Repetitive transcranial magnetic stimulation in Malta – a revolutionary therapy for psychiatric and neurological disorders

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ABSTRACT

Severe depression is one of the most common psychological disabilities, with a global point prevalence of 4.7%. The World Health Organisation predicts it to be the leading cause of disease burden by 2030. With 350 million depressed people, depression is a debilitating condition where only a third of treated patients achieve remission after the first antidepressant treatment. Up to 34% of the patients are treatment resistant, whereas another 15% respond partially, following standard doses of antidepressants for 6 weeks or more. Failure to respond to two consecutive antidepressants leads to greater reductions in remission rates.

Recurrence rates, despite specialised care, are 60% and 85% after 5 and 15 years post-recovery respectively. Inadequate efficacy, adverse effects, and sensitivity to current treatments call for more effective and tolerable treatment options. With over 20 years of research, repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment that alters brain activity and cortical excitability permanently, making it an effective antidepressant treatment beyond the conventional ones, including electroconvulsive therapy (ECT) in some studies.

Furthermore, rTMS is safe, natural, painless, fast acting and approved by the Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE). It has virtually no side effects and only one absolute contraindication (epilepsy). Experience of its use in Malta has shown improvement in diminishing the key symptoms of depression, decreased suicidal ideation and a decrease in other psychiatric and neurological symptoms within hours of the first sessions. Besides providing immediate relief and hope for patients and relatives, this improvement has many clinical and future management implications. Research is now underway to apply this novel technology and its variants to other physical and psychological disorders.

KEYWORDS

Treatment resistant depression; repetitive transcranial magnetic stimulation; intermittent theta burst stimulation; transcranial direct current stimulation

BASIC PRINCIPLES AND HISTORY

Repetitive transcranial magnetic stimulation (rTMS) is a safe, painless, effective, natural, evidence-based treatment for patients suffering from severe unipolar affective disorder/depression who are treatment resistant and/or treatment intolerant, i.e. they are generally labelled as suffering from treatment-resistant severe/major depression (TRD) (Carpenter et al., 2012; Connolly et al., 2012). Others find rTMS appealing as they may be sceptical of conventional treatment.

Revolutionary in its approach to treating TRD, rTMS is the brainchild of Baker and his colleagues who have been experimenting with single pulse TMS in Sheffield, UK since the 1980s (Hotlzheimer and Mc Donald, 2014). The UK team pioneered stimulating the human brain's cortex after being inspired by Galvani and Aldini's eighteenth century experiments on electrically stimulating the peripheral muscles of dead animals and humans respectively. Their objective at the time was to map the cortex and elicit a corresponding short-lived motor stimulation of peripheral muscles (Baker, Jalinous and Freeston, 1985). Technological developments subsequently produced repetitive pulse TMS which was shown to have long lasting effects on the cortex that

persisted beyond the stimulus delivery (Pascual-Leone et al., 1996; Maeda et al., 2000).

This non-invasive and novel treatment is based on the discoveries of British nineteenth century physicist Michael Farady, whose Law of Electromagnetic Induction predicts how a changing magnetic field will interact with an electric circuit to produce an electromotive force - a phenomenon called electromagnetic induction. In essence, exposing a conductor to a rapidly changing magnetic field will induce a current in the conductor. rTMS works by inducing a rapidly changing magnetic field in a "depression sensitive" brain/cortical area, which is populated by neurons and is located just under the skull. This rapidly changing field induces a current in the neurons (the conductor). Hence, the area is stimulated to be more electrically active.

To achieve this, TMS devices consist of a large capacitor, a control mechanism that enables the capacitor to be rapidly discharged, and a conductive coil through which the current travels to generate a powerful and fluctuating magnetic field (Barker, 1999). Through the process of electromagnetic induction described above, this rapid pulse of electric current induces a rapidly fluctuating magnetic field, which in turn induces an electric current in the underlying brain neurons (Wagner, Valero-Cabre and Pascual-Leone, 2007). How much brain tissue is stimulated is dependent on the shape of the coil as well as the intensity of the stimulation i.e. amount of current discharged by the machine (Pascual-Leone et al., 2002).

In biophysiological terms, several studies concerning depression show that the left dorso-lateral pre-frontal cortex (LDLPFC), along with deeper cortical structures such as the limbic system, are associated with mood regulation. Hence the LDLPFC is a lynchpin in the pathogeneses of an affective illness. Overall, a depressed patient's brain is less active than a healthy brain, as evidenced by several neuroimaging studies. One study in particular demonstrates that depressed patients have fewer brain receptors, less circulating neurotransmitters (e.g. serotonin) and fewer healthy synaptic connections between neurons (Psych Central, 2008).

rTMS addresses this neuronal "apathy" (or hypoactivity) by progressively re-stimulating a current in the LDLPFC neurons (i.e. a wave of depolarisation down the neuron membranes), so as to eventually restore the balance of neurotransmitters and healthy nerve contacts with each other. The postulated principle which keeps neurons healthy, active and interconnected is based on the principle of Hebbian neuroplasticity (i.e. the development of new specialised neural networks, which allows for sustained improvement over time). Hebbian neuroplasticity resembles the long term potentiation (LTP) or long term depression (LTD) of neurons. LTP implies an increase in the development of synaptic transmission of neurotransmitters, which induces a wave of depolarisation along the neuronal membrane. This depolarisation is thus the generated current running down the neuron. The opposite of LTP is LTD, which produces a long lasting decrease in synaptic activity.

The positive behavioural effects of this technology persist after a course of rTMS treatment through neuroplasticity (Christyakov et al., 2010). Bickford and his colleagues first extended the domain of TMS research into neuropsychiatry in 1987. Transient mood elevation in healthy subjects receiving single-pulse stimulations to the motor cortex was described (Bickford et al., 1987). This triggered the scientific investigation of the effects of depolarising magnetic fields in a variety of neuropsychiatric disorders. The clinical utility breakthrough came in 2008 to treat patients suffering from severe depression, who had not responded to at least one antidepressant in their current episode (i.e. they were deemed to be treatment-resistant or intolerant according to FDA criteria) (Herwig et al., 2007; O'Reardon et al., 2007; George et al., 2010). The LDLPFC was targeted with very positive outcomes.

EXPERIMENTAL AND THERAPEUTIC FUNCTIONS - THE E/I RATIO

rTMS is used both experimentally and therapeutically. In the experimental domain TMS can be applied in single pulses to depolarize a small population of neurons in a targeted brain region. Cortical motor outputs can thus be mapped, central motor conduction times can be assessed and the cortical silent period can be measured (a measure of intracortical inhibition). These parameters may be affected by pathologies of the central nervous system such as autism (Kobayashi and Pascual-Leone, 2003). Therapeutically, trains of rTMS pulses can be applied at various stimulation frequencies and patterns to modulate local cortical excitability beyond the duration of the stimulation itself. Depending on the parameters of stimulation, the excitability can be either facilitated or suppressed (Pascual-Leone et al., 1994). The after-effects of rTMS are thought to be related to changes in efficacy (in either the positive or negative direction) of synaptic connections of the neurons being stimulated

(Hoogendam, Ramakers and Di Lazzaro, 2010). These after-effects have thus been used to study cortical plasticity mechanisms in a number of populations (Pascual-Leone et al., 2011).

rTMS has the potential to detect and define the Excitatory/Inhibitory (E/I) ratio for a particular disorder. E/I ratios are a measure of the activity-dependent neural feedback systems that tightly control network excitability. Thought to be crucial for proper brain development, the relative degree of excitatory and inhibitory drive in a neural circuit reflects a form of homeostatic plasticity that helps to maintain neuronal activity within a narrow, safe range. Processing of neural information is thought to occur by integration of excitatory and inhibitory synaptic inputs. As such, precise control mechanisms must exist to maintain an appropriate balance between each synapse type. Altered E/I ratios are noted in neuropsychiatric disorders including depression, Obsessive Compulsive Disorder (OCD), schizophrenia, epilepsy and autism.

As E/I ratios are specific for a disorder, they may thus provide a screening/confirmatory test for physical and psychological conditions which are difficult to detect clinically. rTMS can then be used therapeutically for these disorders as it alters the relative excitability and inhibition (E/I ratio) in targeted circuits to restore these networks to a healthy baseline.

Table 1: Some neurological and psychiatric disorders where rTMS is being applied

Anorexia nervosa
Autism
Bipolar affective disorder
Cocaine dependence
Depersonalisation Disorder
Fibromyalgia
Migraine
Neuropathic pain
Obsessive Compulsive Disorder (OCD)
Parkinson's disease
Post Traumatic Stress Disorder (PTSD)
Stroke
Suicidal ideation (rapidly reduced with rTMS)
Tinnitus

Clinically, there is much research for various neurological and psychiatric conditions. The list continues to grow as researchers alter the neurostimulator settings, type of magnetic field, and the cortical area to be stimulated (see Table1).

EFFICACY

While antidepressants, psychotherapies and electroconvulsive therapy (ECT) are effective in treating depression, a substantial proportion of patients fail to respond to these treatment regimens and hence are known as treatment-resistant depression (TRD) patients. TRD is estimated to occur in around 50 to 60% of all patients (i.e. 5 out of 100 people in the general healthy population) (Fava and Davidson, 1996). Despite providing relief to a proportion of patients, other interventions bear weak or inconsistent evidence for routine clinical recommendation.

Table 2 summarises the various characteristics of the routine, evidence-based available treatments for TRD compared to rTMS. The evidence base for psychological and other therapies is variable or incomplete. This is due to many factors including the heterogeneous therapies available, lack of standardised data and sample populations, study design, and funding. This does not mean, however, that such therapies do not have an important role to play in the management of depression. The most widely researched therapies to date are CBT and mindfulness-based therapies.

rTMS does not require hospital admission or anaesthesia, unlike another more commonly used form of brain stimulation namely electroconvulsive therapy (ECT) (Cusin and Dougherty, 2012). Apart from the potential anaesthetic complications (e.g. nausea and heart problems), ECT is known to cause deficiencies with respect to remembering facts and with learning new material, as well as inducing post ictal confusion and muscle aches, among others. Many researchers argue that rTMS is poised to dethrone ECT as the 'gold standard' treatment for TRD.

TREATMENT RESISTANT DEPRESSION PROTOCOL, FDA AND NICE APPROVAL

A specific protocol defining the dose and frequency of the magnetic pulses delivered by rTMS has been widely studied for TRD. This protocol has been used in several countries after approval was granted by the American FDA (FDA Approval K061053) (Horvath et al., 2010).

Table 2: Characteristics of routine, evidence-based available treatments for TRD compared to rTMS

	Antidepressants	ECT	Psychological / other therapies	rTMS
Effectiveness	28 - 59% (Geddes et al., 2003; Sinyor, Schaffer & Levitt, 2010)	60 - 80% (Geddes et al., 2003)	Comparable to medication?	Comparable to ECT or better (O'Connor et al., 2003; Schulze-Rauschenbach, 2005; Rosa et al., 2006)
Beginning of therapeutic effect	4 - 6 weeks	1 week	Weeks	<1 week
Common side effects	Headache; Dry mouth; Dizziness; Constipation; Nausea; Blurred vision; Urinary retention; Sexual issues	Loss of memory; Muscular pain; Nausea; Headache	Stress which may cause symptom exacerbation: Emotional turmoil; Higher expressed emotions in families	Self limiting mild headache or resolves with a single dose of paracetamol
Incidence of side effects	Up to 86% will experience at least one significant adverse event (Hu et al., 2004); Up to 34% will experience secondary sexual dysfunction due to medication (Hu et al., 2004)	29 - 55% (Rose et al., 2003)	Unknown	Up to 20% (Carpenter, 2005)

rTMS was also approved by other countries, including by NICE in the U.K. in 2015 (IPG542) (NICE, 2015). Moreover, it has been suggested that the clinical effectiveness could be improved by developing further novel protocols and identifying local brain regions using neuro-navigation to improve the targeted pulse delivery (Fitzgerald et al., 2009; Fox et al., 2012). Hybrid protocols are also being devised to reduce the duration of the session, while maximising the efficacy of treatment. These protocols also include adding standard treatments to achieve remission faster.

ADMINISTERING rTMS

After an initial assessment and after obtaining consent, rTMS treatment is administered by sitting in a comfortable, reclining airline-like chair (Figure 1). The treatment coil is placed on the scalp over the LDLPFC, as shown in Figure 2. The patient then receives a sequence of several short "trains" (or pulses) of stimulation for up to 40 minutes. Throughout the entire procedure, the patient remains awake and alert. He can read a magazine, watch TV or even undergo psychological therapy during the session. No extra medication is administered. Clinical experience has shown that patients often need less regular medication as they improve with rTMS, as endorsed by NICE in 2015.

ADVANTAGES, SAFETY AND SIDE-EFFECTS OF rTMS

rTMS has a number of advantages over other treatments as listed below:

- Natural, evidence-based, non-invasive, localised, and harmless treatment.
- No debilitating side effects related to pills or psychotherapy.
- No anaesthesia required (i.e. it is non-systemic).
- rTMS is an outpatient treatment, with no restriction of daily activities.

- The patient remains awake (can talk, listen to music, etc).
- Rapid improvement in the patient's symptoms (3 – 7 days for depression).
- No adverse side effects in the vast majority of patients.
- Reduce need for regular medication.
- Can be used concurrently with medication/ psychological therapies.

rTMS is now widely used and has been approved by major centres worldwide (including Mayo Clinic, Johns Hopkins, Yale, Nottinghamshire NHS Trust, New South Wales University, and Sydney University). Butler Hospital in Providence, Rhode Island, USA is one such centre of excellence and a pioneer in the field. Headed by world expert Professor Linda Carpenter, Butler Hospital has conducted more than 10,000 active treatments to date without adverse outcomes or severe side effects (Carpenter, 2015).

The most frequently experienced side effect of rTMS is a mild headache that responds to a low dose of paracetamol. This is reported in only about 1 in 10 patients. Headaches tend to diminish over the course of treatment, although adjustments can be made immediately in coil positioning and stimulation settings to remove the discomfort. To date, no single serious side effect has been encountered in the local cohort, ever since the start of rTMS treatments in 2016.

Seizures are a theoretical possibility and hence the only absolute contraindication for TMS is a history of active epilepsy. However, less than 20 cases of TMS induced seizures have been reported out of more than 10, 000 subjects in the past 25 years. To put this in perspective, the risk of a seizure is much more likely to occur by ingesting co-amoxyclav. In other words, this minute risk is considered to be less than 0.01% (Rossi et al., 2009).

In summary, the established benefits of treatment by far outweigh the probability of side effects.

rTMS IN PREGNANCY AND IN CHILDREN

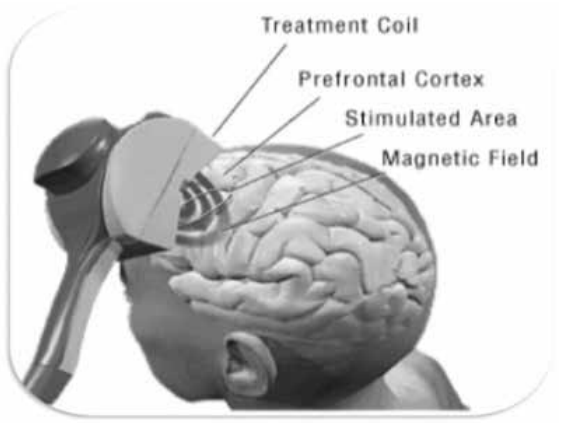
So far, there is no long term safety data available on pregnancy, nursing women or children. A recent study has demonstrated that rTMS can be used effectively in pregnant patients (Kim et al., 2015). Studies are ongoing on the use of rTMS in children. More research is however needed to address the safety and efficacy of rTMS in these special populations.

PROMISING FUTURE STIMULATION THERAPIES

Other treatments like direct current stimulation, vagal nerve stimulation, and deep brain stimulation are also being actively investigated and researched. Deep brain stimulation in particular, which uses an H-shaped coil as opposed to a standard figure of eight coil, is emerging as a promising "close second" to rTMS. This was indicated in a recent multi-centre randomised control study, which concluded that the effects appear "durable", and a "clinically significant improvement" was seen in patients resistant to multiple antidepressants (Levkovitz et al., 2015). A further recent analysis corroborated these findings (Hardy et al., 2016).

Figure 1: An image showing the set up of an rTMS Clinic in Malta

Figure 2: The position of the rTMS treatment coil on the scalp



INTERMITTENT THETA BURST STIMULATION

A recent protocol has been devised as a variant of rTMS for TRD. This protocol, now available locally, delivers theta waves in 'bursts' to the brain, hence the term 'intermittent theta burst stimulation' (iTBS). Theta waves are naturally present over the cortex and hippocampus and are readily detectable by electroencephalography (EEG). In the right concentration and location, these waves are associated with healthy cognitive function, levels of alertness, and mood (Lega, Jacobs & Kahana, 2012).

The principle of electromagnetic induction also applies here in order to revive the depressed person's brain (Chung, Hoy & Fitzgerald, 2014). Being similar to classic rTMS in terms of administration and preparation, preliminary data shows that iTBS has a similar efficacy and side effect profile. The huge advantage of iTBS over rTMS is that the treatment session only lasts 3 minutes.

TRANSCRANIAL DIRECT CURRENT STIMULATION

This technology is easy to use and can be used at home or at work. Transcranial direct current stimulation (tDCS) is a non-invasive method of electrical stimulation of the brain using a weak direct current applied to the scalp through electrodes to treat TRD (Loo et al., 2012). The aim is to modify cortical excitability and activity in the brain areas under the scalp electrodes. It is thought to work through the depolarisation and hyperpolarisation of cortical neurons. The patient, who remains awake and alert during the procedure, is usually seated, while a portable battery-operated stimulator delivers a constant low-strength direct current to two saline-soaked sponge electrodes placed on the scalp. Data on this technology is still inconsistent in terms of efficacy, and scalp burns have been reported. Another concern is that self-medication without professional supervision is a strong possibility. The advantage of tDCS is that it can be used in the privacy of one's own home.

rTMS – THE EXPERIENCE IN MALTA

Crisis Resolution Malta was the first to offer rTMS in Malta to the public since early 2016, having conducted over 1000 sessions so far. Patients have different expectations and fears, hence the need for accurate, evidence-based and patient explanation of the technology. A lot of these fears stem from the novelty and from inaccurate or outdated information on the web. The majority of patients (approximately 70%) improve within a few hours of a single treatment. They may feel somewhat 'lighter' in mood and/or experience better quality sleep. They also tend to feel more refreshed in the morning.

Importantly, suicidal ideation is also markedly reduced after a single session, making the difference between immediate hospitalisation versus supervised discharge home. The implications of the latter cases are significant in many ways from a social, clinical and economic standpoint, among others. On the latter point, there is also potential in rTMS being routinely used by crisis teams. The burden of symptoms in disorders such as post-traumatic stress disorder, obsessive–compulsive disorder (OCD), cocaine dependence and autism are also being reduced. Furthermore, patients have not yet experienced significant side effects.

iTBS has also been carefully introduced with somewhat promising results for other disorders including OCD, eating disorders, cocaine abuse and neuropathic pain. tDCS is now also available under supervision.

CONCLUSION

rTMS and its variants are safe, effective, evidence-based and natural electromagnetic stimulation treatments which have growing applications in physical and psychological health. They provide an appealing alternative to those who are treatment resistant, treatment intolerant or treatment sceptical to conventional therapy for whatever reason. The technology also works fast and synergistically with other established treatments or therapies. This is important in potentially life threatening scenarios. Finally, the side effect profile is very good indeed and there are very few contraindications. Although still in their infancy, other future therapies look promising.

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