CHAPTER 29 **Last modified: July 8, 2006**

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Introduction

The application of electric energy to particular brain sites can have a beneficial effect in the treatment of certain psychiatric disorders. ECT is an example. There are difficulties in focusing electrical current on particular brain sites via skin electrodes. The skull (like wood) is very poor conductor of electricity. Thus, high levels of electrical energy need are needed at the electrodes and the current disperses. For example, during ECT some electricity enters the skull via the eye sockets and auditory canals. In delivering sufficient electrical energy to particular brain regions for an antidepressant effect, energy is delivered throughout the brain, and convulsion and temporary memory difficulties are unavoidable. The convulsion means general anaesthesia is necessary, ushering in further complications.

With neurophysiological apparatus and skin electrodes, it is possible to deliver single pulses of electricity to the motor cortex without triggering seizure, but this is very painful and has not been widely utilized.

Psychiatrists and neurologists hoped for technical advances with would overcome these difficulties. Electromagnetism was an obvious choice, but it was only in the last decades that engineering progress (the development of the thyristor) made this idea a reality.

It became possible to stimulate brain regions with single pulses of transcranial magnetic stimulation (TMS) in the mid 1980's. This form of TMS replaced skin electrode electrical stimulation and became an important tool in clinical neurophysiology.

Some attempts were made using 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 enabled repeated stimulation at frequencies of up to 20 Hz.

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), writer's cramp (Siebner et al, 1999) and stroke (Mansur et al, 2005). TMS may become useful in psychiatric diagnosis (Fitzgerald et al, 2002), however, this chapter the focus will on TMS in the treatment of psychiatric disorder.

Therapeutic TMS has been accepted as a standard treatment of depression in Canada and Israel. An application has been lodged with the FDA (USA) and a positive outcome is anticipated in the next few months. (It has, of course, been sanctioned by the FDA in research settings for many years.) It is widely used in private hospital in Australia.

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 mechanism involves the magnetic field created by the electrical current in the first coil extending 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 (Illustration 29.1) A second coil is not necessary; a secondary current can be induced in any conductor (including brain) which is close to a coil through which a current is pulsed.

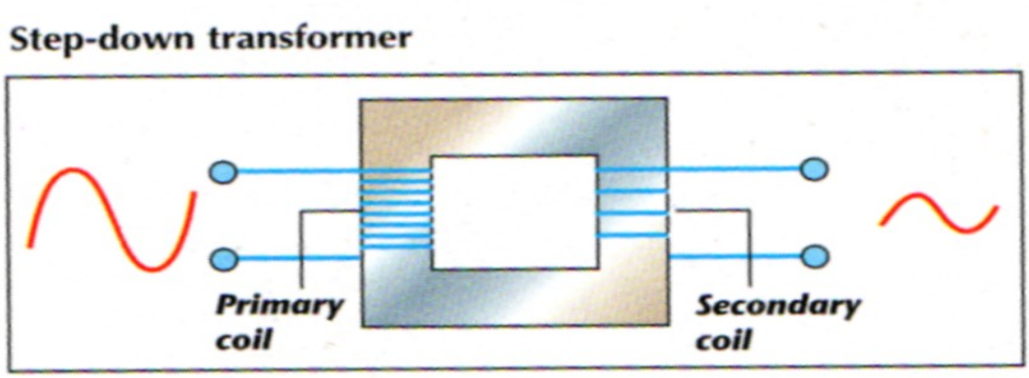

Illustration 29.1. Transformer, see text for details.

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

Physiology

When TMS is applied, the induced electric field causes a flow of current and electric charges accumulates on neural membranes, resulting in depolarization. With currently available apparatus, it appears that depolarization frequently occurs at about the junction of the grey and white matter. At this point, axons with cell bodies in the grey matter bend as they descend into deeper portions of the brain. This is at about 2 cm below the coil, and the induced electric field at this point is about 70 V/m (Ruohonen & Ilmoniemi, 2002).

Neuroplastic change is the result of gene expression (Hyman and Nestler 1993). It can be triggered by a range of inputs, from learning experiences 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).

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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 components purchased] and a coil, connected to the stimulator by a thick, insulated conducting cable.

Along with other components, stimulators contain capacitors which store charge, and a thyristor, a special electronic switch through which the capacitors are discharged, passing current through the coil. The thyristor makes it possible to start and stop currents within milliseconds.

Coils are of two main types. The first coils available were of circular construction (one or more turns of copper set in non-conducting material) with a diameter of 8-10 cm. Most devices come with a circular coil as a standard attachment, but they are not 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 under the coil.

The coil most commonly used in TMS treatment of psychiatric disorders (figure-8 or butterfly coils) are constructed of two circular coils, about 7 cm in diameter, mounted next to each other (Illustration 29.2). 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].

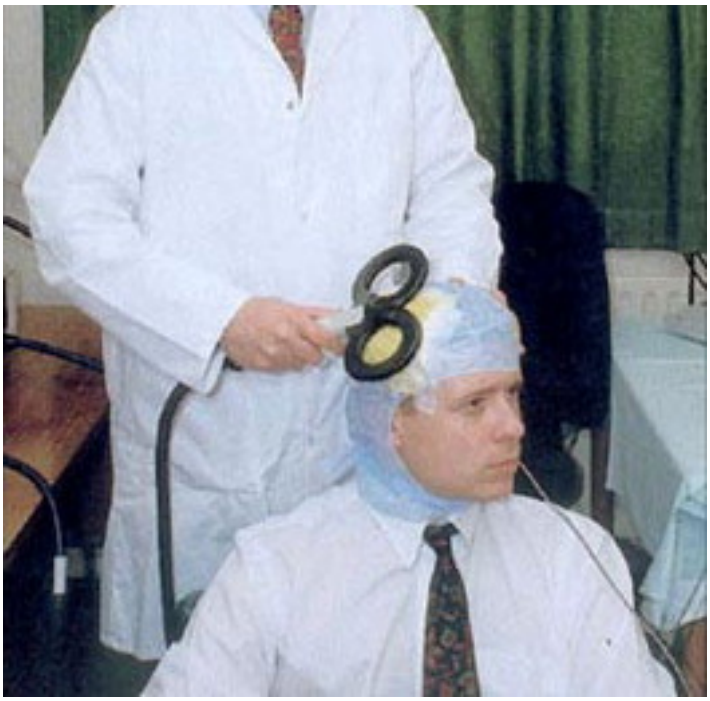

Illustration 29.2. Figure 8 coil.

A new generation “coils” are now being manufactured which may be more efficient and provide other patterns of stimulation. (Illustration 29.3).

Illustration 29.3. A state of the art “coil”. Image courtesy of Neuronetics, Inc. Also, with this device the coil is supported by a gantry, leaving the operators hands free.

Stimulus intensity

To the present, the intensity of the stimulus employed in a particular session of therapeutic TMS has used the motor threshold (MT) as the basic measure. In research the lowest intensity of stimulus has been 80% 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.

Determining stimulus strength using the MT method is far from satisfactory. It is used because the motor cortex is the only brain region which gives an easily detected signal [muscle twitch] when it has been stimulated. Having used the motor threshold to determine the percentage of total machine output which causes depolarization, the coil can be applied to the chosen site for therapeutic stimulation. Depending on the condition being treated, this is usually the prefrontal cortex (depression), but may be the temporal lobes (auditory hallucinations).

Slow and fast rTMS

By convention, “slow” rTMS refers to stimulation at 1 Hertz or less, and “fast” rTMS refers to stimulation at greater than 1 Hz. Slow rTMS decreases (Chen et al, 1997) the excitability, while fast rTMS increases (Pascual-Leone et al, 1994b) the excitability 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. For example, 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 rTMS (George et al, 2000) has been applied to that region. Another approach aimed at bringing the activity of the two hemispheres into balance: slow TMS (Klein et al, 1999) was applied to the right prefrontal cortex. Both methods have beneficial effects.

Side effects

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

Repeated stimulation (the type used in therapeutic TMS) has been a matter of some uncertainty, especially when fast and at 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 such deficits have been found in humans (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 stimulation 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 induced tension headache, and resolves spontaneously or responds to simple analgesics. There is no evidence that TMS can trigger migraine or other serious headache. In fact, hand held machine has recently become available for the treatment of migraine (Illustration 29.3)

Illustration 29.3. 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 rTMS was held in 1996. To that point, 7 seizures which were thought to have resulted from TMS research. Guidelines were produced regarding safe treatment parameter (Wassermann, 1998). In the last decade two possible (evidence not strong) seizures have been reported. 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).

In the early years of TMS research it was considered possible that nearby credit cards, computer discs and other forms of magnetic storage media could be erased. There have been no reports of this side-effect to either patients or operators, but the theoretical risk remains.

After almost two decades, no significant long-term adverse effects of TMS have been detected. While still theoretically possible, long-term adverse effects appear less likely than with pharmacological agents. Nevertheless, caution continues to be recommended (Wasserman, 2000).

Contraindications to TMS

There are few absolute contraindications to TMS treatment. A personal or strong family history of epilepsy is generally regarded to be a contraindication fast TMS. (Slow TMS may prove to be useful in intractable epilepsy (Tergau et al, 1999)).

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 is also generally considered to be a contraindication. The risk to a foetus from TMS to the brain of a mother is probably less than that of medication (Nahas et al, 1999).

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. 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 may 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.

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 usually used 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, 30-40 trains per treatment session. The intensity is usually 100-120% MT. Treatment usually lasts about 20 minutes per day. Treatment is usually delivered 5 days per week for 2-4 weeks.

Conditions treated

Depression

The vast majority of therapeutic TMS research has been in depression. Large studies have demonstrated the statistical superiority of TMS over placebo (George et al, 2000; Fitzgerald et al, 2003; Rossini et al, 2005). While there have been some which have failed to show TMS superiority (Loo et al, 2003), meta-analyses (McNamara et al, 2001; Holtzheimer et la, 2001; Burt et al, 2002; Martin et al, 2002] and expert reviews (Loo & Mitchell, 2005) confirm an overall antidepressant advantage.

Some commentators hold that while there is a statistical advantage for TMS, the clinical effect is not great. Treatment response depends to a large extent on the stimulation parameters chosen, and further research is expected to maximize the antidepressant effect.

TMS has been compared to ECT in a number of studies. While one found a distinct advantage for ECT (albeit with more side-effects), the majority have 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).

Auditory hallucinations

TMS has been applied to the left temporoparietal cortex for the treatment of medication-resistant hallucinations. Slow stimulation (which has the ability to reduce the activity of the cortex) has been employed.

The majority of studies have shown a statistical superiority for active over placebo TMS (Hoffman et al, 2003; Poulet et al, 2005; Brunelin et al, 2006). Not all studies have reported positive responses, however, research is continuing.

Other conditions

TMS is being explored in the treatment a range of psychiatric and medical conditions, but there is insufficient research to the present to make categorical statements. TMS may prove useful in chronic pain (Pridmore et al, 2005) and in tinnitus (Pridmore et al, 2006).

The future

TMS allows the doctor to painlessly reach in and touch 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 others. Thus, with variables at our disposal (intensity, frequency and site of stimulus) and given that psychiatric disorders are so common and disabling, this author has the view that we are standing at the beginning of one of the greatest advances in medicine. (No, I have not been drinking.)

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