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 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, 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.

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 neurological disorders.

At the moment, TMS is only widely accepted as a treatment for major depressive disorder (MDD) (O'Reardon et al, 2007; George et al, 2010). It may be found useful in other psychiatric disorders in the future.

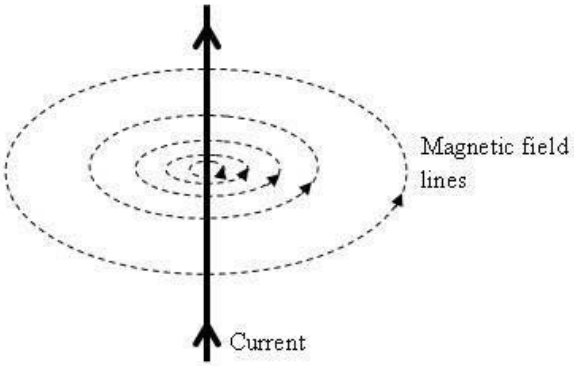
TMS has shown promise in the treatment of some neurological disorders:

- Parkinson's disease (Pascual-Leonie et al, 1994a; Chung & Mak, 2016),
- writer's cramp/dystonia (Siebner et al, 1999; Quartarone et al, 2017),
- stroke (Mansur et al, 2005; Zhang et al, 2017),
- neuropathic pain (Pridmore et al, 2005; Lamusuo et al, 2017),
- fibromyalgia (Short et al, 2011; Saltychey & Laimi, 2017)
- migraine/headache (Clarke et al, 2006; Lan et al, 2017)
- tinnitus (Pridmore et al, 2006; Kreuzer et al, 2017).

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 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.

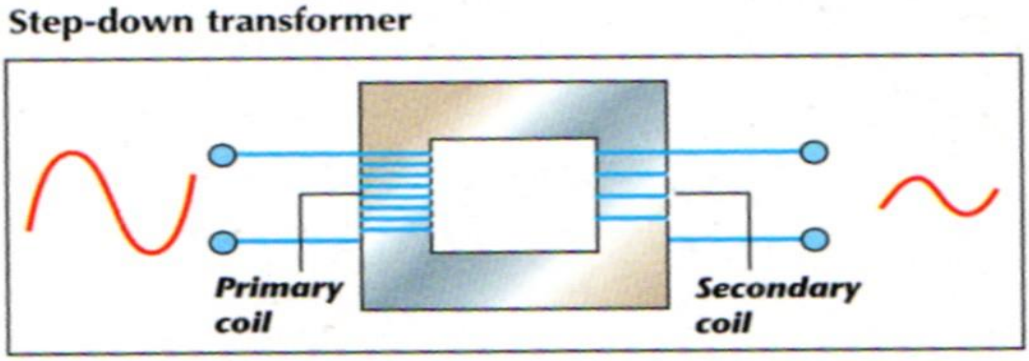


Illustration. Transformer.

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. 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 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, this 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, painlessly and with precision.]

Clinical experience indicates that TMS can produce remission in major depressive disorder, and this remission may persist for many months.

Chervyakov et al (2015) offer possible mechanisms underpinning clinical effects:

1. Low-frequency TMS (defined as stimulation below 1 Hz) reduces neuronal excitability, whereas high-frequency TMS (defined as greater than 5 Hz) increases neuronal excitability.
   Long-term potentiation (LTP) and long-term depression (LTD) refer to changes in synaptic strength (efficiency) associated with TMS. LTP is caused by high-frequency stimulation, LTD is caused by low-frequency stimulation LTP and LTD are probably the key mechanisms supporting long-term effects of TMS.

2. TMS stimulation induces gene expression and enhances the production of a number of enzymes, including NO synthase.

3. In Parkinson's disease, TMS increases the concentration of endogenous dopamine.

4. TMS affects the expression of various receptors, including NMDA receptors.

5. TMS increases the mRNA expression of c-fos.

6. The response of patients to TMS is influenced by polymorphisms within the genes that encode for serotonin (5-HT) carriers, 5-HT_{1a} receptors, and brain derived neurotrophic factor (BDNF).

7. A neuroprotective mechanism may be important. May et al (2007) found that 1 Hz stimulation to the left superior temporal gyrus on 5 days led to 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.

Imaging, MDD and TMS

Imaging is a rapidly developing field, and the physiology of MDD and the effects of TMS are not yet fully understood. Nevertheless, important observations are being made and we need to try to make sense of them.

TMS was applied to the frontal cortex because 'hypo-frontality' (decreased blood flow in frontal regions) was described in MDD. TMS was effective in correcting this pathological state (Speer et al, 2000).

It has been recently demonstrated that the brain is organized into functional networks. One of these is the default mode network (DMN) – a collection midline and lateral structures – it is active when the mind is not actively focused, and is relatively inactivated when the mind is actively focused. In MDD there is elevated functional connectivity in the DMN, which is believed to underpin the characteristic, excessive negative rumination, characteristic of this condition (Liston et al, 2014).

[Of particular interest is increased functional connectivity between the Left DLPFC and the sub-genual anterior cingulate cortex (sgACC)].

Another functional network is the central executive network (CEN) which plays a role in regulating attention, working memory, and decision making. In MDD there is much reduced functional connectivity in the CEN, which may contribute to the cognitive difficulties which may accompany MDD.

TMS treatment normalizes the hyper-connectivity of the DMN – but not that of the CEN (Liston et al, 2014)

Clinical improvement in MDD is associated with significant GABA (inhibitory neurotransmitter) concentration increases in the DLPFC (Baeken et al, 2014).

A related study of MDD found TMS produced significant clinical improvement in mood which was associated with significant reduction in DLPFC-left caudate connectivity (frontostriatal network) (Kang et al, 2016).

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.

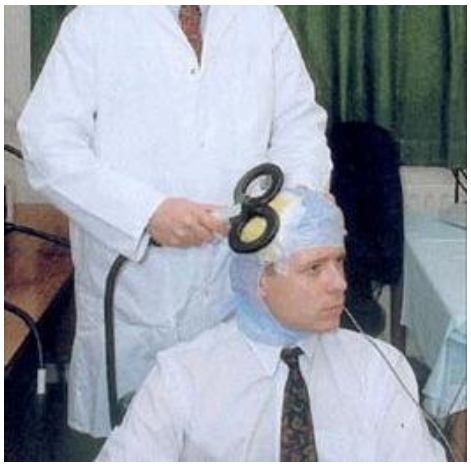


Illustration. 1990s figure-8 (or butterfly) coil.

Every year manufacturers produce new models, and they 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 device, this can be a simple adjustable arm (as below) or a more complex system built into the patient chair.

Illustration. Current device with a simple 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.

Low- and high-frequency rTMS

This topic was touched on under the heading of physiology – it is repeated here - it is a fundamental quality of the stimuli applied in treatment.

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 (Chen et al, 1997), while HF-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 are 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, 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 (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 the early years of TMS treatment, the stimulus intensity was often 80% of MT, but now, 110-120% MT is common.

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

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.

A stimulus [at the desired percentage of MT] can then 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 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.

Treatment parameters

In therapeutic TMS, the parameters are chosen with at least three factors in mind: desire for a therapeutic effect, the comfort of the patient, and the risk of seizure.

In HF-TMS treatment of MDD, the stimulus is applied to the Left DLPFC: 100-120% MT, 10 Hz stimulation, 75 trains per day, 4 second trains, separated by 26 rest periods. The intensity is usually 100-120% MT. (A total of 3000 pulses per second in 37.5 minutes per session.) A course: 20 treatments, 5 per week (O'Reardon et al, 2007; George et al, 2010).

In LF-TMS treatment of MDD, the stimulus is applied to Right DLPFC at 1Hz, to a total of 900 pulses per day. Also at 100-120% MT, 5 treatments per week for 4 weeks.

Side effects

Single pulses of TMS are considered 'relatively' (Mills, 1999) and probably completely safe.

Repeated TMS has been a matter of some uncertainty, especially when HF and high intensity pulses are employed. The noise of TMS is loud, but no hearing deficits have been found in humans treated with rTMS (Pascal-Leone et al, 1992). Nevertheless, hearing protection is recommended.

Headache localized to the site of rTMS is not uncommon, occurring in up to 30% of patients following some treatments. It is due to stimulation of scalp muscles, similar to a localized tension headache, resolves 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. The risk of seizure is very slight, and less than with antidepressant medication (Milev et al, 2016).

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 HF-TMS. (LF-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, 2014; Eryilmaz et al, 2015).

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

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, at least 59 sham controlled trials have been conducted, the majority finding beneficial effects (Lefaucheur et al, 2014). There have been 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), Canadian Network for Mood and Anxiety Treatments (Milev et al, 2016) and an especially commissioned

group of European experts (Lefaucheur et al, 2014). Among others are the Australian and New Zealand College of Psychiatrists, 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 medication (Nguyen et al, 2015) and ECT (Magnezi et al, 2016).

Other psychiatric disorders

Some years ago, there was much enthusiasm for treating a range of psychiatric disorders with TMS. Unfortunately, any benefit seems very modest for auditory hallucinations (He et al, 2017), negative symptoms of schizophrenia (Wang et al, 2017) and obsessive convulsive disorder (Zhou et al, 2017).

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.

Similarly, TMS may, at some stage, have a place in the treatment of Parkinson's disease, dystonia, stroke, neuropathic pain, fibromyalgia, migraine and tinnitus – see the Introduction for references.

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