

# Noninvasive Brain Stimulation: Challenges and Opportunities for a New Clinical Specialty

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Noninvasive brain stimulation refers to a set of technologies and techniques with which to modulate the excitability of the brain via transcranial stimulation. Two major modalities of noninvasive brain stimulation are transcranial magnetic stimulation (TMS) and transcranial current stimulation. Six TMS devices now have approved uses by the U.S. Food and Drug Administration and are used in clinical practice: five for treating medication refractory depression and the sixth for presurgical mapping of motor and speech areas. Several large, multisite clinical trials are currently underway that aim to expand the number of clinical applications of noninvasive brain stimulation in a way that could affect multiple clinical specialties in the coming years, including psychiatry, neurology, pediatrics, neurosurgery, physical therapy, and physical medicine and rehabilitation. In this article, the authors

review some of the anticipated challenges facing the incorporation of noninvasive brain stimulation into clinical practice. Specific topics include establishing efficacy, safety, economics, and education. In discussing these topics, the authors focus on the use of TMS in the treatment of medication refractory depression when possible, because this is the most widely accepted clinical indication for TMS to date. These challenges must be thoughtfully considered to realize the potential of noninvasive brain stimulation as an emerging specialty that aims to enhance the current ability to diagnose and treat disorders of the brain.

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The idea of stimulating the brain to treat neurological and psychiatric disorders dates back thousands of years, but only in recent decades has this approach become a reality.<sup>1</sup> Electroconvulsive therapy and deep brain stimulation are currently in mainstream clinical use throughout much of the world and have substantial evidence-based support. More recently, the field of noninvasive brain stimulation (NIBS), or noninvasive neuromodulation, has emerged as a promising diagnostic and therapeutic modality. NIBS refers to a set of technologies and techniques with which to transcranially (i.e., noninvasively) modulate excitability of specific brain areas and the large-scale networks in which they participate. Two major modalities of NIBS are transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). In this article we briefly review TMS and tCS before exploring some of the formidable challenges faced in bringing these tools into the clinical realm, focusing on efficacy, safety, economics, and education. When possible, we discuss these topics using examples from TMS in the treatment of medication refractory depression, given the large body of research in this area.

## TRANSCRANIAL MAGNETIC STIMULATION

TMS was developed in 1985 and has been utilized intensively over the last 30 years as a research tool in neurophysiology.<sup>2</sup>

TMS provides a way to induce electrical current in the brain without the need for invasive surgery. It involves passing an electric current through conductive wires of an insulated coil to induce a local magnetic field, which transfers energy across the skull to induce a secondary electric current in the brain.<sup>3</sup> A single pulse from TMS can trigger an action potential in the neurons underlying the site of stimulation.<sup>4,5</sup> For example, applying TMS to the motor cortex triggers contralateral movements in the motor group stimulated,<sup>6</sup> whereas stimulation of the visual cortex can trigger visual percepts.<sup>7</sup> A variety of TMS protocols have been developed to assess specific aspects of motor cortex physiology, such as timed paired pulses in which the first pulse modifies the effect of the second, which can probe a variety of neurophysiological parameters and neurotransmitter systems.<sup>8,9</sup> TMS has also been coupled with EEG so that responses of the brain to TMS can be probed without relying on motor output.<sup>10</sup> These features of TMS may have utility for diagnostic applications across a variety of disorders.<sup>11,12</sup>

Of greatest relevance for the use of TMS as a therapeutic tool is the development of repetitive TMS (rTMS).<sup>13,14</sup> When TMS pulses are applied in rapid succession, the underlying cortex has a more sustained alteration in excitability.<sup>15</sup> For example, a high-frequency pattern called

“intermittent theta burst stimulation” applied to the motor cortex for 3 minutes may increase excitability of that site for 30 minutes or longer.<sup>16</sup> When applied daily, these effects can last for days, weeks, or even months.<sup>15,17,18</sup> Moreover, the modulatory effect is not limited to the site being stimulated locally but includes the network of structures connected to that site.<sup>19,20</sup> As such, rTMS has the potential to focally alter the activity of a targeted network for a sustained period, which holds therapeutic potential.

## TRANSCRANIAL CURRENT STIMULATION

The use of tCS dates back to the 19th century, but a resurgence of this technique has occurred over the last 15 years.<sup>21</sup> Transcranial direct current stimulation (tDCS) was the first modern tCS technique developed and has received the most attention to date. tDCS involves the application of a low-amplitude, direct current (typically 0.5–4 mA) to the scalp via electrodes. Electric current flows from the negatively charged cathode to the positively charged anode, penetrating the skull and modifying neuronal transmembrane potentials in the current path. The effect is to modulate the excitability of a given region and alter the probability of firing an action potential, but unlike TMS, tDCS does not induce action potentials.<sup>22–25</sup> tDCS is also a much more diffuse form of stimulation than TMS, though smaller electrodes and multielectrode arrays can be used to improve the spatial resolution.<sup>26</sup> As with TMS, the effect of tDCS on the brain depends on several factors, including electrode location, intensity, duration, electrode size, electric field orientation, and the activity of the stimulated brain region.<sup>25,27,28</sup> The cortex underlying the anode typically becomes more excitable, whereas the cathode site has decreased excitability. When several sessions are applied, the effects can last for longer periods, which has been leveraged for therapeutic effects.<sup>29–31</sup>

Transcranial alternating current stimulation (tACS) is similar to tDCS, but the current alternates at a frequency specified by the operator. This can alter the oscillatory frequencies in the brain regions being stimulated.<sup>32,33</sup> Given the role of abnormal oscillatory activity in a wide variety of pathological conditions,<sup>34</sup> there is optimism that tACS may be able to normalize pathological oscillatory patterns with therapeutic effect. tDCS and tACS have not been investigated to the same extent as TMS as a clinical tool to date, yet their low cost and ease of use warrant further investigation into possible therapeutic uses.

## CLINICALLY APPROVED DEVICES

The rapid advances in NIBS technology have set the stage for these techniques to be used clinically. Neuronetics created the first TMS device to gain U.S. Food and Drug Administration (FDA) approval for the treatment of medication-resistant depression in 2008, with other devices following thereafter, including Brainsway (2013), Magstim

(2015), MagVenture/Magvita (2015), and TeleEMG Neurosoft (2016). TMS is also FDA approved for use in mapping of the motor cortex and language areas (Nexstim, 2012). To date, there are no FDA-approved applications of tCS, though some devices used for tCS have FDA clearance for transdermal iontophoresis. Several large, randomized, multisite, sham-controlled trials are ongoing, which aim to expand upon the current clinical indications for NIBS.

## EFFICACY

NIBS cannot be viewed as a single treatment modality. The varied molecular configurations that contribute to the diversity of medication efficacy are matched by the vast number of variables that can be modified to alter the efficacy of even a single type of NIBS, such as rTMS. This feature of NIBS holds great potential but also presents challenges in establishing and optimizing clinical efficacy.

### Target Site

The typical target site of high-frequency rTMS in the treatment of depression is 5 to 6 cm anterior to the left motor cortex<sup>14</sup> or F3 in the 10–20 EEG coordinate system.<sup>35</sup> There is emerging evidence that identifying a stimulation target on the basis of one’s individual anatomy may improve efficacy,<sup>36,37</sup> as well as selecting a target on the basis of one’s functional connectivity.<sup>38–41</sup> Although improving upon the current target site in the left dorsolateral prefrontal cortex is an important aim, it leaves open a variety of other possibilities. For example, it is possible that multiple targets are best. It has been shown that low-frequency rTMS to the right dorsolateral prefrontal cortex is equally effective,<sup>42,43</sup> and recent efforts have explored targeting the right and left dorsolateral prefrontal cortices in sequence.<sup>44</sup> Targeting other sites in the prefrontal cortex,<sup>45</sup> regions outside the prefrontal cortex,<sup>46</sup> or multiple sites simultaneously remains a relatively unexplored but promising line of research.

### Frequency

The frequency of stimulation is likely another key variable. For the treatment of depression it is not clear whether 10 Hz or 20 Hz is optimal,<sup>14</sup> let alone intermittent theta-burst stimulation or the myriad of other possible frequencies and stimulation patterns that have not yet been explored.<sup>47–49</sup> One can imagine using frequencies that optimally modulate the targeted network, but it is not yet clear what those frequencies are or how variable they are between individuals.<sup>50</sup>

### Dose

Dosing in rTMS refers to the intensity of stimulation and the number of pulses applied in a session. The intensity relates to the strength of the induced magnetic field and can be adjusted by the operator. The intensity applied to treat depression is typically set as a percentage of one’s individual motor threshold, though the excitability of the motor cortex does not necessarily correspond to the excitability of the

target site in the prefrontal cortex. A higher magnetic field has been related to improved treatment efficacy for special populations (geriatric).<sup>51,52</sup>

The number of pulses per session is another key variable in dosing, and interindividual differences in response to TMS may relate to this factor.<sup>53</sup> Treatment for depression typically includes 3,000 pulses over 20 to 37.5 minutes.<sup>14,54</sup> Over time there has been a gradual progression of more pulses per treatment session associated with improved efficacy.<sup>55</sup> Higher-dose TMS treatments appear to be safe, but it is not yet clear how the clinical efficacy compares to standard dosing.<sup>56</sup> Related to this topic, it is not known whether a single treatment session per day is best versus other potential schedules, such as multiple sessions per day.<sup>57</sup>

### Duration

The optimal duration of the overall treatment course is similarly unclear. The typical duration of treatment for depression is 4 to 6 weeks. Maintenance schedules that aim to prolong the therapeutic gains have only recently emerged and will require continued investigation.<sup>54,58</sup>

### Brain State

The effect of NIBS results from an interaction between the exogenous stimulation and endogenous neural activity. In addition to the parameters that can be manipulated exogenously, neuronal activity can be modified to potentially enhance the effect of NIBS. It is known, for instance, that caffeine, amount of sleep, medications, NIBS priming, and ongoing cognitive processing all modify the effects of NIBS.<sup>59–64</sup> How these modifications could be incorporated to improve rTMS for depression to enhance clinical efficacy remains relatively unexplored. Most individuals receiving rTMS for depression do not undergo any specific tasks before, during, or after the treatment, such as cognitive-behavioral therapy, though this has been shown to influence tCS efficacy.<sup>65</sup> Moreover, there exists the possibility that modifying the chemical milieu of the brain may enhance the effect of NIBS. This could be through pharmacological means<sup>66,67</sup> or even by taking advantage of endogenous modifiers, such as brain-derived neurotrophic factor release with exercise.<sup>64,68</sup> Finally, there is emerging evidence that more stable traits may influence response to NIBS, such as genetics or age, which could identify subjects most likely to benefit from NIBS.<sup>69–71</sup>

### Treatment of Depression

Although it is almost certainly the case that the ideal rTMS protocol for treating depression remains to be discovered, there is substantial evidence supporting the most commonly used protocol, 10-Hz rTMS stimulation of the left dorsolateral prefrontal cortex.<sup>14,72</sup> In randomized clinical trials, 46.4% of patients have shown a 50% or greater reduction in symptoms of depression, with 26.0% achieving a full remission of their depression in an open-label extension.<sup>72,73</sup>

This is particularly important, considering that those receiving rTMS have failed multiple medication trials in most cases.<sup>74</sup>

Given the vast number of parameters that could modify NIBS, as has been reviewed above, and the likely incremental effect that any individual variable has on the overall clinical impact, there is an enormous challenge associated with continued optimization of treatment protocols. To manipulate one variable at a time and to compare this modified protocol to a standard protocol in a large clinical trial that is powered to detect a small difference presents a formidable challenge. Moreover, a diagnosis such as depression can stem from divergent etiologies and symptom profiles that likely will respond differently to various TMS protocols, but individualizing the treatment protocol presents additional challenges using current clinical trial designs. The establishment of biomarkers indicating treatment response that may be evident before a full treatment course is complete would greatly benefit the field.<sup>75</sup>

### SAFETY

The overall safety profile of NIBS is excellent when the safety guidelines outlined by an international panel of experts in 2009 are adhered to closely.<sup>76</sup> The most significant risk of rTMS is that of inducing a seizure during the stimulation session, but this risk is quite low.<sup>77</sup> Another concern is the potential for hearing loss from the loud clicks of TMS, but this risk is mitigated through the use of earplugs.<sup>76</sup> The most prevalent side effect of TMS is headache and pain at the site of delivery, which affects as many as 40% of patients, but this is temporary and responds to analgesic medications.<sup>54,78</sup> A variety of excellent reviews on TMS safety are available.<sup>76,78,79</sup> TCS has similarly had an excellent safety record to date. There have not been any seizures reported, and the main side effect is scalp discomfort.<sup>80</sup>

Although the safety data to date are encouraging for NIBS, as with any proposed clinical technique, a high degree of caution is still warranted. Whether NIBS-facilitated improvements in one domain may lead to decrements in another domain is a topic requiring additional research.<sup>81–83</sup> Moreover, the safety profile may differ for special populations. For instance, although results are encouraging for the pediatric population, much more study is needed.<sup>79</sup> The interaction of medications with NIBS is similarly poorly understood.

Finally, the optimism about the continued safety of NIBS within the confines of well-designed research and clinical programs stands in stark contrast to the deep concerns about unregulated use of tCS devices marketed directly to consumers.<sup>84</sup> Companies producing these devices can avoid the high regulatory hurdles faced for medical devices by using language that avoids medical terms in favor of enhancement-related terminology (e.g., “improves mood” as opposed to “treats depression”). This raises the very real possibility that people may be experimenting with stimulation

protocols outside of established safety parameters and without the oversight of a trained professional.

Even in the absence of direct-to-consumer marketing of tCS devices, there is a “do-it-yourself” community that constructs their own tCS devices, and they are actively involved in self-experimentation.<sup>85,86</sup> Efforts must be focused on establishing regulations for clinical and at-home use, and it will be increasingly important for researchers and clinicians to keep the public informed about NIBS safety.<sup>87</sup>

## ECONOMICS

The economics of using rTMS in treating depression can be evaluated at multiple levels. Globally, depression is the second most devastating disorder in terms of economic impact.<sup>88</sup> Given the evidence that rTMS results in a significant reduction in symptoms in patients with treatment-resistant depression, the widespread use of rTMS could have a hugely favorable economic impact at a national or international level.

To reach widespread clinical use and potentially have a global economic impact, rTMS must first show a favorable cost-benefit ratio in relation to alternative therapies. This is an increasingly relevant concern among efforts to deliver optimal care in a cost-effective manner. However, detailed economic analyses of rTMS as a treatment for depression are challenging. The cost of providing the treatment varies, depending on multiple factors, including the device used, the cost of the space in which the treatment is administered, the size and cost of the team involved in providing the treatment, the treatment session duration (20- to 37.5-minute sessions), and the treatment course duration (4 to 6 weeks). Despite this variability, a few analyses have addressed this topic.

For use in the United States, the cost of a single 30-minute treatment of rTMS was estimated at \$300 in 2009, with a 6-week course costing \$9,000.<sup>89</sup> On the basis of these figures, it was concluded that rTMS was a cost-effective treatment for depression. A large-scale analysis in 2012 by the New England Comparative Effectiveness Public Advisory Council supported this view. Their model showed that insurance coverage of rTMS would increase per-member per-month costs by only \$0.21.<sup>90</sup> As such, the insurance landscape has been changing rapidly, with a steady progression of increasing coverage in the United States, for both federally funded programs (Medicare) and major commercial providers.

A few studies have specifically compared the cost effectiveness of TMS with electroconvulsive therapy, resulting in mixed conclusions.<sup>91-93</sup> Moreover, the cost effectiveness of TMS may vary by location; for example, one analysis performed outside the United States, in Spain, did not support the cost effectiveness of rTMS,<sup>92</sup> whereas another conducted in Australia found rTMS to be more cost effective than antidepressant medication for patients with treatment-resistant depression.<sup>94</sup>

Comparing the cost effectiveness of TMS with that of other treatments will continue to be challenging because the treatment protocol is likely to undergo continued modification and improvement over time, and the business models of TMS device manufacturers will likely continue to change over time. Continued research on the cost effectiveness of NIBS will be a key variable to consider as individuals and organizations consider whether to incorporate NIBS into their clinical programs, hospitals, or insurance policies.

## EDUCATION

NIBS is still quite new in relation to other areas of medicine, and as a result, there is not yet an educational infrastructure for this field. This challenge, in our view, presents one of the greatest hurdles to the widespread incorporation of NIBS into the clinic.

### Physicians

The use of rTMS in treating depression has been FDA approved for nearly a decade and is currently offered at hundreds of sites in the United States. However, many psychiatrists do not consider this treatment option. Many, if not most, patients referred to the Berenson-Allen Center for Noninvasive Brain Stimulation report learning about TMS on their own and requesting a referral for TMS from their psychiatrists. Those who are referred for rTMS have already failed an average of 3.7 antidepressant medication trials.<sup>74</sup> The lack of physician education can be addressed through educational sessions on TMS at national meetings. Moreover, journals dedicated to NIBS and the exponential rise in the number of NIBS-related publications in recent years will help. The challenge of educating physicians will likely arise anew, as indications are established in fields other than psychiatry in the near future.

### Physicians-in-Training

The need for increased educational opportunities has been documented across the field of invasive and noninvasive brain stimulation in both neurology and psychiatry.<sup>95,96</sup> To address this need, our center recently initiated a four-session pilot course on neuromodulation as a required didactic in the psychiatry residency curriculum. We implore psychiatry and neurology residency program directors at other institutions to consider similar initiatives.

### NIBS Specialists

In addition to training resident physicians, there is a growing need for formal postresidency training programs for NIBS specialists. Currently, there are no requirements or certifications governing a provider's proficiency or knowledge regarding NIBS before using it therapeutically. Experts recommend that all physicians administering rTMS undergo “rigorous training.”<sup>14</sup> Intensive educational courses are available through academic institutions via continuing medical education courses, but these courses have long wait

times owing to their high demand, and they were not designed to train clinicians for a career in NIBS. The Berenson-Allen Center and the University of Iowa have both recently launched unique interdisciplinary fellowships with integrated training in neurology and psychiatry that facilitate extensive exposure to the clinical applications of NIBS. This training answers prior calls to form organized neuromodulation training programs in neurology and psychiatry.<sup>95,96</sup> We would welcome the development of greater numbers of like-minded training programs.

## Public

Equally important as educating physicians is the need to educate the general public about NIBS. The field of NIBS lends itself to sensationalized reporting of provocative scientific findings by the media. There is a risk that the public will interpret the safety and efficacy data of pilot trials as sufficient evidence to attempt “over-the-counter” nonmedical use of tCS. To develop and maintain the public’s support for NIBS, it will be critical for the field to proceed cautiously in an evidenced-based manner and for any new clinical indications to be preceded by robust clinical trial data. Along these lines, we applaud attempts by researchers to make safety and efficacy information accessible to the general public.<sup>84,86</sup>

## CONCLUSIONS

NIBS is emerging as a clinically viable option for diagnosing and treating a variety of brain disorders. The use of rTMS has a growing body of evidence supporting its efficacy and safety in treating depression, and its use should continue to be optimized through additional research. The more widespread application of NIBS will depend on demonstrated efficacy from sham-controlled multicenter trials, but current signs point to NIBS making a meaningful impact in the treatment of disorders encountered in a variety of specialties, including neurology, psychiatry, pediatrics, physical therapy, and physical medicine and rehabilitation. By orienting readers to some of the challenges facing the field, we hope to facilitate the thoughtful expansion of NIBS from the research realm to the clinical realm and, in doing so, to unlock the tremendous potential for noninvasive brain stimulation to diagnose and treat brain disorders.

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