in previous chapters, rTMS can have powerful effects on the brain. These effects can be neurophysiological (e.g. altering inhibition and plasticity), clinical (e.g. improvement of symptoms in patients with treatment-resistant depression) and cognitive (i.e. transient cognitive lesions, cognitive enhancement). As well as the development of rTMS methods for depression, in the last two decades there has been significant investigation into the treatment of numerous other psychiatric and neurological disorders. Whilst a comprehensive review of all of these findings is beyond the scope of this chapter, we will focus on psychiatric disorders in which initial evidence exists for the clinical utility of rTMS approaches or in which there has been particular therapeutic interest.

10.2 Mania

Due to the promising therapeutic effects of rTMS in depression, interest in the use of the treatment for mania developed early. In an initial study, 16 patients were randomised in a controlled trial of right versus left high-frequency (20 Hz) prefrontal stimulation [1]. Greater therapeutic benefits were seen with right-sided stimulation compared to left-sided stimulation, an observation that has been subsequently used to support notions of left and right-sided laterality activity differences in depression and mania. The therapeutic possibilities with high-frequency right-sided stimulation were also supported in two subsequent case series [2, 3].

However, data from sham-controlled trials is not consistent. In the first of these studies involving 25 patients, no difference between active and sham stimulation was seen [4]. However, in a recent study of 41 patients, a significant benefit of active over sham 20 Hz stimulation was seen with stimulation over a 10-day period [5].

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_10,

10.2.1 Summary

A limited body of research suggests that high-frequency stimulation applied to the right DLPFC may have some anti-manic effects, but this treatment needs to be more systematically evaluated.

10.3 Anxiety Disorders

10.3.1 Obsessive-Compulsive Disorder (OCD)

There is a compelling argument for evaluating the use of rTMS in obsessive-compulsive disorder (OCD). OCD can be highly disabling and patients with OCD often respond poorly to psychotherapy and/or serotonergic antidepressants, the standard forms of treatment. Moreover, unlike MDD which responds well to ECT, there is little to no evidence for therapeutic improvement of OCD with ECT. There is also a compelling mechanistic link between treatment mechanisms linked to rTMS and those mechanisms that are aberrant in OCD. For example, rTMS has been reported to potentiate GABAergic neurotransmission, particularly at high frequencies [6, 7]. rTMS can also modulate NMDA neurotransmitter mechanism [8] both of which have been associated with dysfunction in OCD [9, 10]. As such, not only is there an urgent need for newer treatments in OCD, but rTMS may target putative mechanisms in the cortex that are associated with OCD pathophysiology.

Greenberg et al. initially explored the efficacy of rTMS for OCD [11]. Twelve patients received 20 Hz rTMS at 80 % of the motor threshold to the right or left lateral prefrontal cortex or a control site. Right prefrontal stimulation decreased compulsions and improved mood to a greater degree than left-sided stimulation or control site stimulation. Several studies that have subsequently explored high-frequency stimulation applied to the left DLPFC have reported disappointing results [12, 13], but follow-up studies exploring high-frequency right-sided stimulation have not been systematically conducted.

Several studies have explored low-frequency approaches, generally without positive effects. For example, Alonso et al. reported the effects of 1 Hz rTMS applied to the right DLPFC over eighteen 20-min daily sessions [14]. There were no significant effects on obsessions or compulsions reported. Prasko et al. also used 1 Hz stimulation but applied to the left DLPFC [15]. They also failed to find therapeutic effects. One final study did suggest therapeutic effects of 1 Hz stimulation but applied in this case to the left orbitofrontal cortex [16]. Sixteen patients received active stimulation and seven patients received sham stimulation. They reported a significant difference between active and sham treated for up to 10 weeks after rTMS was completed.

A novel and promising approach has adopted a significantly different target, the bilateral supplementary motor area. An open and a second controlled study conducted by Mantovani et al. has suggested the possible therapeutic value of 1 Hz rTMS applied bilaterally to this site [17, 18]. The supplementary motor area is strongly

connected to the anterior cingulate, a cortical region that was previously reported to be closely associated with the pathophysiology of OCD [18]. However, one subsequent study combining both 1 Hz stimulation of the right DLPFC and 1 Hz stimulation of the supplementary motor area failed to find positive results [19].

10.3.1.1 Summary

Research has not supported the initial contention that DLPFC stimulation may have therapeutic benefits in OCD although high-frequency right-sided stimulation has not been systematically adequately evaluated despite initial promise. The supplementary motor area or orbital frontal cortex appears promising targets, but more detailed research is required to establish efficacy of stimulation at these sites.

10.3.2 Post-traumatic Stress Disorder

A series of relatively inconsistent studies have explored the potential application of rTMS in post-traumatic stress disorder (PTSD). The first of these explored the application of very low-frequency stimulation (0.3 Hz) applied to both the left and right motor cortex, producing a reduction in PTSD symptoms [20]. However, this was an uncontrolled study. Subsequently, studies have investigated a variety of stimulation paradigms including low- and high-frequency stimulation applied to the left DLPFC and low- and high-frequency stimulation applied to the right DLPFC [21–24]. Right-sided high-frequency stimulation has shown the greatest therapeutic promise in two studies which have evaluated stimulation to both hemispheres or compared different frequencies of stimulation applied to the right DLPFC [22, 23]. Given that neuroimaging-based models of PTSD have suggested that hypoactivity of the DLPFC is associated with hyperactivity of the amygdala and underlying illness symptoms and that right-sided changes are predominant in PTSD, a high-frequency approach to right-sided stimulation has some therapeutic rationale [25].

10.3.2.1 Summary

High-frequency stimulation applied to the right DLPFC appears to be the most promising rTMS approach to the treatment of PTSD but requires further evaluation.

10.3.3 Panic Disorder and Generalised Anxiety Disorder

Following several case reports, two randomised controlled trials have explored the use of rTMS in panic disorder, both investigating 1 Hz stimulation applied to the right DLPFC. In the first study, no significant difference was seen between active and sham stimulation in 15 medication-resistant patients [26]. The second study, in a slightly larger sample size ($n=25$), did find significant differences in response between active and sham stimulation [27].

Only one study has explored the possible use of rTMS in generalised anxiety disorder (GAD). This was an open-label study where 1 Hz stimulation was applied to the right DLPFC with the site determined by an fMRI activation scan [28]. Six out of ten patients met remission criteria for reduction in anxiety symptoms within this study.

10.3.3.1 Summary

Only limited research has explored the application of rTMS in panic disorder and GAD. There appears to be a possibility of therapeutic value of 1 Hz stimulation applied to the right DLPFC, but at this stage this has very limited empirical support.

10.4 Schizophrenia

Despite some advances in pharmacotherapy over the last 20 years, a significant percentage of patients with schizophrenia experience disabling refractory symptoms. Furthermore, side effects are common with current pharmacotherapy for schizophrenia resulting in high rates of early treatment discontinuation [29]. Thus, researchers and clinicians have sought novel treatments to target refractory symptoms. rTMS has been relatively extensively investigated as a treatment for schizophrenia vis-a-vis positive (e.g. hallucinations and delusions) and negative symptoms of schizophrenia, as well as cognitive dysfunction.

Increasingly schizophrenia researchers consider this disorder to be highly heterogeneous. Therefore, it follows that specific treatment of individual subcomponents of the syndrome, such as the negative symptoms or hallucinations, may yield greater success than non-specific treatments applied to all patients. It is unlikely that a brain stimulation technique that targets one brain region would be likely to improve multiple dimensions of the illness but may have specific value in ameliorating particular symptoms.

In this regard, rTMS protocols for treatment-resistant schizophrenia have targeted two main cortical areas with differing aims. Dysfunction in the prefrontal cortex is thought to underlie some of the positive and negative symptoms in schizophrenia. Initial treatment protocols targeting the DLPFC in schizophrenia were inspired by treatment protocols used for major depression. Analogous to the situation in depression, hypoactivation in prefrontal regions is thought to correlate with negative symptoms [30]. Thus, it was hypothesised that high-frequency rTMS applied to the DLPFC may improve negative symptoms by increasing cortical activity [31]. The other main cortical region targeted in rTMS studies has been the temporoparietal cortex (TPC). Although there are some contradictory findings, a number of studies have suggested that the pathophysiology of auditory hallucinations is related to hyperactivity in the left TPC [32, 33]. Based on this understanding, Hoffman et al. developed a low-frequency rTMS protocol applied to the left TPC to modulate the overactive state underpinning auditory hallucinations [34, 35].

10.4.1 Prefrontal Stimulation in Schizophrenia

Early rTMS studies in schizophrenia targeted the DLPFC as a non-specific treatment. The first published study used only 30 single rTMS pulses applied openly in a single treatment session and described some short-lived therapeutic effects [36]. In a second small open study, a statistically significant decrease in Brief Psychiatric Rating Scale (BPRS) scores was observed after ten sessions of 1 Hz stimulations applied to the right DLPFC [37]. The improvement was primarily seen in non-specific symptoms, such as anxiety and tension, rather than in the core symptoms of schizophrenia. A larger, controlled study with similar stimulation parameters failed to confirm any significant improvement in schizophrenia symptoms when rTMS was compared to a sham control [38].

High-frequency stimulation to the DLPFC as a treatment for positive symptoms was first studied in a small crossover design comparing left-sided active versus sham stimulation [39]. A significant reduction in BPRS scores was seen with active but not sham stimulation. However, three other studies of high-frequency stimulation of the left DLPFC have failed to demonstrate an improvement in positive symptoms [40–42]. A recent meta-analysis concluded that high-frequency stimulation of the DLPFC has failed to show improvement in positive symptoms as assessed by the positive and negative symptom scale-positive symptom score (PANSS-P) or the scale for the assessment of positive symptoms (SAPS) [43].

In contrast to the negative results found when targeting positive symptoms with high-frequency rTMS to the DLPFC, the treatment of negative symptoms with this approach has yielded somewhat more encouraging results. There have been a series of small parallel design trials. In several studies, there were no differences between active and sham groups [40, 44, 45]. However, four studies have shown a significant advantage of active over sham stimulation [42, 46–48]. Three of these studies [42, 46, 47] used higher stimulation intensity (>100 % of the standard resting motor threshold) and one of the studies used a longer treatment duration (15 days) than the negative studies (10 days) [46]. One of these two positive studies also carefully controlled for the possible confound of improved depressive symptoms using scores on the Calgary Depression Scale for Schizophrenia as a covariate: improved depression did not account for the observed improvement in negative symptoms [42]. Another study compared 20 Hz stimulation to stimulation provided at the patient's individual α-frequency with a sham condition [49]. α-Frequency stimulation was calculated as the patient's peak α-frequency from five frontal EEG leads. The rationale for enhancing activation by using the patient's own α-frequency was based on the hypothesis that a deficiency in oscillation at this frequency is related to the underlying pathophysiology of negative symptoms. Stimulation at the patient's α-frequency resulted in a significantly greater reduction in negative symptoms than the other three conditions. Two studies investigating the use of bilateral high-frequency stimulation have both reported no improvement in negative symptoms [50, 51].

Overall, the studies targeting refractory negative symptoms that used high-frequency stimulation targeted to the DLPFC have produced mixed results. The outcome of the studies may have been hindered by the short duration of treatment typically applied and low doses of rTMS used.

Until recently, no studies have specifically investigated the effect of rTMS applied to the DLPFC on cognition in patients with schizophrenia. Impaired cognition has been increasingly recognised as a primary deficit in schizophrenia [52]. Recent data suggests that high-frequency rTMS applied to DLPFC can improve performance on higher-order cognitive functions and selectively modulate γ-oscillations in frontal regions [53]. Given the prominence of cognitive deficits in patients with schizophrenia and the potential relationship of aspects of cognition such as working memory to high-frequency EEG oscillations, it seems worthwhile to investigate the effect of high-frequency rTMS of the DLFPC on cognition. Recently Barr et al. reported that bilateral rTMS applied at 20 Hz and targeted to the DLPFC could improve working memory deficits in schizophrenia in a study including 27 patients [54]. Working memory was assessed using the N-back task. rTMS significantly improved 3-back accuracy to targets compared to sham. There was also a trend towards significance for the effects of rTMS on the 1- versus 3-back suggesting that rTMS was more effective on working memory performance as difficulty increased. This small study suggests that rTMS should be investigated further as a possible treatment option for cognitive symptoms in schizophrenia.

10.4.2 Temporoparietal Cortex rTMS and Auditory Hallucinations

The most extensively investigated application for rTMS in schizophrenia has been the use of low-frequency stimulation applied to the left TPC (see Fig. 10.1), in an effort to ameliorate auditory hallucinations (AH). Initial studies were of a relatively short duration, but they still demonstrated a decrease in the frequency and intensity of AH [34, 35]. A larger, controlled study of 9 days of low-frequency left-sided (LFL) stimulation of the TPC found a substantial and significant reduction in AH compared to sham. Furthermore, this improvement was sustained in more than half of the improved subjects at 15 weeks posttreatment [55]. In an even larger controlled study, the efficacy finding was confirmed and the treatment demonstrated an excellent safety and tolerability profile (a consistent finding across subsequent studies) [56].

Several investigators have attempted to replicate and extend these findings using open, crossover and parallel randomised controlled designs with mixed results [57–68]. Of note, however, is an open study that correlated response to treatment with reduction in cortical metabolism (as measured by PET imaging) beneath the site of stimulation, substantiating the theoretical rationale for this treatment [65]. The mixed results likely relate to heterogeneity in the duration and intensity of treatment. Interestingly, two of the randomised controlled studies have found significant reduction in frequency and intensity of AH with less than 10 days of treatment [57, 58].

An initial meta-analysis of all acute rTMS treatment studies of AH found an effect size of 0.76 (95 % CI = 0.36–1.17) for LFL rTMS applied to the left TPC, despite variation in the duration and methods of stimulation [69]. Two recent meta-analyses confirmed the finding of a medium to large effect size [43, 70]. The authors point out that there is a large degree of heterogeneity in these studies. Heterogeneity issues included: protocol duration and intensity, differing placebo controls, lack of

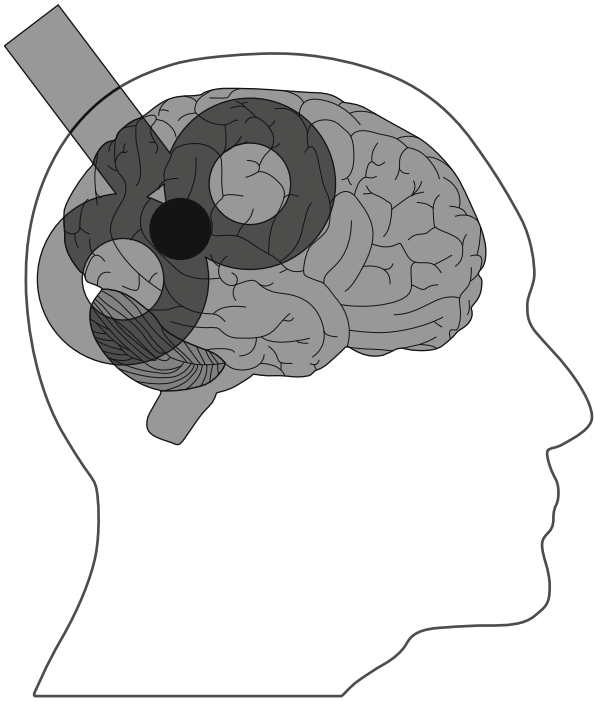


Fig. 10.1 The localization of the TMS coil over temporoparietal junction

adequate control of medications and inadequate assessment of treatment resistance. Furthermore, these authors comment about the need for better follow-up and the need for studies of maintenance treatment in patients that respond to an acute course of rTMS.

In an attempt to optimise efficacy, investigators have started to explore bilateral and right-sided TPC stimulation. Another approach taken to optimising efficacy has been the utilisation of MRI and fMRI to more specifically target the neuroanatomical structures involved in auditory hallucinations. The first study found no specific benefit of rTMS or of MRI-based localization [71]. A second study found an overall benefit with rTMS, but again no improvement with fMRI-based localization [72]. In another study, LFL rTMS was applied to a series of sites activated on fMRI scan for eight intermittent hallucinators or to a series of sites functionally coupled to Wernicke's area in eight patients with continual hallucinations [73]. Stimulation at the left TPC site resulted in a greater rate of reduction in auditory hallucination severity compared to stimulation at other sites. A novel imaging and treatment protocol in a case report has recently been published [74]. The investigators identified the area of highest activation during a language task using fMRI. The area correlated with the left superior temporal gyrus. They theorised that high-frequency stimulation (20 Hz) may reduce AH based on work showing disruption in higher cognitive functions such as speech production [75]. A follow-up study with rTMS targeted to the site identified on individual fMRI scans, in a group of 11 patients,

demonstrated decreased global severity and frequency of AH in 8 of 11 patients, with a large effect size after only 2 days (2,600 pulses) of treatment [76]. This is a striking finding that warrants further investigation with a randomised controlled study. The improvement was present 10 days after treatment in the whole sample and sustained for a mean of approximately 2 months. However, the cost of fMRI localization may be prohibitive for application to the wider population of patients experiencing refractory AH. Therefore, refinements in defining an optimal TPC site that can be found by approximation are necessary.

Beyond some follow-up data provided in a minority of studies, there is minimal data on the longer-term implications of treating AH with rTMS [56]. Fitzgerald et al. reported the successful retreatment of two patients who had relapsed following successful rTMS treatment, one of them on two occasions [77]. There is a report of maintenance rTMS in a patient for 6 months with some decrease in severity but no delay in relapse [78] and a second case where maintenance treatment was successful over an 8-month period [79]. One further case report described a patient who experienced improvement in AH after 1 week of treatment (twice daily low-frequency stimulation to the left TPC) and also in the second occasion following relapse 6 months later. After the relapse, the patient had sustained improvement over 1 year with once monthly treatment [80].We have treated a number of patients with repeated courses of rTMS for relapse of hallucinations and achieved consistent responses over time. We have also successfully utilised a clustered maintenance schedule (5 treatment sessions over 3 days every 4 weeks) in a small sample of patients with particularly difficult to treat symptoms and frequent relapse.

10.4.3 Summary

Evidence currently does not support the clinical use of rTMS in the treatment of negative symptoms or cognitive dysfunction in patients with schizophrenia. However, studies using longer-term and high-dose treatment are required to establish whether rTMS is effective for negative symptoms. Treatment of cognitive dysfunction with rTMS is a promising but new area of research. A more substantial research base has indicated that low-frequency rTMS applied to the left temporoparietal cortex appears to have some therapeutic benefits in ameliorating auditory hallucinations. Given the often disabling nature of these symptoms, clinical use of this technique could be justified in certain cases although overall response rates are not likely to be high.

10.5 Pain

Due to the long-standing and often disabling nature of chronic pain, rTMS and other novel approaches using brain stimulation techniques have been investigated over a number of years.

Approaches to the treatment of chronic pain with rTMS have focused on several different cortical sites. The main site for investigation, however, has been the primary motor cortex. Studies since 2001 have utilised high-frequency stimulation

applied to the motor cortex to try to transiently or persistently ameliorate chronic pain. In the first study of this sort, investigators applied 10 Hz stimulation to the primary motor cortex of patients with intractable neurogenic pain. Pain relief was achieved with a single session of stimulation, but this was short lasting and of modest effect [81]. A similar effect was seen in a second study investigating 10 Hz stimulation applied in patients with unilateral complex regional pain syndrome type I of the hand [82]. Subsequent studies have explored longer periods of stimulation. For example, Picarelli et al. randomised 23 patients with complex regional pain syndrome type 1 in the upper limb to commence standardised pharmacological treatment and either active or sham rTMS delivered in ten sessions at 10 Hz to the motor cortex contralateral to the affected side [83]. It was found that rTMS reduced pain intensities, particularly with ten treatment sessions, in a manner that was related to positive affective aspects of pain.

However, the analgesic effects of rTMS have not been consistent across studies with a number of negative studies reported (see review in [84]). Low-frequency rTMS appears to be less effective than high-frequency [85] and response appears to be dependent on the type of pain syndrome with facial pain, especially trigeminal neuralgia, appearing to respond better than other types of pain syndromes [84]. A recent Cochrane review, including 19 rTMS studies, concluded that there was evidence for short-term analgesic effects of single rTMS sessions, but limited evidence at this stage of longer-term treatment benefit [85].

A second site for potential treatment of chronic pain with rTMS is the dorsolateral prefrontal cortex (DLPFC) due to its role in top-down modulation of pain. Tolerability of experimentally induced pain has been shown to be modulated both by high-frequency stimulation of the left DLPFC [86] and low-frequency stimulation of the right DLPFC [87], both antidepressant rTMS paradigms. Early studies have begun to explore the potential of this form of stimulation in patients with chronic pain. For example, Borckardt et al. found analgesic effects of high-frequency left DLPFC stimulation in a small group of patients with neuropathic pain [88]. In contrast, 1 Hz stimulation applied to the right DLPFC may produce benefit in patients with pain related to fibromyalgia [89]. Notably, both of these approaches appeared to produce therapeutic effects that persisted over time and interestingly unilateral stimulation was able to achieve bilateral effects, something not seen with primary motor cortical stimulation. These characteristics make the potential applicability of prefrontal rTMS potentially greater than that of motor cortical stimulation. Interestingly, we have occasionally seen a reduction in chronic pain in patients receiving prefrontal rTMS treatment for depression with improvement in pain not necessarily correlated with improvement in depression severity

10.5.1 Summary

Promising initial research suggests that rTMS may be able to modulate chronic pain. Prefrontal stimulation appears to have considerable potential for clinical applicability but requires ongoing research.

References

1. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH (1998) Transcranial magnetic stimulation in mania: a controlled study. Am J Psychiatry 155(11):1608–1610
2. Michael N, Erfurth A (2004) Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. J Affect Disord 78(3):253–257
3. Saba G, Rocamora JF, Kalalou K, Benadhira R, Plaze M, Lipski H et al (2004) Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients. Psychiatry Res 128(2):199–202
4. Kaptsan A, Yaroslavsky Y, Applebaum J, Belmaker RH, Grisaru N (2003) Right prefrontal TMS versus sham treatment of mania: a controlled study. Bipolar Disord 5(1):36–39
5. Praharaj SK, Ram D, Arora M (2009) Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a randomized sham controlled study. J Affect Disord 117(3):146–150
6. Daskalakis ZJ, Moller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R (2006) The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. Exp Brain Res 174(3):403–412
7. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP (2006) Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology 67(9):1568–1574
8. Huang YZ, Rothwell JC, Edwards MJ, Chen RS (2008) Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. Cereb Cortex 18(3):563–570
9. Zai G, Arnold P, Burroughs E, Barr CL, Richter MA, Kennedy JL (2005) Evidence for the gamma-amino-butyric acid type B receptor 1 (GABBR1) gene as a susceptibility factor in obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet 134B(1):25–29
10. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL (2006) Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. Arch Gen Psychiatry 63(7): 769–776
11. Greenberg BD, Martin JD, Cora-Locatelli G, Wassermann EM, Benjamin J, Grafman J et al (1997) Effects of single treatment with rTMS at different brain sites in depression. Electroencephalogr Clin Neurophysiol 103:A77
12. Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS (2007) Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychol Med 37(11):1645–1649
13. Sarkhel S, Sinha VK, Praharaj SK (2010) Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. J Anxiety Disord 24(5):535–539
14. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM et al (2001) Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. Am J Psychiatry 158(7):1143–1145
15. Prasko J, Paskova B, Zalesky R, Novak T, Kopecek M, Bares M et al (2006) The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuro Endocrinol Lett 27(3):327–332
16. Ruffini C, Locatelli M, Lucca A, Benedetti F, Insacco C, Smeraldi E (2009) Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry 11(5):226–230
17. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S (2006) Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). Int J Neuropsychopharmacol 9(1):95–100
18. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH (2010) Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 13(2):217–227

19. Kang JI, Kim CH, Namkoong K, Lee CI, Kim SJ (2009) A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. J Clin Psychiatry 70(12):1645–1651
20. Grisaru N, Amir M, Cohen H, Kaplan Z (1998) Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. Biol Psychiatry 44(1):52–55
21. Rosenberg PB, Mehndiratta RB, Mehndiratta YP, Wamer A, Rosse RB, Balish M (2002) Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. J Neuropsychiatry Clin Neurosci 14(3):270–276
22. Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N (2004) Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. Am J Psychiatry 161(3):515–524
23. Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanha C et al (2010) Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J Clin Psychiatry 71(8):992–999
24. Watts BV, Landon B, Groft A, Young-Xu Y (2012) A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimul 5(1):38–43
25. Paes F, Machado S, Arias-Carrion O, Velasques B, Teixeira S, Budde H et al (2011) The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review. CNS Neurol Disord Drug Targets 10(5):610–620
26. Prasko J, Zalesky R, Bares M, Horacek J, Kopecek M, Novak T et al (2007) The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: a randomized, double blind sham controlled study. Neuro Endocrinol Lett 28(1):33–38
27. Mantovani A, Aly M, Dagan Y, Allart A, Lisanby SH (2013) Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. J Affect Disord 144(1–2):153–159
28. Bystritsky A, Kaplan JT, Feusner JD, Kerwin LE, Wadekar M, Burock M et al (2008) A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder. J Clin Psychiatry 69(7):1092–1098
29. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO et al (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353(12):1209–1223
30. Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL et al (1997) Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 349(9067):1730–1734
31. Cohen E, Bernardo M, Masana J, Arrufat FJ, Navarro V, Valls S et al (1999) Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study. J Neurol Neurosurg Psychiatry 67(1):129–130
32. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK (2000) Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 57(11):1033–1038
33. Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S et al (1995) A functional neuroanatomy of hallucinations in schizophrenia. Nature 378(6553):176–179
34. Hoffman RE, Boutros NN, Berman RM, Roessler E, Belger A, Krystal JH et al (1999) Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated voices. Biol Psychiatry 46(1):130–132
35. Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney DS (2000) Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 355(9209):1073–1075
36. Geller V, Grisaru N, Abarbanel JM, Lemberg T, Belmaker RH (1997) Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 21(1):105–110
37. Feinsod M, Kreinin B, Chistyakov A, Klein E (1998) Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. Depress Anxiety 7(2):65–68

38. Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999) Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. Biol Psychiatry 46(10):1451–1454
39. Rollnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengler R et al (2000) High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. Neuroreport 11(18):4013–4015
40. Holi MM, Eronen M, Toivonen K, Toivonen P, Marttunen M, Naukkarinen H (2004) Left prefrontal repetitive transcranial magnetic stimulation in schizophrenia. Schizophr Bull 30(2):429–434
41. Sachdev P, Loo C, Mitchell P, Malhi G (2005) Transcranial magnetic stimulation for the deficit syndrome of schizophrenia: a pilot investigation. Psychiatry Clin Neurosci 59(3):354–357
42. Hajak G, Marienhagen J, Langguth B, Werner S, Binder H, Eichhammer P (2004) High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study. Psychol Med 34(7):1157–1163
43. Freitas C, Fregni F, Pascual-Leone A (2009) Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophr Res 108(1–3):11–24
44. Mogg A, Purvis R, Eranti S, Contell F, Taylor JP, Nicholson T et al (2007) Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: a randomized controlled pilot study. Schizophr Res 93(1–3):221–228
45. Novak T, Horacek J, Mohr P, Kopecek M, Skrdlantova L, Klirova M et al (2006) The double-blind sham-controlled study of high-frequency rTMS (20 Hz) for negative symptoms in schizophrenia: negative results. Neuro Endocrinol Lett 27(1–2):209–213
46. Prikryl R, Kasparek T, Skotakova S, Ustohal L, Kucerova H, Ceskova E (2007) Treatment of negative symptoms of schizophrenia using repetitive transcranial magnetic stimulation in a double-blind, randomized controlled study. Schizophr Res 95(1–3):151–157
47. Jandl M, Bittner R, Sack A, Weber B, Gunther T, Pieschl D et al (2005) Changes in negative symptoms and EEG in schizophrenic patients after repetitive transcranial magnetic stimulation (rTMS): an open-label pilot study. J Neural Transm 112(7):955–967
48. Goyal N, Nizamie SH, Desarkar P (2007) Efficacy of adjuvant high frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. J Neuropsychiatry Clin Neurosci 19(4):464–467
49. Jin Y, Potkin SG, Kemp AS, Huerta ST, Alva G, Thai TM et al (2006) Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphaTMS) on the negative symptoms of schizophrenia. Schizophr Bull 32(3):556–561
50. Barr MS, Farzan F, Tran LC, Fitzgerald PB, Daskalakis ZJ (2012) A randomized controlled trial of sequentially bilateral prefrontal cortex repetitive transcranial magnetic stimulation in the treatment of negative symptoms in schizophrenia. Brain Stimul 5(3):337–346
51. Fitzgerald PB, Herring S, Hoy K, McQueen S, Segrave R, Kulkarni J et al (2008) A study of the effectiveness of bilateral transcranial magnetic stimulation in the treatment of the negative symptoms of schizophrenia. Brain Stimul 1(1):27–32
52. Heinrichs RW (2005) The primacy of cognition in schizophrenia. Am Psychol 60(3): 229–242
53. Barr MS, Farzan F, Rusjan PM, Chen R, Fitzgerald PB, Daskalakis ZJ (2009) Potentiation of gamma oscillatory activity through repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. Neuropsychopharmacology 34(11):2359–2367
54. Barr MS, Farzan F, Arenovich T, Chen R, Fitzgerald PB, Daskalakis ZJ (2011) The effect of repetitive transcranial magnetic stimulation on gamma oscillatory activity in schizophrenia. PLoS One 6(7):e22627
55. Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K et al (2003) Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Arch Gen Psychiatry 60(1):49–56
56. Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT et al (2005) Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biol Psychiatry 58(2):97–104

57. Brunelin J, Poulet E, Bediou B, Kallel L, Dalery J, D'Amato T et al (2006) Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. Schizophr Res 81(1):41–45
58. Chibbaro G, Daniele M, Alagona G, Di Pasquale C, Cannavo M, Rapisarda V et al (2005) Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations. Neurosci Lett 383(1–2):54–57
59. d'Alfonso AA, Aleman A, Kessels RP, Schouten EA, Postma A, van Der Linden JA et al (2002) Transcranial magnetic stimulation of left auditory cortex in patients with schizophrenia: effects on hallucinations and neurocognition. J Neuropsychiatry Clin Neurosci 14(1): 77–79
60. Fitzgerald PB, Benitez J, Daskalakis JZ, Brown TL, Marston NA, de Castella A et al (2005) A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. J Clin Psychopharmacol 25(4):358–362
61. Jandl M, Steyer J, Weber M, Linden DE, Rothmeier J, Maurer K et al (2006) Treating auditory hallucinations by transcranial magnetic stimulation: a randomized controlled cross-over trial. Neuropsychobiology 53(2):63–69
62. McIntosh AM, Semple D, Tasker K, Harrison LK, Owens DG, Johnstone EC et al (2004) Transcranial magnetic stimulation for auditory hallucinations in schizophrenia. Psychiatry Res 127(1–2):9–17
63. Poulet E, Brunelin J, Bediou B, Bation R, Forgeard L, Dalery J et al (2005) Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. Biol Psychiatry 57(2):188–191
64. Saba G, Schurhoff F, Leboyer M (2006) Therapeutic and neurophysiologic aspects of transcranial magnetic stimulation in schizophrenia. Neurophysiol Clin 36(3):185–194
65. Horacek J, Brunovsky M, Novak T, Skrdlantova L, Klirova M, Bubenikova-Valesova V et al (2007) Effect of low-frequency rTMS on electromagnetic tomography (LORETA) and regional brain metabolism (PET) in schizophrenia patients with auditory hallucinations. Neuropsychobiology 55(3–4):132–142
66. Bagati D, Nizamie SH, Prakash R (2009) Effect of augmentatory repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia: randomized controlled study. Aust N Z J Psychiatry 43(4):386–392
67. Vercammen A, Knegtering H, Bruggeman R, Westenbroek HM, Jenner JA, Slooff CJ et al (2009) Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: a randomized controlled trial. Schizophr Res 114(1–3):172–179
68. Rosa MO, Gattaz WF, Rosa MA, Rumi DO, Tavares H, Myczkowski M et al (2007) Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. J Clin Psychiatry 68(10):1528–1532
69. Aleman A, Sommer IE, Kahn RS (2007) Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. J Clin Psychiatry 68(3):416–421
70. Tranulis C, Sepehry AA, Galinowski A, Stip E (2008) Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis. Can J Psychiatry 53(9): 577–586
71. Schonfeldt-Lecuona C, Gron G, Walter H, Buchler N, Wunderlich A, Spitzer M et al (2004) Stereotaxic rTMS for the treatment of auditory hallucinations in schizophrenia. Neuroreport 15(10):1669–1673
72. Sommer IE, de Weijer AD, Daalman K, Neggers SF, Somers M, Kahn RS et al (2007) Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? Schizophr Res 93(1–3):406–408
73. Hoffman RE, Hampson M, Wu K, Anderson AW, Gore JC, Buchanan RJ et al (2007) Probing the pathophysiology of auditory/verbal hallucinations by combining functional magnetic resonance imaging and transcranial magnetic stimulation. Cereb Cortex 17(11): 2733–2743

74. Dollfus S, Larmurier-Montagne A, Razafimandimby A, Allio G, Membrey JM, Delcroix N et al (2008) Treatment of auditory hallucinations by combining high-frequency repetitive transcranial magnetic stimulation and functional magnetic resonance imaging. Schizophr Res 102(1–3):348–351
75. Pascual-Leone A, Gates JR, Dhuna A (1991) Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 41(5):697–702
76. Montagne-Larmurier A, Etard O, Razafimandimby A, Morello R, Dollfus S (2009) Two-day treatment of auditory hallucinations by high frequency rTMS guided by cerebral imaging: a 6 month follow-up pilot study. Schizophr Res 113(1):77–83
77. Fitzgerald PB, Benitez J, Daskalakis JZ, De Castella A, Kulkarni J (2006) The treatment of recurring auditory hallucinations in schizophrenia with rTMS. World J Biol Psychiatry 7(2):119–122
78. Poulet E, Brunelin J, Kallel L, Bediou B, Dalery J, D'Amato T et al (2006) Is rTMS efficient as a maintenance treatment for auditory verbal hallucinations? A case report. Schizophr Res 84(1):183–184
79. Thirthalli J, Bharadwaj B, Kulkarni S, Gangadhar BN, Kharawala S, Andrade C (2008) Successful use of maintenance rTMS for 8 months in a patient with antipsychotic-refractory auditory hallucinations. Schizophr Res 100(1–3):351–352
80. Poulet E, Brunelin J, Kallel L, D'Amato T, Saoud M (2008) Maintenance treatment with transcranial magnetic stimulation in a patient with late-onset schizophrenia. Am J Psychiatry 165(4):537–538
81. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP (2001) Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 12(13):2963–2965
82. Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M (2004) Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett 356(2):87–90
83. Picarelli H, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT et al (2010) Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain 11(11):1203–1210
84. Plow EB, Pascual-Leone A, Machado A (2012) Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. J Pain 13(5):411–424
85. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH (2011) Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis. Eur J Phys Rehabil Med 47(2):309–326
86. Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z et al (2007) Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag 12(4):287–290
87. Graff-Guerrero A, Gonzalez-Olvera J, Fresan A, Gomez-Martin D, Mendez-Nunez JC, Pellicer F (2005) Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. Brain Res Cogn Brain Res 25(1):153–160
88. Borckardt JJ, Smith AR, Reeves ST, Madan A, Shelley N, Branham R et al (2009) A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med 10(5):840–849
89. Sampson SM, Kung S, McAlpine DE, Sandroni P (2011) The use of slow-frequency prefrontal repetitive transcranial magnetic stimulation in refractory neuropathic pain. J ECT 27(1):33–37

Equipment and rTMS Programme Set-Up 11

11.1 TMS Equipment

There are currently a progressively increasing number of TMS equipment manufacturers. However, the accessibility of equipment for the provision of rTMS treatment will vary greatly country by country, limited by local regulatory approval and the availability of local distribution.

Beyond these obvious practical issues, a number of factors should be taken into account when selecting TMS equipment for clinical application. One of the most important is the capacity of stimulators to provide stimulation in the manner required for particular treatment protocols. There is variation across stimulation devices in the ranges of frequencies and intensities able to be provided, especially at stimulation frequencies greater than 20 Hz. A common and critical consideration is whether the coil being utilised for stimulation will provide an adequate number of pulses without overheating. There is considerable variation in the systems used to provide long periods of stimulation without coil overheating across device manufacturers. These include the development of iron core coils, the integration of fluid cooling systems and fan-based cooling systems. Prior to the selection of a stimulator and coil, potential users should ensure that a sufficient number of pulses at high intensity can be provided for each individual treatment session but also that individual treatment sessions can be provided consecutively with only short between patient intervals if required.

It is also important to confirm that the system is provided with adequate accessories to ensure the smooth operation of treatment sessions. Coil stands and localisation positioning systems vary substantially across equipment manufacturers and should be evaluated prior to equipment purchase. The software system to control stimulation protocols should also be evaluated: these are progressively improving but some systems are not very end user-friendly.

A final but critical consideration is the availability of timely on-site equipment support. rTMS equipment is technically complex and utilises high electrical voltages. As such, equipment malfunction should be expected to occur occasionally and local technical staff may not be qualified to service and repair equipment. As most equipment is quite heavy and bulky, shipping back to a device manufacturer for

P.B. Fitzgerald, Z.J. Daskalakis, *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders*, DOI 10.1007/978-3-642-36467-9_11,

repair can be expensive, slow and problematic. In establishing a clinical service, thought may be given to ensuring the availability of backup equipment to prevent the interruption of clinical programmes should equipment fail. It seems sensible and financially viable to ensure the local availability of backup coils; however, resourcing local backup stimulators may well be more problematic. Questions should be asked of distributors as to whether replacement devices on loan are available during equipment repair.

The following is a brief description of a number of currently available TMS devices and manufacturers:

11.1.1 MagVenture

MagPro TMS stimulators have been produced since the early 1990s by Tonica Elektronik in Denmark and over time sold under the brands of Dantec, Medtronic and currently MagVenture. Several MagPro devices are currently available, servicing both clinical and research TMS communities. For the treatment of depression, the most commonly utilised devices are likely to be the MagPro R30 and the MagPro R100. These machines are very similar in design and utilise the same stimulation coils. The main difference is the frequency/intensity at which stimulation can be provided: The MagPro R30 is effectively limited to below 30 Hz, whilst the MagPro R100 can provide stimulation at up to 100 Hz. In the routine treatment of depression utilising protocols in the 1–20 Hz range, this difference is insignificant and a MagPro R30 is likely to suffice. If there is a need for more experimental protocols, for example, considering theta burst and higher stimulation intensities, a R100 device may be considered appropriate.

The MagPro R30 device is relatively compact and is sold with optional accessories including a coil stand, stimulator trolley and device for displaying EMG data during the assessment of resting motor thresholds. There are a number of coils available. The most useful coil for clinical applications is a ‘dynamically’ cooled figure-of-eight coil, which is sold with a separate fluid-based cooling system. In our experience, this allows long stimulation protocols without any substantial coil overheating during or between closely spaced patient sessions. The MagPro systems have been CE approved in Europe for ‘treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from two prior antidepressant medications, at or above the minimal effective dose and duration in the current episode’.

11.1.2 Magstim

Magstim has also been selling TMS systems for many years for a variety of research and clinical applications. There are several Magstim systems available that are suitable for clinical use. These include the Magstim Rapid2, the Super Rapid and Super Rapid Plus. These three units essentially vary only in the stimulation frequencies

and intensities that are able to be applied during stimulation protocols. A choice between these devices, like the choice between the MagPro R30 and R100, will be predominately driven by user needs. A series of different coil types are available for the Magstim systems. These include a cooled coil using a fan mounted close to the coil itself. Coil stands and other accessories are also available.

11.1.3 Neuronetics

Neuronetics is an American company that has developed and commercialised the NeuroStar TMS treatment system, which has been commercially available in the USA since 2008. The system was approved by the FDA for the treatment of major depressive disorder in patients who had failed to receive benefit from antidepressant therapy based on a large multisite trial conducted across a number of countries. The device is sold as an integrated system with stimulator, coil, coil positioning system and software for assisting in estimation of the motor threshold. The commercial devices can only operate with a single use disposable 'SenStar' device in place, which is proposed to ensure adequate coil functioning and localisation. There is a significant cost for each of these devices, and they cannot be reused across treatment sessions even within an individual patient's course.

11.1.4 Other

Brainsway is an Israeli company that is in the process of commercialising a system for deep TMS using a proprietary 'H-coil'. In April 2012, the company announced positive results from a clinical trial evaluating deep TMS treatment of 233 patients across 14 sites. CE marks for marketing and sale of deep TMS systems in Europe have been granted for a number of psychiatric indications including major depression and bipolar disorder.

Nexstim is a Finnish company that manufacturers a TMS device that is predominately marketed for use in neurosurgical planning due to its integration with neuroimaging capacity. Cervel Neurotech is a venture capital-backed start-up company that is currently attempting to develop a system for deeper rTMS stimulation for clinical applications. Several other TMS manufacturers are producing devices in other countries, for example, in China and Russia.

11.2 Treatment Programme Establishment

There are potentially a number of models for the provision of an rTMS clinical service, and the appropriateness of these to local clinical and organisational needs should be considered. It is possible that rTMS could be provided within the office-based practice of an individual psychiatrist or small group of clinicians. However, this type of approach may prove problematic if insufficient patients are regularly in

treatment to justify the employment of an individual to actually provide treatment. Alternatively, rTMS treatment centres may be established on a local or regional basis, receiving referrals from a network of referring doctors and providing rTMS treatment only. This model may provide a more sensible concentration of expertise, but issues relating to the separation of rTMS from other forms of clinical care will need to be managed.

The set-up of TMS programmes will by necessity have to follow the local regulatory frameworks, including for the credentialing of TMS clinic staff. Issues to be considered and clearly articulated include the establishment of referral pathways and processes for routine and emergency clinical review. The degree to which the provision of treatment with TMS is integrated with the referred patient's overall treatment programme is something that can be established on a patient-to-patient basis but should be at least in part determined by local policy. For example, when a patient is referred to a TMS clinical programme, a clinician within the programme, preferably a psychiatrist, will need to make ongoing decisions about TMS provision: for example, whether a sufficiently adequate course has been tried, should stimulation parameters change, when treatment should stop and whether maintenance treatment should be considered.

However, simultaneously, decisions may need to be made in regard to altering other forms of treatment such as antidepressant or other medication. Regardless of whether these decisions are made by the TMS programme psychiatrist or the patient's original treating psychiatrist, communication is essential to ensure that problems do not eventuate. For example, motor threshold may need to be reassessed if medications are changed. In establishing a TMS programme, thought should be given to establishing protocols to determine how these relationships are managed. In addition, it should be clear to the patient who is responsible for routine review of their mental state and for responding to psychiatric emergency such as an escalation of suicidal ideation.

In addition, formal protocols should be developed for emergency responses during rTMS provision. These will include a seizure response protocol and a protocol for response to other forms of loss of consciousness such as syncope. Documentation is required for the prescription of rTMS treatment and recording of all aspects of stimulation provided (see examples in the following chapter).

11.3 Patient Information and Consent

As with all significant medical procedures, patients should be provided with sufficient verbal and written information as to the nature of rTMS treatment, its risks and its potential benefits to allow them to provide informed consent. This information should include a discussion of the short-term nature of the research trials from which rTMS treatment has evolved, the potential risk of seizure induction

and the possibility of side effects such as treatment-related discomfort, pain and headache. Patients should be informed in advance of the need to disclose any changes in medical status or medication treatment and drug or alcohol consumption during the course of rTMS therapy. Ideally they should also be informed as to the processes for emergency responses during the course of rTMS treatment and the roles of clinicians with whom they will have contact.

Index

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