

CHAPTER 29

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Introduction

ECT demonstrates that in certain psychiatric disorders, the application of electric energy to the brain can have a beneficial effects. But, using skin electrodes, there are difficulties in focusing electrical current on particular brain sites. The skull (like wood) is very poor conductor of electricity. Thus, high levels of electrical energy are needed at the skin electrodes and the current spreads out. For example, during ECT some electricity enters the skull via the eye sockets, nasal passages and auditory canals. In delivering sufficient electrical energy to particular brain regions for an antidepressant effect (the precise regions remain to be identified), energy is widely dispersed throughout the brain, making convulsion and temporary memory difficulties unavoidable. The convulsion means general anaesthesia is necessary, ushering in further potential complications.

In the mid 1980s it became possible to stimulate cortical regions with single pulses of transcranial magnetic stimulation (TMS). Immediately, TMS became an important tool in clinical neurophysiology.

Attempts were made, with some success, to use single pulse TMS in the treatment of psychiatric disorders. However, the great surge in TMS studies of the treatment of psychiatric disorders commenced in the mid 1990's, when machines became available which were capable of repeated cortical stimulation at frequencies of up to 25 Hz.

When stimulation is repeated at one site the term rTMS is sometimes employed. The "r" stands for "repeated", not "rapid".

In addition to use as a diagnostic tool in neurophysiology, TMS has potential in the treatment of some neurological disorders:

- Parkinson's disease (Pascual-Leonie et al, 1994a; Yang et al, 2013),
- writer's cramp (Siebner et al, 1999; Havrankova et al, 2010),
- stroke (Mansur et al, 2005; Emará et al, 2010),
- neuropathic pain (Pridmore et al, 2005; Rokyta and Fricova, 2012),
- fibromyalgia (Short et al, 2011; Lee et al, 2012)
- migraine/headache (Clarke et al, 2006; Magis et al, 2012)
- tinnitus (Pridmore et al, 2006; Chung et al, 2011; Theodoroff and Folmer, 2013).
- epilepsy (Tergau et al, 1999; Hsu et al, 2011)
- psychogenic movement disorders (Garcin et al, 2013)
- auditory hallucinations in schizophrenia (Voineskos & Daskalakis, 2013)
- eating disorders (McClelland et al, 2013)
- psychiatric diagnosis (Fitzgerald et al, 2002)

Most of these uses are yet to be fully substantiated.

TMS is a proven treatment of depression. It is an accepted, as a standard treatment of depression in USA, Canada, UK, Australia and Israel.

Basic principles

Electromagnetism

When an electric current passes along a wire a magnetic field is induced in the surrounding space. In 1831 **Michael Faraday** found that when two coils are close together (but not touching) and a current is passed through one, as the current is turned on and off, a brief pulse of electricity passes through the second coil. The magnetic field created by the electrical current in the first coil extends into the second coil, and when this magnetic field starts and stops, it creates a current in that coil. These are termed the primary and secondary currents. The principle is used in transformers to alter voltage. A second coil is not necessary; a secondary current can be induced in any conductor (water-melon, brain) which is close to a coil through which a primary current is pulsed.

Step-down transformer

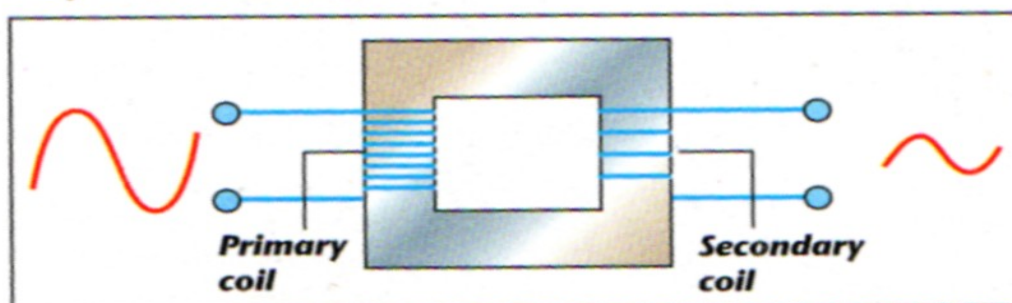


Illustration. Transformer.

We have all moved a paper-clip around on a wooden tabletop with a magnet held underneath. This demonstrates that magnetic fields, unlike electricity, pass relatively unimpeded, through non-conductors of electricity. This allows the TMS operator (unlike the ECT operator) to place a (secondary) current in a precise location in the cerebral cortex.

Physiology

When TMS is applied, the induced electric field causes a flow of current, electric charge accumulates on neural membranes, causing depolarization. With the flat, figure-of-eight coil which is in common use, depolarization occurs at about the junction of the grey and white matter. At this point, axons with cell bodies in the grey matter bend (altering physical properties) as they descend deeper into the brain. This is at about 2 cm below the face of the coil, and the induced electric field at this point is about 70 V/m (Ruohonen & Ilmoniemi, 2002). [Interestingly, the stimulation is electrical, and not a magnetic effect. Thus, for purists, this is not “magnetic” stimulation. The magnetic aspect is important in getting the electricity to the other side of the skull.]

Neuroplastic change is the result of gene expression. It can be triggered by a range of inputs, from the learning process and psychotherapy to psychotropic medication, and by electrical perturbation. It is probable that therapeutic effects of TMS are the result of induced neuroplastic changes. The details of the mechanisms remain uncertain, but

may include effects on catecholamine and brain-derived neurotrophic factor (Yukimasa et al, 2006).

Some evidence suggests that TMS applied to those suffering tinnitus is associated with alterations in grey matter volume (Lehner et al, 2014), and to those suffering major depression is associated with alteration in event-related potential (ERP) amplitude (Choi et al, 2014).

TMS Apparatus

The apparatus consists of a stimulator about the size of a large brief case [up to the size of three large brief cases, depending on the manufacturer] and a coil, connected to the stimulator by a thick, insulated cable.

Along with other components, stimulators contain capacitors which store charge, and a thyristor, which makes it possible to start and stop currents very abruptly.

Coils are of different types. The first coils available were of circular design (one or more turns of copper set in non-conducting material) with a diameter of 8-10 cm. Now, these are rarely used in psychiatric treatment. Counter to intuition, there is little if any electrical activity under the centre of the coil. Instead, activity is strongest under the outer edge of the coil. The magnetic field thus resembles a doughnut half above and half below the coil.

The coil most commonly used in TMS treatment of psychiatric disorders is the figure-8 or butterfly coil. These are constructed of two circular coils, about 7 cm in diameter, mounted next to each other. The magnetic field intensity directly below the junction is multiplied. The volume beneath the junction which is strongly stimulated is of the order of 3 cm long, by 2 cm wide, by 2-3 cm deep [Bohning 2000].

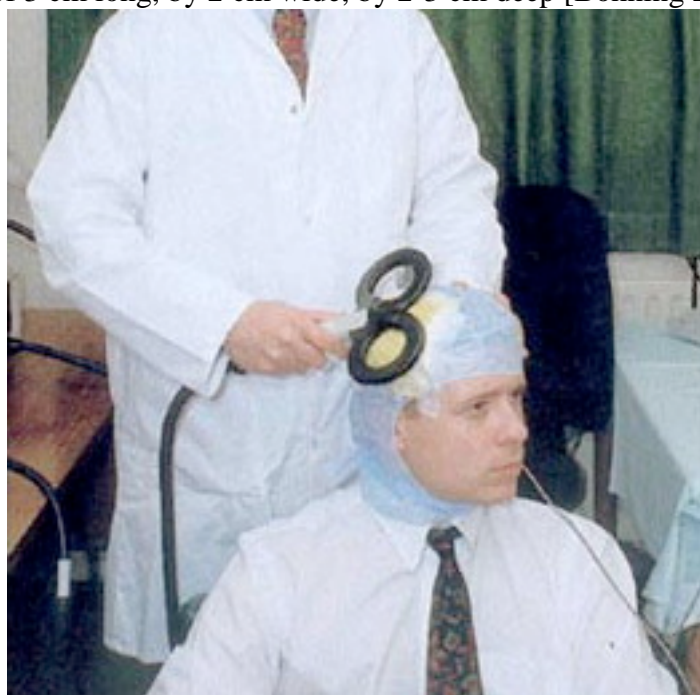


Illustration. Figure-8 (or butterfly) coil.

A new generation of ‘coils’ are now being manufactured – they are less prone to overheating and allow deeper penetration. The ‘double-cone coil’ is similar to the figure-8 coil, but is moulded so that it is cup-like and fits onto the head. It has recently been described as effectively stimulating the cerebellum (Hardwick et al, 2014) (which has been difficult/impossible with the figure-8 coil). ‘Deep TMS coils’ also known as ‘H-coils’ have a more complex design – various elements are mounted into a helmet – and can stimulate up to a depth of 6 cm (Bersani et al, 2013).

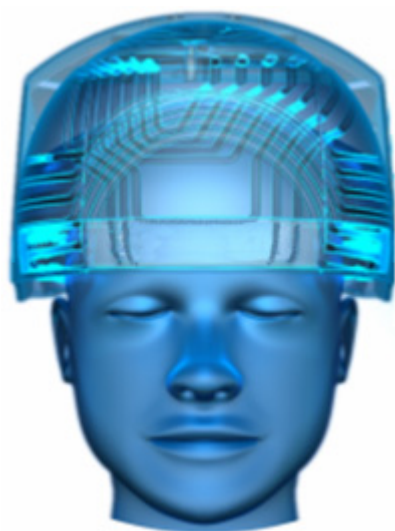


Illustration: An advertisement picture of the H-coil offered by Brainsway Co. It does not explain much, but it suggests greater complexity than present in the figure-8 coil.

Slow and fast rTMS

By convention, “slow” TMS refers to stimulation at 1 Hertz or less, and “fast” (sometimes called “rapid”) TMS refers to stimulation at greater than 1 Hz. Slow rTMS decreases the excitability (Chen et al, 1997), while fast TMS increases the excitability (Pascual-Leone et al, 1994b) of the motor cortex.

Whether these observations hold for all individuals and for all parts of the cortex is yet to be confirmed. Nevertheless, these observations have been used in devising therapeutic approaches.

Imaging studies have shown that in major depressive episode, the left prefrontal cortex is less active than the right. Accordingly, with the aim of increasing the activity of the left prefrontal cortex, fast TMS (George et al, 2000) is applied to that region. Another approach aimed at bringing the activity of the two hemispheres into balance: slow TMS (Klein et al, 1999) is applied to the right prefrontal cortex. Both methods have beneficial effects.

Stimulus intensity

To the present, the intensity of the stimulus employed in treatment has used the motor threshold (MT) as the basic measure. In research the lowest intensity of stimulus used has been 80% of MT and the highest has been 120% MT.

To determine the MT, the coil is placed over the motor cortex and moved until the smallest possible impulse produces either a small motor evoked potential (MEP; usually 50 microvolts; Rossini et al, 1994) or a visible movement of the thumb, wrist or fingers (Pridmore et al, 1998) in at least half of 10 stimulations.

The MT is found at a particular level of the machine output. The smallest % of the total machine output which causes depolarisation is equal to 100% MT.

The MT is used as a measurement index because the motor cortex is the only brain region which gives an easily detected signal [muscle twitch] when depolarized.

As stimulus [according to the desired percentage of MT] can then be applied to the appropriate stimulation site.

The appropriate site depends on the condition being treated, this is usually the prefrontal cortex (depression), but may be the temporal lobes (auditory hallucinations).

Using the MT to determine the stimulus strength is far from satisfactory. It is based on assumptions that the cortex is the same distance from all points on the skull (which is known to be incorrect), and that the sensitivity is the same all over the cortex (which is unproven). New methods of stimulus intensity determination can be anticipated in the future.

Parameters

In therapeutic TMS, the parameters are chosen with at least three factors in mind: the desire for a therapeutic effect, the comfort of the patient, and the risk of seizure. Fast TMS is usually used in the treatment of depression, slow TMS is also used in depression, and in the treatment of auditory hallucinations. The site of stimulation is another important variable.

A common setting in the treatment of depression to the left prefrontal cortex is 10 Hz stimulation in 4 second trains, separated by 26 or 56 rest periods. The intensity is usually 100-120% MT. Treatment is usually delivered 5 days per week.

Recent major studies have used 120% MT, 10Hz, 4 second trains, 75 trains, inter-train interval of 26 seconds (giving a total of 3000 pulses per second in 37.5 minutes), applied to the left prefrontal cortex, for 4 to 6 weeks (O'Reardon et al, 2007; George et al, 2010).

Side effects

Single pulses of TMS are considered to be ‘relatively’ (Mills, 1999) and probably completely safe.

Repeated TMS has been a matter of some uncertainty, especially when fast and high intensity pulses are employed. There was an early report of permanent hearing threshold shift in animals, due to the acoustic artefact (noise) of TMS. However, no hearing deficits have been found in humans treated with rTMS (Pascal-Leone et al, 1992). Another early report described microvacuolar changes in the cortical neuropil of rodents exposed to high-intensity stimuli. However, attempts to replicate these changes have been unsuccessful, and no relevant histopathology was found in brain tissue from human subjects who received TMS prior to anterotemporal epilepsy surgery (Gates et al, 1992).

Headache localized to the site of rTMS is not uncommon, occurring in up to 30% of patients following some treatments. This is due to stimulation of scalp muscles, similar to a localized tension headache, and these resolve spontaneously or responds to simple analgesics. There is no evidence that TMS can trigger migraine or other serious headache. In fact, a hand held machine has recently become available for the treatment of migraine.

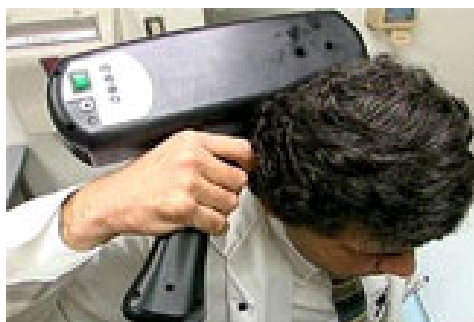


Illustration. A portable TMS device marketed for the self-treatment of migraine.

The most worrying issue has been the possibility of triggering seizures. An international workshop on the risk and safety of TMS was held in 1996. To that point, 7 seizures were thought to have resulted during (as a result of) research TMS. Guidelines were produced regarding safe treatment parameters (Wassermann, 1998) with the result that seizures became freak events. A subsequent consensus conference (Rossi et al, 2009) found that seizures were “extremely rare” and mainly occurred when stimulation exceeded guidelines. Thus, the risk of seizure is very slight, and less than with many forms of medication.

Adverse cognitive effects have not been found with either 1 Hz or 20 Hz stimulation (Little et al, 2000; Speer et al, 2001).

A neuroprotective effect of TMS has been demonstrated in rodents (Post et al, 2001).

After two decades, no significant long-term adverse effects of TMS have been detected.

Contraindications to TMS

There are few absolute contraindications to TMS treatment. A personal or strong family history of epilepsy is generally regarded a contraindication for fast TMS. (Slow TMS may prove to be useful in intractable epilepsy.)

Patients with serious medical conditions or excessive use of alcohol may be excluded from TMS therapy, if it is considered they have a lowered seizure threshold. Pregnancy was early considered to be a contraindication, but the risk to a foetus from TMS to the brain of a mother is certainly less than that of medication (Nahas et al, 1999), and treatments have been administered without adverse effects (Hizli-Sayar et al, 2013).

Intracranial metal objects are generally considered to be a contraindication to TMS. The theoretical risks are that these may be caused to move or heat. Most intracranial metal clips are non-ferrous, thus not induced to move in a magnetic field. These risks appear to be small, and there are no reports of brain damage resulting from the influence of TMS on intracranial metal objects.

There may be a problem with pacemakers. This is not so much a risk to the patient, but to the pacemaker. Conceivably magnetic field fluctuations could interfere with pacemaker settings. In specialized units people with pacemakers have been treated; the precaution taken is to turn the pacemaker off during TMS, and on again at completion of the treatment session.

Conditions treated

Recently, group of European experts made a statement regarding the efficiency of TMS in the treatment of various disorders (Lefaucheur et al, 2014). Reference will be made to this report.

Major Depressive Episode

Lefaucheur et al (2014) found treatment of major depression with rapid rTMS over the left DLPF to have definite efficiency.

Many moderately large studies (around 60 patients) have demonstrated the statistical superiority of TMS over placebo (George et al, 2000; Fitzgerald et al, 2003; Rossini et al, 2005). O'Reardon et al, (2007) studied 301 depressed patients in double-blind, controlled, multi-centre study and found TMS to be superior to sham and effective in the treatment of depression. George et al (2010) studies 190 depressed patients and found the remission rate of active TMS (14.5%) to be statistically superior to that of the sham treatment (5.1%). In open-label follow-up treatment, remission occurred in 30%.

TMS has been compared to ECT. Early studies found these treatments to have similar efficacy (Pridmore et al, 2000; Dannon et al, 2002; Janicak et al 2002; Grunhaus et al,

2003; Schulze-Rauschenbach 2005). However, recent studies have found a distinct anti-depressant advantage for ECT (Eranti et al, 2007; Berlim et al, 2013).

Evidence indicates that TMS is as effective as antidepressant medication (Demitrack & Thase, 2009).

Treatment response depends on the stimulation parameters chosen, and further research is expected to identify those which maximize the antidepressant effect. McDonald et al (2011) have shown that patients who fail to respond to fast rTMS to the left prefrontal cortex, may respond to slow rTMS to the right. Efforts are being made to discover physiological markers which will indicate potential responders (Kito et al, 2011; Paillere Martinot et al, 2011).

Auditory hallucinations

Lefaucheur et al (2014) found treatment of auditory hallucinations with slow rTMS over the left temporoparietal cortex to have possible efficiency.

Slow stimulation (1Hz; which has the ability to reduce the activity of the cortex) is the most common method.

Many studies have shown a statistical superiority for active over placebo TMS (Hoffman et al, 2003; Vercammen et al, 2009; Hoffman et al, 2013). Not all studies have had positive results (Slotema et al, 2011), but meta-analyses have been supportive (Aleman et al, 2007; Slotema et al, 2012). More research is required.

Other psychiatric disorders

Negative symptoms of schizophrenia – no conclusive evidence, although Lefaucheur et al (2014) found treatment of negative symptoms of schizophrenia with fast rTMS to the left DLPFC to have probable efficiency.

There is some evidence to suggest TMS may have a place in the treatment of medication resistant obsessive-compulsive disorder (Mantovani et al, 2009; Blom et al, 2011). Three stimulation sites have been investigated (Jaafari et al, 2011).

Eating disorders – some encouraging studies (McClelland et al, 2013).

Smoking cessation – some evidence of beneficial effect with standard and deep rTMS (Dinur-Klein et al, 2014).

Anxiety – no conclusive evidence (Paes et al, 2011).

Other medical disorders

A role for rTMS in the treatment of chronic pain (a major public health problem) was suggested by Pridmore & Oberio in 2000. Lefaucheur et al (2014) found treatment of chronic pain with fast rTMS over the motor cortex contralateral to the pain to have definite efficiency.

Lefaucheur et al (2014) found treatment of tinnitus with slow rTMS over the left temporoparietal cortex to have possible efficiency.

Parkinson's disease has been treated with rTMS, but with no clear benefit.

The future

TMS allows the clinician to painlessly reach in and tickle the brain. Slow and fast stimulation appears to have different effects on neural tissue. We know that perturbing nuclei causes cellular modification (as sunlight causes sun tan). We know that the brain is an incomprehensibly complex organ, an organ of interconnections, and that applying a stimulus at one site will have impacts at many other sites. Thus, given that psychiatric disorders are so common and disabling, the potential for TMS to benefit patients must be taken seriously.

The future includes the potential to identify with greater accuracy, those patients who will benefit from TMS (Kito et al, 2011; Paillere Martinot et al, 2011). Also, while we currently have certain variables at our disposal (intensity, frequency and site of stimulus), others will become available. For example, theta burst stimulation – 50Hz trains of 3 pulses, repeated every 200 ms, when applied intermittently leads to increased cortical excitability, but when applied continuously leads to decreased cortical excitability (Huang et al, 2005). We can also look forward to new technology, such as coils which will allow us to stimulate brain regions beyond our current reach (Roth et al, 2007).

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