SOUTHEASTERN PSYCHIATRIC ASSOCIATES

The science of TMS (for clinicians and other interested parties)

Until very recently our only choices for treating major depression were the various psychotherapies, antidepressants, and ECT. With the advent of repetitive Transcranial Magnetic Stimulation, or rTMS, we have now added another arrow to our quiver, one that is focal, safe, and effective.

The history of neuromodulation dates back to the 19th century. In 1874, Dr. Robert Bartholow used Faraday's principle of electromagnetic induction to produce muscle movement by stimulating exposed motor cortex (1). In 1985, Barker, Jalinous, and Freeston (2) published the first description of Transcranial Magnetic Stimulation. In 1995, George et.al. (3) reported on the first use of TMS for the treatment of depression. After multiple studies documenting its efficacy, in 2008 the FDA cleared the first Transcranial Magnetic Stimulation device as a treatment for medication-resistant depression.

How TMS works

TMS involves placing an electromagnetic coil against the scalp and delivering repetitive, pulsed stimuli, generally at a frequency of 10 Hz. This magnetic field penetrates the skull and induces a shallow electric current in the underlying cortex. This current enhances the firing rate in the neurons in that region (a 1 Hz stimulus has an inhibitory effect.) According to the principle of long-term potentiation, the synapses involved in this stimulated region are strengthened; "if it fires together, it wires together." This has the effect of increasing neural plasticity. TMS effectively puts the brain into learning mode and exercises it.

Although many cortical regions have been studied for a variety of effects, the target of the clinical treatment of depression is the left dorsolateral prefrontal cortex, or l-DLPFC. This region is part of a network of cortical and limbic regions that are involved in emotion. More specifically, the limbic regions (amygdala and insula) generate the negative affect, while the cortical regions are inhibitory.

By stimulating the DLPFC we enhance the inhibition of the affect, and this is the presumed mechanism of action for TMS. In this way, TMS assists the conscious mind in its attempts to control depression coming up from deeper parts of the brain.

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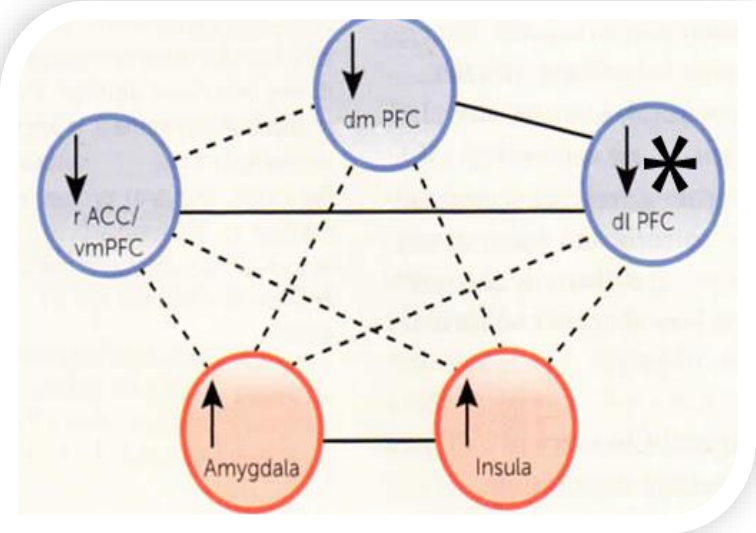


Other effects on neurotransmitters and hormones include enhancing dopamine release in the caudate (4), mesolimbic, and mesostriatal regions (5); downregulation of 5HT2 receptors in the frontal cortex (6); upregulation of beta adrenergic receptors in the frontal cortex (7); downregulation of beta adrenergic receptors in the striatum (8); normalization of the Dexamathosone Supression Test (9); and stimulation of TSH release (10). TMS is protective of hippocampal plasticity in animal models of depression.

By trial and error 10 Hz was found to be a more effective frequency. The 10 Hz frequency is in the range of the alpha waves. The alpha rhythm serves to coordinate neural activity and synchronize firing. TMS entrains alpha, but just what this means is an area of ongoing research. There is new research into using higher frequencies in the theta range.

The Treatment Procedure

TMS is an office procedure. As there is no anesthesia or seizure activity, there is no cognitive impairment, and the patient can drive him- or herself to and from the treatment session. During the treatment the patient is seated comfortably in a chair with the magnetic coil in contact with the scalp. The patient remains alert and conversant throughout the treatment.

In the first session, measurements of the size and shape of the skull are taken to identify and mark the location of the DLPFC. The next step is to determine the optimal power output level, as this varies from patient to patient. Since this requires something observable, it is accomplished by delivering single pulses to search for the area of the motor strip that will induce movement of the thumb. Once this location is identified, the power output is titrated so that 50% of the pulses produce thumb movement. Treatment is now ready to begin.

Standard protocol calls for 75 trains of 40 pulses over 4 seconds (10Hz) with a 26-second rest period in between pulses. The subjective sensation is that of a finger being tapped firmly against the forehead. Twitching of the eyebrow (orbicularis oris) or sometimes the jaw (temporalis) is the only common side effect, and patients usually quickly accommodate to this. If not, the angle of the coil can be changed, or it can be repositioned up to a cm, since the DLPFC is about the size of a half dollar while the field is about as big as the bottom of a coffee cup. A rather loud clicking sound is heard, so earplugs are provided. Patients usually watch TV or converse with a companion during the session. Some even fall asleep. After 37-1/2 minutes, the session is complete and the patient can immediately resume normal activities.

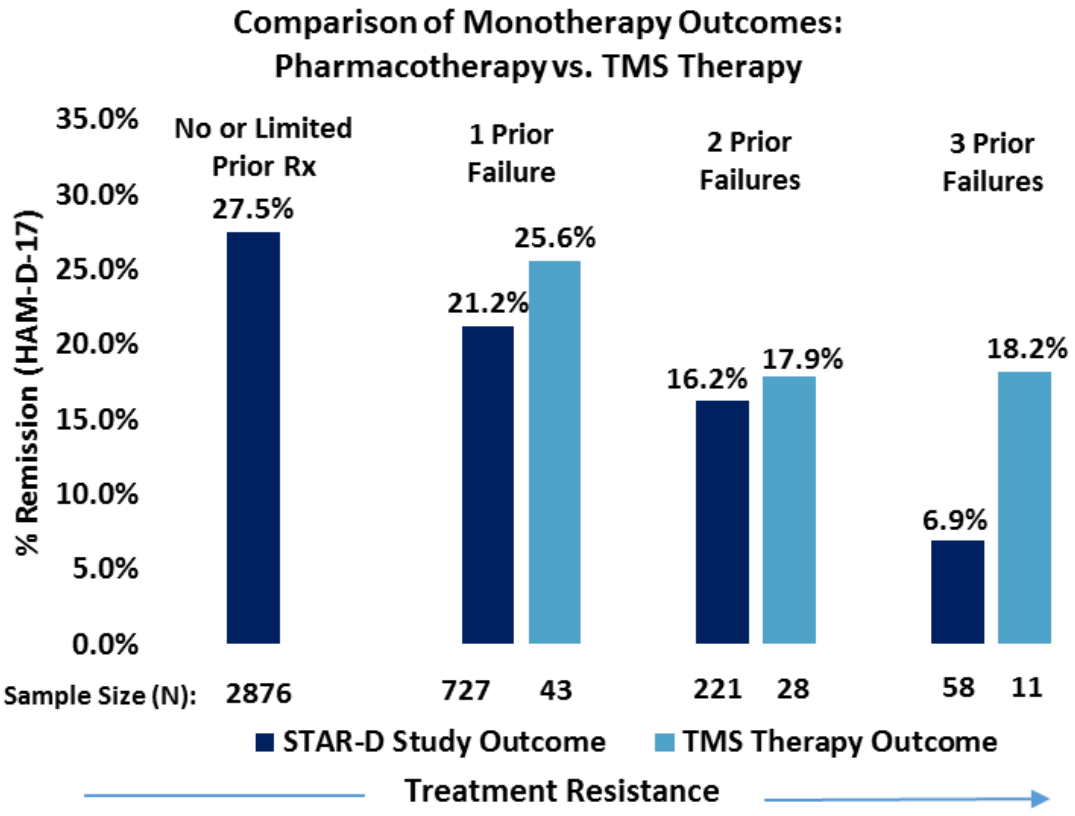
A full course of treatment usually involves 36 sessions: six weeks of 5 days a week, followed by a three-week taper. If a session is missed, it can be added on at the end.

The above-mentioned muscular twitching is not usually experienced as painful. As can happen with antidepressants, sometimes patients can get activated or even have a manic switch. There is a 1/1000 incidence of seizures which only occur during the treatment, and a physician is required to be in the office during all treatments.

Research

TMS is FDA cleared only for the treatment of treatment resistant depression (TRD). This is defined as a failure of 3 antidepressant trials either due to lack of efficacy or side effects. Consequently, although TMS is being actively researched for a variety of conditions, and is also effective as a first- or second-line treatment for depression, it is only reimbursable by insurances for TRD.

The rationale for this is that the research has shown that three medication failures is the point at which TMS clearly becomes more effective than another medication trial. To put it another way, logistical considerations aside, your patients with TRD are more likely to respond to TMS than to medications.



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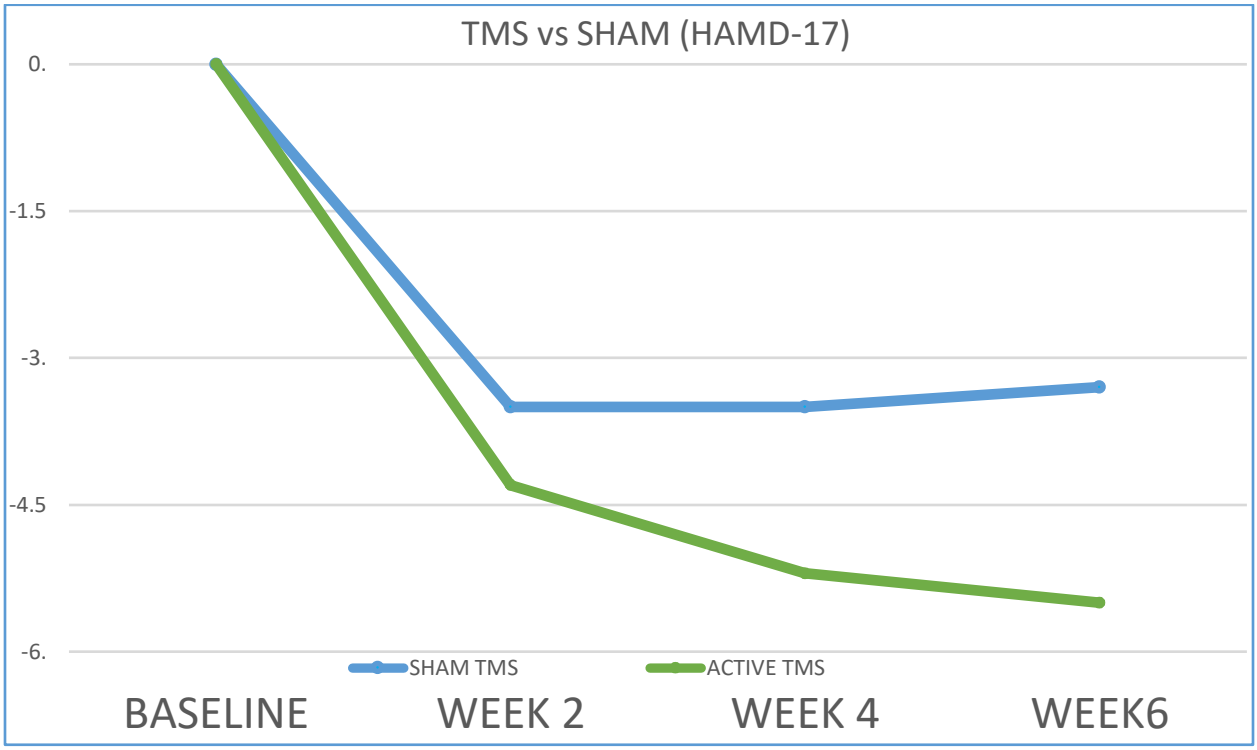
By synthesizing data from his own study and the STAR-D trial, Avery (11) demonstrated the comparable rates of response to medications vs. TMS after different numbers of medication failures.

As this is the synthesis of two different studies and not a true head-to-head study, there are a number of methodological issues with this approach. There were factors that might have skewed the results towards either medications or TMS.

Several well-designed randomized, prospective, sham-controlled studies exist. Any understanding of the literature should be interpreted in light of the fact that this is a young, evolving field, and some of the research, especially prior to 2008, involves protocols now felt to be less effective.

In 2007, O'Reardon (12) reported on a large multisite study with a modern protocol, except the target was 1 cm posterior to the one used now. Patients could be moved to the unblinded limb and counted as nonresponders at 4 weeks, whereas we now know many patients take the whole 6 weeks to respond. There was a large effect size. The response rate (24.5% vs. 13.7%), and remission rate (15.5% vs. 8.9%) were approximately double the sham rate (P=0.006). The discontinuation rate of ~5% was similar to sham.



** P < 0.01 Adapted from O'Reardon et al. 2007 **

In 2010, George et.al. (13) conducted a very large study vs. sham involving over 800 subjects. The absolute response and remission rates are uninterpretable as the study was designed only to compare rates. Patients who didn't respond by the end of 3 weeks were counted as

nonresponders LOCF and put in open label. The TMS response rate was 4.6 times the sham rate.

Several meta-analyses from 2014 of sham-controlled studies exist, although all include some outdated protocols. Gaynes, Lloyd, and Lux (14) calculated a remission rate 5x higher than sham and a response rate 3x higher. Liu et al. (15) found a response/remission rate of 46.6% vs sham 22.1%. Berlim (16) reported a response rate of 29.3% vs 10.4% and remission 18.6% vs 5%.

Open label studies (17, 18, 19) showed a response rate of 50-58% and remission 25-37% and were highly significant (P<0.0001).

In conclusion, given that all patients referred for TMS are already treatment resistant, both the percentage of patients successfully treated and the magnitude of the effect are very substantial.

TMS Versus ECT

In most studies, ECT was superior to TMS, although in some it was comparable. A recent meta-analysis (20) found ECT to have a superior response rate (64.4% vs. 48.7%) and remission rate (52.9% vs. 33.6%) with similar discontinuation rates. TMS, however, lacks many of the liabilities of ECT in that there is no anesthesia, no seizure is induced, it is an office procedure, and the patient can drive him- or herself to and from the treatment. Also ECT is well known to produce memory and cognitive deficits, whereas TMS, if anything, has a pro-cognitive effect (20, 21).

Durability

Several researchers have looked at the durability of the effect. Recurrence of depressive symptoms is considered to be the rule rather than the exception, and TMS is not immune from this phenomenon. Criteria and methods vary from study to study, but Dunbar (22) found 62% of remitters and responders still meeting response criteria at one year. Janiack (23) reports 38% worsened at 6 months with 10% meeting criteria for relapse. Montovani (24) studied remitters and found 58% still in remission and 13.5% relapsed at 3 months.

Patients who do worsen or relapse may come back for “tune up” sessions. This usually involves a significantly shorter series of treatments. Fortunately, 82.5% of those that worsened achieve symptomatic relief (23).

Other Areas of Research

TMS in either the stimulatory or inhibitory frequencies is being studied for a variety of conditions, including—

- Anxiety
- Mania
- PTSD

- Substance Abuse
- Autism
- OCD
- Tremor
- Vertigo
- Tinnitus
- Parkinson's Disease
- Inhibiting the R language analog area after aphasic stroke may improve regaining of language function

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2. https://www.ncbi.nlm.nih.gov/pubmed/2860322
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7. Fleischmann A, Sternheim A, Etgen A, Li C, Grisaru N, Belmaker R. Transcranial magnetic stimulation down-regulates beta-adrenoreceptors in rat cortex. J. Neural Transm. 1996; 103: 1361–1366.
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