CHAPTER 29

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Introduction

ECT demonstrates that, for certain psychiatric disorders, the application of electric energy to certain regions of the brain can have beneficial effects. But, when the electricity is provided from outside, via skin electrodes, there are difficulties in focusing it on particular sites. The skull (like wood) is a poor conductor of electricity. Thus, to reach the brain, high levels of electrical energy are needed at the skin electrodes and the current spreads out and is difficult to focus. 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, energy is widely dispersed throughout the brain, making convulsion and temporary memory difficulties unavoidable. The convulsion means that a general anaesthic is necessary, ushering in further potential complications. [There are some difficulties with ECT – however, it remains a most valuable treatment.]

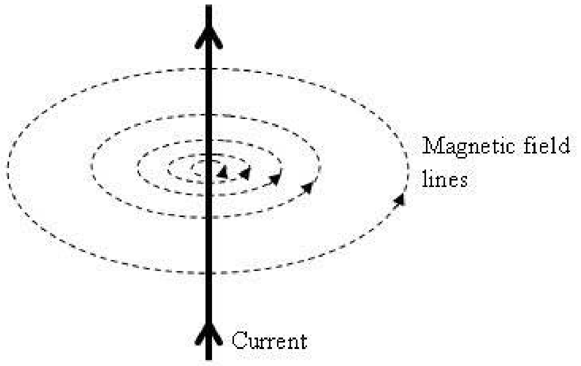
In the mid 1980s it became possible to stimulate cortical regions with single pulses of transcranial magnetic stimulation (TMS). Immediately, TMS became an important tool in clinical neurophysiology.

Subsequently, machines were developed which the capacity to provide repeated (r) stimulation – from 1–50 Hz. (rTMS and TMS are essentially alternative terminologies.) This capacity opened the possibility of TMS as a treatment for psychiatric and possibly neurological disorders.

At the moment, TMS is only widely accepted as a treatment for major depressive disorder (MDD) which has not responded to medication (McClintock et al, 2018). It may be proven useful in other psychiatric disorders in the future.

Electromagnetism

When 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. This is because, when the magnetic field created by the electrical current in the first coil extends into the second coil, it creates a current in the second 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 will be induced in any conductor (water-melon, brain) which is close to a coil, through which a primary current is pulsed.

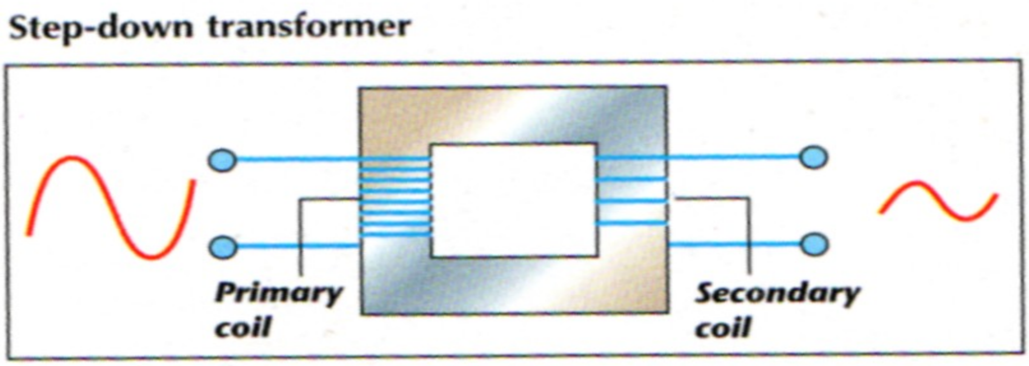


Illustration. Transformer.

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. Thus TMS makes it possible (unlike ECT) to place a (secondary) current in a precise location in the cerebral cortex.

Physiology

The TMS induced electric field causes a flow of current and electric charge accumulates on neural membranes, causing depolarization. With the flat, figure-of-eight coil, 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 into the brain - that is, at about 2 cm below the face of the coil, and the induced electric field is about 70 V/m (Ruohonen & Ilmoniemi, 2002). [Interestingly, at this level, stimulation is electrical, and not magnetic. Thus, for purists, this is not "magnetic" stimulation. The magnetic aspect is important in getting the electricity to the other side of the skull, painlessly and with precision.]

Physiology, MDD and TMS

MDD has 'hypo-frontality' (decreased blood flow in frontal regions) as a prominent feature. This is the reason TMS was first applied to the prefrontal regions – and TMS corrects this pathological feature (Speer et al, 2000; Li et al, 2015a).

MDD is often associated with increased activity in the subgenual anterior cingulate cortex (sgACC).

May et al (2017) found that 1 Hz stimulation to the left superior temporal gyrus increased grey matter volume at this site. These macroscopic changes were likely dependent on synaptogenesis, angiogenesis, gliogenesis, neurogenesis, increased cell size, and increased blood flow.

Hayasaja et al (2017) found that conventional TMS significantly increased the volume of the left hippocampus (+3.4%) – indicating a remote neuroplastic effect through the cingulum bundle.

TMS to dorsolateral prefrontal cortex (DLPFC) increases dopamine release in the striatum. Dopamine signalling in the striatum is important for reward processing and movement. Thus, TMS to the DLPFC may help with anhedonia and psychomotor retardation.

A connection from the left DLPFC to the sgACC was recently demonstrated (Vink et al 2018). TMS stimulation of the left DLPFC propagates activity to sgACC in about half healthy volunteers.

Connectivity

Brain Connectivity is a new and complicated concept. A full discussion is beyond the knowledge of the current author, and the needs of the reader. One definition: **Brain connectivity** refers to a pattern of anatomical links ("anatomical **connectivity**"), of statistical dependencies ("functional **connectivity**") or of causal interactions ("effective **connectivity**") between distinct units within a nervous system. It seems to have to do with the frequency/ease with which one region of the brain communicates with another.

In recent times, in major depressive episode the connectivity of various neural loops have been found to be pathologically increased or decreased (Brakowski et al, 2017). Some details are listed below, but the important point is that TMS has the ability to correct/normalize these abnormalities, whether they be increases or decreases.

Cortex to cortex connectivity
Connectivity abnormality described by Dubin 2017

Cortex to striatum connectivity
In MDD: DLPFC-left caudate connectivity was found to be increased. TMS produced improvement in mood and reduction in DLPFC-left caudate connectivity (Kang et al, 2016). (Also, Salomons et al, 2014; Avissar et al, 2017)

Cortex to thalamus connectivity
Connectivity abnormality described by Li et al, 2013.

Cortex to Limbic system connectivity
In bipolar patients and their siblings – hypoactive glucose utilization in DLPFC and hyperactivity in the amygdala Li et al (2015b) - suggests diminished control by the prefrontal cortex of the limbic system.
Also described by Kito et al (2017).

Default mode network [DMN] connectivity
DMN - various structures including the medial prefrontal cortex (mPFC), posterior cingulate cortex and the angular gyrus – assumed to be active when the individual is not focused on the outside world, meditation and during wakeful rest.
It is suggested that the increased connectivity of the DMN in depression leads to increased negative rumination and the inability to experience pleasure.

The depressed state is characterized by elevated functional connectivity of the DMN (Liston et al, 2014). TMS treatment normalizes the hyper-connectivity of the DMN.

Cognitive executive network (CEN) connectivity
The structures involved have not been clearly defined, but include the DLPFC, anterior cingulate and orbito-frontal cortex. CEN plays a role in regulating attention, working memory, and decision making. Connectivity in the CEN is decreased in depression – and this may explain the slowness and impairment of cognition in severe depression.

The decreased connectivity of the CEN normalizes with TMS.

Contraindications to TMS

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

Other factors which generally exclude patients are features which raise the risk of seizure - pre-existing neurological disorders and excessive use of alcohol – particularly during withdrawal.

Pregnancy - because of the potential risk to a foetal brain - is widely considered a contraindication. However, there are a number of reports of treatment without evidence of damage to the foetus (Nahas et al, 1999; Hizlie Sayar et al, 2014;

Eryilmaz et al, 2015). RANZCP (2018) does not find pregnancy a categorical contradiction, but recommends caution, the weighing of risk of treatment against the risk of no treatment, and against the risks of other treatments. Full involvement of the patient and family is mandatory

Metal implants and electronic devices were once a categorical contraindication. RANZCP (2018), however, only recommends caution – with consideration of the distance between the coil and the object.

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.

Side effects

Position Statement of the RANZCP (2018) list the most common side effects as local scalp discomfort/pain and post treatment headache. Scalp discomfort can be managed by reducing the stimulus intensity or moving the coil slightly – this side-effect generally reduces during the course of treatment. Localized headache (post-treatment; is not uncommon, visiting 30% of patient) is generally mild and responds to simple analgesics. TMS does not cause migraine, if fact, special self-held TMS devices are commercially available for the treatment of migraine.

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

The noise of TMS is loud, but no hearing deficits have been found with human treatment (Pascal-Leone et al, 1992). Nevertheless, hearing protection is recommended.

The most worrying issue has been the possibility of triggering seizures. The risk is less than that of antidepressant medication (Milev et al, 2016). Nevertheless, those at high risk of seizure are not treated (see Contraindications).

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

Treatment parameters

Frequency

By convention, “low-frequency” (LF) TMS refers to stimulation at 1 Hz or less, and “high-frequency” (HF) TMS refers to stimulation at greater than 5 Hz (some contend, greater than 1Hz). LF-TMS decreases the excitability of neural matter (Chen et al, 1997), while HF-TMS increases this excitability (Pascual-Leone et al, 1994).

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, HF-TMS (George et al, 2000) is applied to that region.

Another approach, aimed at bringing the activity of the two hemispheres into balance: LF-TMS is applied to the right prefrontal cortex (Klein et al, 1999). Both methods have beneficial effects.

Stimulus intensity

To the present, the intensity of the stimulus employed in treatment has used the resting motor threshold (RMT) as the basic measure. The stimulus intensity most commonly employed is 110-120% RMT.

To determine the RMT, 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 movement of the thumb, wrist or fingers is visibly detected, in at least half of 10 stimulations (Pridmore et al, 1998).

The RMT 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.

A stimulus [at the desired percentage of RMT] can be applied to the desired stimulation site.

The appropriate site depends on the condition being treated, this is usually the prefrontal cortex (depression). Other sites being explored in research include the medial prefrontal cortex (depression) and the temporal lobes (auditory hallucinations).

Using the RMT 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.

Choosing treatment parameters

Treatment parameters are chosen with three factors in mind: 1) desire for a therapeutic effect, 2) the comfort of the patient, and 3) the risk of seizure.

The common setting in the treatment of MDD: HF-TMS applied to the Left DLPFC: 100-120% MT, 10 Hz stimulation, 4 second trains, separated by 20 second rest periods, 75 trains per day. This provides a total of 3000 pulses per second in 37.5 minutes per session. A course: 20 treatments, 5 per week (George et al, 2010), although, courses of 36 treatments have been given.

MDD can also be managed with LF-TMS. The stimulus is applied to Right DLPFC at 1Hz, to a total of 1200-1800 pulses per day (RANZCP, 2018). Also at 100-120% MT, 5 treatments per week for 4 weeks (or more).

Conditions treated

As mentioned in the Introduction, TMS is only universally accepted as a treatment of MDD. A fuller discussion follows.

Major Depressive Episode

The safety and therapeutic benefits of TMS in the treatment of MDD (which has not responded to medication) was first demonstrated in 1995 (George et al, 1995). Subsequently, about 100 sham controlled trials have demonstrated efficacy (McClintock et al, 2018). There have been at least 30 systematic reviews and meta-analyses (Loo et al, 2003; Fitzgerald et al, 2003). There have also been naturalistic studies which have demonstrated the effectiveness of TMS in the treatment of medication resistant MDD in the real-life clinic (Galletly et al, 2014).

Many professional and service bodies endorse TMS as a treatment of medication resistant MDD - to list them all would exceed the reference limit. Prominent examples include the American Psychiatric Association (APA, 2010), the Canadian Network for Mood and Anxiety Treatments (Milev et al, 2016), the Australian and New Zealand College of Psychiatrists (RANZCP, 2018), the National Institute for Health and Care Excellence (NICE) in the UK, and the international World Federation of Societies of Biological Psychiatry.

TMS has been compared to ECT. Recent studies have found a distinct anti-depressant advantage for ECT (Berlim et al, 2014). However, patients prefer TMS, which is more cost effective than either medication (Nguyen et al, 2015) or ECT (Magnezi et al, 2016).

Other psychiatric disorders

Some evidence suggests a modest benefit in the treatment of auditory hallucinations (He et al, 2017). RANZCP (2018) condones such use in specialized units where data can be collected and reported. The negative symptoms of schizophrenia (Wang et al, 2017) and obsessive convulsive disorder (Cocchi et al, 2018) may prove responsive.

PTSD, addiction and autism spectrum disorders are all receiving some attention.

Other medical disorders

A role for rTMS in the treatment or 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. Recent success has been reported with neuropathic pain (Lamusuo et al, 2017) and fibromyalgia (Saltychey & Laimi, 2017).

TMS showed early promise in the treatment of some neurological disorders, but this has contributed little to clinical practice. There may be a place for TMS in stroke (Zhang et al, 2017), and migraine/headache (Lan et al, 2017). Parkinson’s disease – in spite of early suggestions, TMS is of insignificant value in the treatment of motor symptoms - but may have a place in associated mood and cognitive difficulties. There was early excitement about a place for TMS treatment of tinnitus, but this is no longer pursued enthusiastically.

TMS Apparatus

The basic apparatus consists of a stimulator (a box which provides electrical pulses), a ‘coil’ for placing against the hair/scalp and a thick, insulated coil which connects these two parts.

In the 1990s the stimulator was bigger than currently and the coil was held on the head by the hand of an operator.

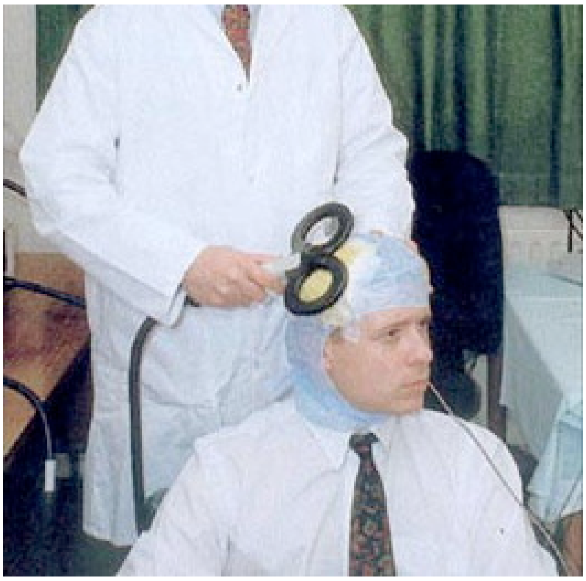


Illustration. 1990s figure-8 (or butterfly) coil.

Manufacturers produce new models, and some now look like props from a Star Wars movie. Two factors have driven these changes. First, the coil can get very hot (and cease to function), so modern coils have a cooling system. Second, coils are now held in position by a mechanical arm.

Illustration. Current device with a simple mechanical arm for positioning the coil. One of the boxes at the lower level contains a cooling system.

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].

Various 'coils' are now being manufactured – they are less prone to overheating and are said to provide 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. '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). Clinical advantages of one coil over another are yet to be proven.

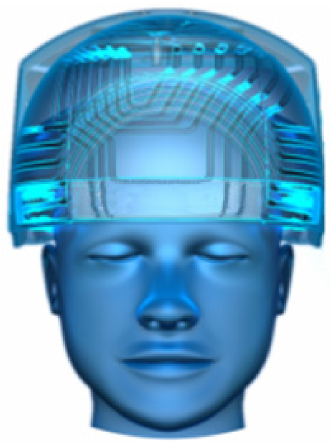


Illustration: An advertisement picture of the H-coil offered by Brainsway Co.

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