CHAPTER 29

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS has been ‘available’ for over 20 years – it is an effective treatment of severe depression (George, 2019). By ‘available’ is meant the devices have been available for sale around the world – and authorities have approved TMS as treatment. However, the purchase of devices and training of staff (relatively simple) is occurring very slowly (various reasons) – thus, patient access is limited. Recent cost-utility analyses have found TMS was less costly and produced better health outcomes than ECT (Zhao et al, 2018; Fitzgibbon et al, 2019).

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 the energy on particular brain 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, thus 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 enough 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 anaesthetic is necessary, ushering in further potential complications. [While there are some difficulties with ECT, 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.

Currently, TMS is only widely accepted as a treatment for acute major depressive disorder (MDD) which has not responded to medication (McClintock et al, 2018). It has shown promise in the treatment of posttraumatic stress disorder, anxiety/OCD and various neurological problems. This is an exciting, expanding area.
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 (watermelon, brain) which is close to a coil through which a primary current is pulsed.

![Transformer diagram]

Transformer.

We have all moved a paperclip 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 small current in a precise location in the cerebral cortex.

TMS Apparatus

The basic apparatus consists of a stimulator (a box which provides electrical pulses) and a ‘coil’ which is placed against the hair/scalp. These are connected by insulated wires. There is also a cooling mechanism which pumps fluid out to the coil and back.
The coil most commonly used in the 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 is highest directly below the junction. 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].

In the 1990s the stimulator was bigger than currently, and the coil was held on the head by the hand of an operator, throughout the entire treatment!!!

New models look like props from a Star Wars movie. Two factors have driven these changes. First, the coil can get a cooling system. Coils are now held in position by a mechanical arm.

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

**Conditions treated**

TMS is only universally accepted as a treatment of MDD – although beneficial effects on other disorders have been reported.
Major Depressive Episode

The safety and therapeutic benefits of TMS in the treatment of acute 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). 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.

Professional and service bodies endorse TMS as a treatment of medication resistant MDD - 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 found more cost effective in the treatment of acute MDD than either medication (Nguyen et al, 2015) or ECT (Zhao et al, 2018; Fitzgibbon et al, 2019).

Severe MDD features a high risk of relapse, which may occur within weeks of successful acute treatment. Such relapse does not indicate that TMS is a ‘wea’k treatment, but rather, that the disorder may be ‘strong’.

A system of remission ‘maintenance’ TMS has been described (Fitzgerald, 2019). Patients who have relapsed soon after a successful course of TMS may be offered 5 standard treatments over 2.5 days – this is repeated at monthly or greater intervals.

Other psychiatric disorders treated

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

Cui et al (2019) conducted a meta-analysis of TMS in generalized anxiety disorder but could reach a clear conclusion.

Some evidence suggests a modest benefit in the treatment of auditory hallucinations (He et al, 2017) and the negative symptoms of schizophrenia (Wang et al, 2017).

Some evidence suggests conventional TMS is effective in OCD (Cocchi et al, 2018). Strong evidence indicates dTMS reduces OCD symptoms (Carmi et al)(see later).

Medical disorders treated

A role for rTMS in the treatment or chronic pain (a major public health problem) was suggested by Pridmore & Oberio (2000). Lefaucheur et al (2014) found treatment of chronic pain with HF 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).
There may be a place for TMS in stroke rehabilitation (Zhang et al, 2017) and migraine/headache (Lan et al, 2017). TMS showed some early promise in the treatment of motor symptoms of Parkinson’s disease and tinnitus management – but little progress is evident.

**Physiology and TMS**

TMS induced electric fields cause electric charge to accumulate on neural membranes, and depending on strength, cause depolarization. With the flat, figure-of-eight coil, depolarization occurs at about the junction of the grey and white matter – about 2 cm below the face of the coil. At this point - axons bend as they leave their cell bodies in the grey matter and descent into the brain – this bending alters neural physical properties. [Interestingly, the stimulation is electrical - 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 and MDD and TMS**

‘Hypo-frontality’ (decreased blood flow in frontal regions) is a feature of MDD – the reduction is greater on the left than the right.

TMS at rates >1 Hz increases neural activity (Pascual-Leone et al, 1994) [“high-frequency” (HF) TMS], while stimulation of ≤1 Hz suppresses neural activity (Chen et al, 1997) [“low-frequency” (LF) TMS].

Thus, there are two approaches to treatment of MDD – first, stimulation >1Hz is applied to the left dorsolateral prefrontal cortex (L DLPFC) – to increase activity. Second, stimulation at ≤1 Hz applied to the right DLPFC – to reduce the activity on the right and bringing it back into balance with the left. Both are effective (Speer et al, 2000; Li et al, 2015a).

TMS to DLPFC may increase 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.

Levitt et al (2019) found TMS in MDD increased GABA in the DLPFC by 10% - significantly in responders and non-significantly in non-responders.

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.

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 reflects 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. Very importantly, 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 is **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**  
The DMN is composed of 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, that is, during meditation and 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 are not 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.
Recent work from Ge et al (2019) found that brain activity patterns in depression are predictive of treatment response to TMS. Lower functional connectivity of the anterior cingulate to right DLPFC and higher connectivity of the anterior cingulate to the left parietal cortex were associated with a favourable response.

The decreased connectivity of the CEN in MDD 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 to be one.

Other factors which generally exclude patients (because they 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 – has been widely considered a contraindication. The Royal Australian and New Zealand College of Psychiatrists (2018) does not find pregnancy a categorical contradiction but recommends caution. Recent studies have found no particular risks for mother or baby (Cole et al, 2020).

Metal implants and electronic devices were once categorical contraindications. Now, the RANZCP (2018) simply recommends caution.

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**

The most common side effects are local scalp discomfort/pain and post treatment headache. Scalp discomfort can often 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) – it 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.

A portable TMS device marketed for the self-treatment of migraine.
The noise made by the TMS machine 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 a seizure. The risk associated with TMS is less than the risk associated with the use of antidepressant medication (Milev et al, 2016). See Contraindications.

Limits on stimulation parameters (intensities and rates) are recommended by authoritative bodies. These reduce the risk of seizure – some seizures were reported in the early years when this advice was not available.

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

**Treatment parameters - Contemporary**

**The TMS treatment parameters are under constant review – in the search to optimize outcomes.**

**Frequency**

As mentioned above, under “Physiology and MDD and TMS”, currently, there are two standard treatment frequencies – LF (low-frequency) \(<1\) Hz, which is applied to the R DLPFC, and HF (high-frequency) \(>1\) Hz, which is applied to the L DLPFC. [Some prefer to consider HF to be \(\geq 5\) Hz.]

Both of these approaches have been established for two decades: LF TMS to R DLPFC (Klein et al, 1999) – HF TMS to L DLPFC (George et al, 2000). Commonly used HF rates are 10 and 20 Hz.

**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.

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.

**Train interval and ‘Rest Periods’**

To minimize the risk of seizure, in HF stimulation, pulses are applied in short trains: 2 second trains are common with 20 Hz, and 4 second trains with 10Hz. The ‘rest period’ between trains was once 30 seconds but has reduced to 12 or less seconds.

**Number of pulses and length of courses**

A common daily HF treatment is 10 Hz, 4 sec trains, 75 trains – providing 3000 pulses per day. With 20 second rest periods this takes around 40 minutes.

Commonly, a course is 20 treatments, one provided 5 per week (George et al, 2010) - although, courses of 36 treatments are also given.

LF-TMS treatment is almost exclusively 1 Hz. A daily total of 1200-1800 pulses has been recommended (RANZCP, 2018). Again, a course is usually at least 4 weeks.

**Site of stimulation**

The first employed site of stimulation was 5 or 6 cm anterior to the point at which the RMT was identified. More recently, use of the F3 EEG position has been recommended (Beam et al, 2009). In exceptional circumstances imaging methods have been used.

The appropriate site depends on the condition being treated, and any recent advances. For depression the site is the L or R DLPFC. Another sites being explored in depression research is the mPFC. Stimulation of the temporal lobes has been suggested for auditory hallucinations of psychosis and tinnitus.

**Treatment parameters - experimental**

Standard TMS is time greedy, taking more than half an hour a day for at least 20 days. Many experimental protocols have been advanced, aimed at reducing the time requirement.

**Theta-burst stimulation (TBS)**

TBS is believed to have a stronger effect on neural tissue than standard TMS. It is sets of 3 pulses delivered at 50 Hz, with one set occurring 5 times per second (Hz) (Chung et al, 2015).
When TBS is delivered continuously (cTBS) – in 20 or 40 second trains - it suppresses neural activity. When TBS is delivered intermittently (iTBS) – 2 second trains every 10 seconds – it activates neural tissue.

Daily treatments with TMS may take only 5 minutes.

Hopes are high that TBS will prove superior to standard TMS. A recent report indicated no advantages (Fitzgerald et al, 2020).

20 Hz bilateral DMPFC TMS

Miron, Feffer et al (2019) used 20 Hz TMS in trains of 2 seconds with rest periods of (only) 4 seconds – they provided 1200 in 3 minutes to each (left and right) dorsomedial prefrontal cortex (DMPFC) – in 6 minutes. This was an open study – the authors believe the therapeutic effect and patient acceptance was similar to other TMS protocols.

They speculate that treatment to one side may be sufficient – meaning a treatment could be completed in 3 minutes.

These are potentially very influential findings – using standard equipment to produce therapeutic effects in 20-10% of the time of standard treatment!!

1 Hz R DLPFC – a new approach

Miron, Voetterl et al (2019) have suggested a protocol which may dramatically reduce the cost and therefore increase the availability of TSM to patients.

HF TMS is associated with several problems which do not emerge with 1 Hz treatment. For example, HF causes overheating of the coil – thus an expensive cooling system is required – which is not required for 1 Hz treatment. The risk of seizure is higher with HF than with LF TMS.

Customary TMS uses a coil which delivers the stimuli in a highly focused manner (in pursuit of precision and stimulation of specific structures). The use of focused coils calls for highly skilled workers – doctors to identify the best possible position and technicians to place the coil in that position each day.

Miron, Voetterl et al (2019) propose LF of the right prefrontal cortex using a non-cooled coil which stimulates a much wider area (reducing the need for precision placement). This form of treatment is apparently helpful to many – the therapeutic effects compared to the current TMS treatments is not clear. We look to further results with great interest.
New ‘coils’

Various new ‘coils’ are now being manufactured. Some are often described as being 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 may stimulate up to a depth of 6 cm (Bersani et al, 2013).

Clinical advantages of complex coils over standard coils, or of one complex coil over another, are yet to be proven.

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

Huang et al (2019) provide a meta-analysis of deep TMS (dTMS) in the treatment of depression.

Carmi et al (2019) reported that dTMS is effective in the treatment of OCD, and FDA approval has now been granted.

References


Fitzgerald P. Is maintenance repetitive transcranial magnetic stimulation for patients with depression a valid therapeutic strategy? Clinical Pharmacology and Therapeutics 2019 [Epub ahead of print]
George M. Wither TMS: A one-trick pony or the beginning of a neuroscientific revolution? Am J Psychiatry 2019; 176. [Epub ahead of print]


Zhao YJ, Tor PC, Khoo AL, Teng M, Lim BP, Mok YM. Costeffectiveness modeling of repetitive transcranial magnetic stimulation compared to electroconvulsive therapy for treatment-resistant depression in Singapore. Neuromodulation. 2018;21(4):376-382.