2 The History of TMS and rTMS Treatment of Depression

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.

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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