Whither TMS: A One-Trick Pony or the Beginning of a Neuroscientific Revolution?

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Psychiatry has been at the forefront of advancing clinical transcranial magnetic stimulation (TMS) since the mid-1990s, shortly after the invention of modern TMS in 1985 by Barker. Clinical TMS for psychiatric applications is advancing rapidly, with novel methods and innovations for treating depression, as well as a new clinical indication in obsessive-compulsive disorder. This review summarizes the recent findings and peers into the near future of this fertile and rapidly changing field. It is possible that many, perhaps even most, psychiatrists will be incorporating some form of brain stimulation into their practice within the next decade. The author summarizes the reasons for this optimistic view.

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This issue of the *Journal* contains two important articles that report on applications of transcranial magnetic stimulation (TMS), a relatively new technology for psychiatrists. At this stage, one might well wonder: Are these articles the hoof beats of a stampede of new indications using TMS? Will every psychiatrist soon be a brain stimulator of sorts, like most psychiatrists are now trained in psychopharmacology and understand the principles of talking therapies? Or is all this brain stimulation much ado about nothing, and will TMS go the way of insulin therapy for depression (1, 2) or renal dialysis for schizophrenia (3)? I offer here an overview of the issue's theme with the aim of providing a fundamental understanding of the concepts, methods, and future directions of TMS. The question of where TMS is headed may not yet be fully answerable, but in my view, as I will show, there are ample grounds for optimism about its potential.

BACKGROUND

Short History

Psychiatry had an early love-hate relationship with TMS soon after Anthony T. Barker developed it in its modern form in 1985 (4). Some, myself included, were eager to use TMS and perfect it as a treatment (5–7). Other psychiatrists were quite skeptical and resistant (8, 9). TMS involves passing a large but brief electrical current through insulated wires resting on the scalp. The powerful electrical current creates a magnetic field, which penetrates the scalp and skull and then induces electrical currents in the superficial areas of the brain (10). In 1985, Barker was the first to succeed in making a coil and capacitor powerful enough to reach into the spinal cord (his original target) and also the cortex of the brain. In a generous move, Barker then built several machines and helped place them in leading laboratories around the world. One of those laboratories was the National Hospital for Neurology and Neurosurgery, Queen Square, London, where I spent 1989 learning about the entirely new world of functional brain imaging using positron emission tomography (PET), single-photon emission computed tomography (SPECT), and MRI scanning in psychiatry. Luckily, while I was there, I first saw one of Barker's TMS machines, only 4 years after they were invented.

The early 1990s were important in psychiatry, as we could now finally image our organ of study with the new tools of CT and then MRI scans. Fluorodeoxyglucose (FDG) PET scans were starting to tell us about regional brain activity and behavior in health and disease. The new imaging tools and the imaging revolution were developing initial maps of pathological regions in the brain for psychiatric diseases, much like neurology had developed for Parkinson's disease (11). Thus the environment could not have been better for a noninvasive stimulating tool like TMS: we had maps of where to stimulate and a new technology that allowed us to explore and test. Many psychiatrists across the globe, particularly those working in imaging, like myself, who were developing these maps, could see the potential for a relatively noninvasive tool like TMS with the ability to stimulate the cortex of an awake, alert person (7, 12–17). The optimists among us eagerly sought to stimulate cortical regions in patients and see if we could change disease progression. But how to start? There were and still are a dizzying array of complex questions—where to place the coil, how much electricity to deliver, over how long an interval, in what pattern, and so on. In the 25 years since the first TMS clinical trials in depression (5, 7, 13, 14, 18, 19),

we have made remarkable progress in understanding how each of these variables changes what TMS does in the brain. Work in this area is harder than it should be because of certain properties of physics and technological limitations that make it hard to perform preclinical TMS studies. In order to make a TMS coil small enough to proportionately stimulate a mouse or rat brain compared with a human's, one has to deliver massively larger amounts of electricity through smaller coils—and they explode (20–22). Translational neurobiology is not always easy and straightforward!

Why Depression?

Repetitive TMS (rTMS)—a repetitive train of TMS pulses—has had the biggest success as a therapy in treating treatment-resistant depression. Many have wondered why we moved rTMS into the clinic for depression, and not for some other neuropsychiatric illness for which we have a better understanding of the circuits involved, such as stroke recovery, Parkinson's disease, or tinnitus (23). One reason was that ECT had provided clear evidence that regional electromagnetic stimulation could treat the illness (24, 25). Additionally, beginning in the early 1990s, there was an emerging consensus about key cortical and subcortical regions involved in depression, some of which could be directly stimulated with TMS (19, 26, 27). Activity in some of the regions, moreover, correlated with improvements in symptoms following sleep deprivation (cingulate) (28) or ECT (prefrontal cortex) (24, 29). Ironically, some ECT practitioners and researchers were among the most ardent opponents of TMS. Their incorrect logical concern was that TMS was not causing seizures (true) and that seizures were necessary for the antidepressant effects of ECT (also true), so a non-seizure-producing intervention device could not work (false) (30). (We did not then have the exquisite tools of today, which allow us to show changes in regional functional connectivity that mediate the clinical effects of rTMS [31].) Luckily, depression turned out to be a superb initial choice.

Methodically uncovering the details required for clinical use, the community of TMS researchers made initial educated guesses about many issues (coil location, intensity, frequency, pulse width, train length, total number of pulses in a day, dosing schedule, and the number of pulses in a treatment course). We were likely both lucky and relatively clever, and the initial choices proved clinically effective (7, 15, 16). Notably, it took over a decade of work refining these choices in incremental small trials before we were "ready" to launch the first pivotal studies (32, 33). A TMS industry was born, and this initially led to approval from the U.S. Food and Drug Administration (FDA) in 2008 (32, 33) and, not long afterwards, widespread insurance coverage for rTMS to treat acute major depressive episodes.

Depending on your perspective, psychiatrists' uptake of clinical rTMS has been impressive, or disappointing. Historically, psychiatrists as a group may self-select away from specialties in which procedures are performed. rTMS involves a hands-on procedure by psychiatrists, who hire staff and purchase equipment, or send their patients to colleagues who have developed this expertise (34). The rTMS industry was neither large nor initially well capitalized, so there were no national advertising campaigns until recently. Despite these obstacles, there are now at least seven machines with FDA clearance, and TMS is available clinically across the globe. TMS is now daily producing remissions from depression and saving lives.

TMS thus represents a paradigm shift in psychiatry. It is not a talking therapy, does not involve administration of medications by mouth or intravenously, does not involve seizures, and modulates circuit activity in the brain. Because it is focal and noninvasive, it produces no systemic side effects and no drug-drug interactions. It thus is a good choice in medically complicated patients, and it does not involve anesthesia or have deleterious cognitive effects.

Viewed differently, clinical use of rTMS has been disappointing. Over the past 10 years, rates of suicide and depression have increased. TMS has not had a large public health impact on these. Moreover, the FDA-approved treatment requires daily treatments for 6 weeks, and each treatment takes about 30 minutes to an hour. It is highly inefficient, and thus relatively expensive. Maybe TMS is just a one-trick pony?

WHAT IS HAPPENING NOW WITH TMS?

Currently several lines of research with TMS are most promising.

Treatment of Depression

In the area of treating depression, researchers are carefully and appropriately reexamining all the initial choices, and finding that even some simple modifications can improve TMS as an antidepressant treatment.

Whom to treat? The initial studies involved only patients with treatment-resistant depression, and TMS (like all of our treatments) works less well in patients whose illness is more treatment resistant. Studies are now enrolling patients with less treatment-resistant illness. For reasons of both safety and scientific integrity, the early trials enrolled only patients who were weaned off of their antidepressant medications (32). Now, most patients are treated safely and with good efficacy while staying on antidepressant medications (35, 36).

Where to stimulate? This is an exciting area of research. I initially proposed the "5 cm rule," in which the TMS coil was placed 5 cm anterior to the location found to induce a thumb twitch (7, 16, 17). Unfortunately, in perhaps one-third of patients, this does not reach the prefrontal cortex (37–39), and most clinicians now place the coil by using an EEG grid system that accounts for differences in head size (40). The search is on for the best cortical location, either at a group level or individually guided. In a fascinating line of research, it may be that the clinical interview actually corresponds with

the "proper" TMS coil location (41, 42). Fox and colleagues (43) have performed meta-analyses of many TMS trials with differences in the method of coil placement and a range of clinical effects. Merging this information with data from the human connectome, they found that certain coil locations do better for certain symptoms. More anxious and neurotic patients tend to do better with the 5 cm location, while anhedonic and dysphoric symptoms tend to respond better with a more anterior and medial location (44). What an exciting development this might be for psychiatry if the data hold true in prospective trials! A good clinical examination might be able to parse the depressions into different disease subtypes with differential circuit activity requiring a different coil location. We may now be able to "carve nature at its joints" (as Plato put it in the *Phaedrus* dialogue), dissecting different depressions using clinical examinations and TMS response.

Conventional TMS can only stimulate the surface of the brain, but a new series of coils can stimulate deeper into the brain, and across broader areas (45–48). These H-coils are now approved for the treatment of depression (and obsessive-compulsive disorder [OCD], as discussed below) (49). It is unclear whether they are more effective at treating depression than the other coils. The H-coil manufacturer and others also have developed multiple coils that can be used jointly or independently (50). We now can stimulate multiple regions of the brain with different patterns, exciting some regions and inhibiting others. Remarkable technologies are already here with TMS. What is lagging behind is the translational clinical neuroscience informing us on how best to use these tools.

How to stimulate, in terms of patterns and frequencies? One of the most remarkable aspects of TMS is that the brain effects are frequency dependent. That is, slow, low-frequency rTMS over time can temporarily inhibit regional brain activity. In contrast, faster, high-frequency patterns tend to be excitatory. This has enabled various studies to use inhibitory patterns to block or "turn down" a region or excitatory patterns to boost a region. A fascinating new development is theta-burst stimulation (TBS), which was long known to basic neuroscientists but only recently rediscovered by the TMS research community (51). Theta burst is a pattern that is intrinsic to the brain, and it is what you might hear if you could listen in on your hippocampal neurons talking to each other (triplets at 50 Hz, which are then repeated at a frequency of 5 Hz, hence the "theta"). Theta bursting is an electrochemical signaling language of the brain. Fascinatingly, theta-burst patterns can also produce diametrically opposite effects solely on the basis of how the pattern is delivered. Intermittent theta burst (iTBS) is excitatory, while continuous theta burst (cTBS) temporarily inhibits brain signaling. Theta-burst TMS is also much more efficient at producing brain changes than is conventional rTMS at 5 or 10 Hz (52). An important study published last year (53) showed that iTBS for 6 minutes was as effective in treating depression as the standard FDA-approved treatment, which takes 30 minutes. One can obviously treat many more patients in a clinic if the time is reduced fivefold, so this may be an important step forward in improving the efficiency of TMS.

What dose to apply? We have not yet established an upper limit for TMS dose in terms of safety. No one has ever done a comprehensive escalating dosing study with TMS like that required for medications (20, 54, 55). All medications, before they are used in clinical trials, are given to animals first, and then to healthy human volunteers, in ever-larger amounts to determine the doses at which side effects emerge and safety concerns arise. Over the past 25 years, with mounting assurances about TMS safety, there has been a gradual increase in the number of TMS pulses given in a day, or a week, or a treatment course. However, some recent studies have shown that more pulses alone may not be better (56). As in good dancing, the rhythm may be the key. Can one give more treatments in a day and create a more rapid response to TMS? The jury is still out on this, with some case series producing rapid responses (57) and controlled trials using similar approaches and not getting better effects (58). It appears that the initially determined daily treatment pattern is not sacred, and one can deliver TMS treatment sessions in a more creative and flexible pattern than was done in the pivotal clinical trials.

What is the brain doing during treatment? Another exciting area of research involves manipulating what the brain is doing while TMS is being delivered. This research marries the rich tradition in psychiatry of talk and behavioral therapies with the new technology of brain stimulation. In 1949, Donald Hebb (59) theorized that neurons that fire together, wire together (as paraphrased by others later). Applied to TMS, it suggests that the activity, behavior, or state of the person being treated may matter in terms of whether TMS can induce long-term synaptic changes. Thus, researchers are manipulating brain activity during TMS. In many applications, what the patient is doing during stimulation appears to be important, if not critical (60–63). To date, in relation to treating depression, no one has shown that a consistent manipulation of state during TMS treatment produces better outcomes. However, this may be because almost all depressed patients, during a treatment, are likely obsessing about their depression and activating these mood-regulating circuits naturally. That is, during TMS treatments, many patients are likely engaging in "activation" of their internal thoughts and beliefs that are dysphoric or sad. If TMS works through the principles of synaptic plasticity and LTD/LTP (long-term depression/long-term potentiation), it should be possible to add certain medications and boost these effects. There is no convincing evidence to date, however, that any medication enhances or blocks the antidepressant effects of TMS. Some have argued that benzodiazepines may block the antidepressant effect of TMS, but there is a notable confounder in this regard: patients taking benzodiazepines are anxious, and comorbid anxiety is itself a negative response predictor for

antidepressant treatment response to TMS and other interventions (64). Interestingly, pretreatment with naloxone blocks the analgesic effects of TMS, suggesting that prefrontal rTMS releases endogenous opioids (65, 66). It is not clear whether this effect is related to its antidepressant actions.

In summary, TMS continues to rapidly evolve as an antidepressant treatment, with research into the translational neurobiological effects and reexamination of the choices of coils, settings, timing, and concomitant treatments to improve its efficiency.

New Neuropsychiatric Indications

Following in the wake of rTMS's success as an antidepressant, there has been an explosion of research using rTMS as a potential therapy in other neuropsychiatric disorders. For any disease for which there is known regional anatomical dysfunction, rTMS could potentially treat the disorder. A quick search through ClinicalTrials.gov this month shows 1,425 completed and ongoing TMS trials in almost all brain diseases. The listings even include clinical trials in brain diseases without a known specific regional dysfunction, such as the schizophrenia spectrum disorders and autism spectrum disorder. In these diseases, it is common for researchers to focus on a symptom within the overall disorder—say, auditory hallucinations in schizophrenia—and then apply TMS to the regions involved in that one symptom.

Exploring the use of TMS in other indications is starting to bear fruit. TMS is now FDA cleared for OCD, largely on the basis of the clinical trial published in this issue of the *Journal* (67). OCD is notoriously difficult to treat, although exposure therapy and the selective serotonin reuptake inhibitors are partly effective. In the Carmi et al. article in this issue (67), the researchers took a page from Hebb's ideas and performed a 3- to 5-minute individually prepared exposure therapy immediately before TMS: The clinicians made sure that these patients with treatment-resistant OCD were definitely obsessing during the treatment. They then stimulated the medial prefrontal cortex and cingulate gyrus at high frequency, with a deep and broad coil. An earlier pilot study suggested that only high-frequency stimulation worked at this target (68). Other OCD studies have examined the premotor cortex, or the supplemental motor area, reasoning that OCD is related to abnormal motor patterns (69). The important double-blind results reported in this issue showed improvements that were statistically significant and clinically meaningful in a group with treatment-resistant illness. This FDA-approved approach requires a collaboration between providers who understand OCD exposure therapy and those who know how to deliver TMS and manage medications. It is not TMS *or* exposure therapy *or* medication management, but rather a weaving together of all these therapeutic threads. As with the development of TMS for depression, researchers are now examining response predictors, durability of response, and other important clinical questions and outcomes of TMS for OCD.

While the study in this issue by Philip et al. on TMS in the treatment of PTSD (70) has not opened up a new FDA-approved indication, it is an important study along that path. Here, the researchers used the new frequency, theta burst, intermittently (iTBS), thus attempting to excite the right prefrontal cortex. They did not formally manipulate PTSD symptoms, although others have shown that this is possible (71). With a relatively small sample of 50 patients, they found improvements in active and not sham treatment over just 2 weeks, which is a short time for treating PTSD. Larger effects emerged when the treatment continued another 2 weeks, although this second phase was not blinded. Again, larger clinical trials are needed before this approach can be translated into another FDA-approved treatment.

Clearly, rTMS is thus not a one-trick pony, and good clinical rTMS research is under way in many other brain disorders. Depending on the outcomes of these large trials, our field may soon be using rTMS to treat pain, substance use disorders, anxiety disorders, autism spectrum disorder, and some symptoms of schizophrenia. Thus, any brain disease with a known regional anatomical dysfunction might be treatable with skilled application of rTMS, combined in many instances with behavioral challenges and adjunctive medications that help with disease symptoms or actually promote synaptic plasticity and therapeutic change. The future is indeed bright for rTMS, and this treatment tool will only get better as we develop our understanding of the translational effects, identify keys to inducing plasticity, and decipher genetic modifiers.

THE LIKELY AND EXCITING NEXT FEW YEARS

From my vantage point, rTMS is the first wave of an entire new approach to treatment in neuropsychiatry. The rich and fertile field of brain stimulation is rapidly changing and moving forward with many other technologies and overlaps both psychiatry and bioengineering (72). Technology is advancing rapidly, particularly body sensors and the ability to interact through wearable devices. TMS technology itself continues to evolve, as we have seen with the development of new broad and deep TMS coils. However, other competing technologies may develop into clinical applications that are as important as TMS, or even eventually replace TMS. Two candidate therapies are transcranial direct current stimulation (tDCS) (which is less expensive than TMS and likely works through different mechanisms) and transcranial pulsed ultrasound (low-intensity focused ultrasound pulsation).

tDCS involves passing relatively weak direct current through the brain for about 20 minutes per session. It is inexpensive and relatively safe (73). While TMS might accidentally cause a seizure, and is powerful enough to induce a thumb twitch, tDCS cannot cause a seizure and is weak. Thus, most researchers always manipulate behavior while applying tDCS. So far, the clinical outcomes with tDCS have not been impressive and have not resulted in FDA clearance. Perhaps

the most significant clinical study to date was a noninferiority trial of tDCS combined with speech training in patients with aphasia following a stroke (74, 75). Interestingly, a brain-derived neurotrophic factor (BDNF) neuroplasticity gene has been found to be correlated with treatment response (76). As in the early days with TMS, it is still not clear how to dose tDCS, and we currently lack the ability to easily individualize the tDCS dose for each patient and make sure that we are delivering the appropriate amount to interact with their brain.

The holy grail of brain stimulation treatment is a tool that is cheap, portable, and painless, can be applied in awake, alert humans, and can penetrate deep in the brain and focally modulate a specific region and only that region. Low-intensity focused ultrasound pulsation (LIFUP) may be the next big thing in clinical brain stimulation, as it may have many or all of these attributes (77). For reasons that are unclear, neurons will fire if they receive pulsed ultrasound signals (not the constant ultrasound signal used in ultrasound imaging). This is not due to heating or damage. Clever researchers have figured out ways to deliver ultrasound through the intact skull, focus it deep in the brain, and not cause tissue damage as with the ablative ultrasound used in neurosurgery (78, 79). Currently, LIFUP must be performed in an MRI scanner, but it will likely be able to be moved into the clinic, with image guidance systems. It may or may not be necessary to stimulate focally and deep. There may be intrinsic homeostatic and circuit-regulating behaviors that are best suited to modification by cortical stimulation, as with TMS. But it will be important to have the tools to figure out which brain diseases are best treated with our various approaches—broad and cortical, as with TMS, versus focal and deep, as with ultrasound.

It is clear that we are well on the way to understanding the recipes of brain activation during stimulation, behavior, dosing and timing, and local pharmacology, and to being able to sculpt and change regional brain activity. Keep watching the brain stimulation revolution as it unfolds. We are just at the beginning, with TMS as the vanguard. Work in this area will advance our field and the treatment of our patients. TMS is not a one-trick pony, and the best is yet to come.

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