

Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns

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ABSTRACT

Transcranial Magnetic Stimulation (TMS) is a non-invasive neurostimulatory and neuromodulatory technique increasingly used in clinical and research practices around the world. Historically, the ethical considerations guiding the therapeutic practice of TMS were largely concerned with aspects of subject safety in clinical trials. While safety remains of paramount importance, the recent US Food and Drug Administration approval of the NeuroStim NeuroStar TMS device for the treatment of specific medication-resistant depression has raised a number of additional ethical concerns, including marketing, off-label use and technician certification. This article provides an overview of the history of TMS and highlights the ethical questions that are likely arise as the therapeutic use of TMS continues to expand.

INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is a non-invasive neurostimulatory and neuromodulatory technique increasingly used in clinical and research practices around the world. Although originally developed as a diagnostic tool, TMS can transiently or lastingly modulate cortical excitability (either increasing or decreasing it) via the application of localised magnetic field pulses. This and other neurobiological effects can be leveraged for therapeutic applications in neurology, psychiatry and rehabilitation. Historically, the ethical considerations guiding the therapeutic practice of TMS were largely concerned with aspects of subject safety in clinical trials. While safety remains of paramount importance, the recent US Food and Drug Administration (FDA) approval of the NeuroStim Inc. (Malvern, PA, USA) NeuroStar TMS device for the treatment of specific medication-resistant depression has raised a number of additional ethical concerns. Some of these are derivatives of previously identified issues, but others, such as marketing, off-label use and technician certification, have not been well explored. As the therapeutic potential for TMS expands to include a wide range of neuropsychiatric conditions, including those where patients have few alternative treatment options, ethical issues are likely to continue to grow rapidly. This article provides an overview of the historical, present and future ethical issues associated with the therapeutic use of TMS and discusses ways in which these issues might be addressed.

A TMS PRIMER

TMS is a neurophysiologic technique that allows for non-invasive stimulation of the human brain.^{1 2} Introduced approximately 25 years ago, TMS can be combined with various brain mapping methodologies (eg, electroencephalography, positron emission tomography or functional MRI), to study intra-cortical excitation and inhibition balance, cortico-cortical and cortico-subcortical connectivity and interactions, and brain plasticity. Repetitive transcranial magnetic stimulation (rTMS) has been shown to transiently disrupt neuronal activity for periods exceeding stimulation duration. This modulated brain activity may prove useful in both the determination of causal relationships between focal brain activity and emergent behaviour as well as in the treatment of numerous neurological and psychiatric illnesses.

The physical principles of TMS were discovered in 1881 by English physicist Michael Faraday, who observed that a pulse of electric current passing through a wire coil generates a magnetic field. The rate of change of this magnetic field determines the induction of a secondary current in a nearby conductor. During TMS, the stimulating coil is held over a subject's head and produces an electric current in the subject's brain via electro-magnetic induction. This current in turn depolarises neurons and can generate various physiological and behavioural effects depending on the targeted brain area. Because magnetic fields can pass the skull with almost no resistance, TMS can induce relatively large currents in targeted cortical areas.

The design of magnetic stimulators is relatively straightforward, consisting of a main unit and a stimulating coil. The main unit is composed of a charging system, one or more energy storage capacitors, a discharge switch and circuitry used to control pulse-shape, energy recovery and other variable functions. The factors essential to the effectiveness of a magnetic stimulator are the speed of magnetic field rise time and the maximisation of the peak coil energy. Therefore, large energy storage capacitors and efficient energy transfer from the capacitor to the coil are important (typically energy storage capacity is around 2000J with a 500J transfer from the capacitor to the stimulating coil in less than 100 microseconds via a *thyristor*, an electrical device capable of switching large currents in a short time). The peak discharge current needs to be several thousand amperes in order to induce currents in the brain of sufficient magnitude to depolarise neural elements (about 10 mA/cm²).

The precise mechanisms underlying the neural effects of TMS are largely unknown.¹ Currents induced by TMS typically flow parallel to the plane of the stimulation coil. Therefore, in contrast with electrical cortical stimulation, TMS preferentially activates neural elements oriented horizontally to the brain surface. However, exactly which neural elements are activated remains unclear and, in fact, might vary across different brain regions and different subjects. Recent animal studies have begun probing these important mechanistic questions.^{3–5}

PRE-HISTORY OF TMS: AN ETHICAL PERSPECTIVE

The field of electrophysiology was born in 1771 with the discovery of bioelectricity by the Italian physician Luigi Galvani. Soon thereafter, Galvani's nephew, Giovanni Aldini, began touring the European countryside promoting his belief that bioelectricity could unlock the secrets to dead tissue reanimation. To prove his theory, Aldini staged macabre public demonstrations during which, via the application of direct electric current, he induced muscular contractions in dead animals, and, in 1803, the lifeless body of executed convict George Forster.⁶ Through this incident, several important ethical considerations began to emerge. Scientific advancements may harness great potential, but this does not exempt scientists from asking whether such potentialities *should* be explored. How might a system of ethics be maintained that serves to protect research subjects and to protect the integrity of and respect for both science and mankind?

In 1874, scientific exploration of bioelectricity within muscles and nerve fibres reached an apex when American physician Robert Bartholow applied electrical current to the exposed dura of Cincinnati housewife Mary Rafferty. After successful induction of slight muscular twitches, Bartholow increased the applied current until distress, convulsion and eventually, coma were reported.^{7 8} Rafferty died 72 h later. This incident highlights a dilemma pervasive throughout medical science: in the quest for knowledge, too often experimenters can become blind to the potentially deleterious effects of their actions. Overzealousness often clouds typically sound judgement, illustrating the importance of and need for outside, independent risk-to-benefit assessment. Today such assessment is provided by the Institutional Review Boards. However, the responsibility for the proper conduct and sound ethical grounding of a given experiment ultimately remains in the hands of the investigators.

The development of electroconvulsive therapy (ECT) in 1937 ushered the field of brain stimulation into the modern 'medical device' age. Developed by Italian physicians Cerletti and Bini, ECT was intended to treat the manic symptoms of schizophrenic inpatients. However, as the popularity of the device grew, practitioners quickly elevated ECT to the status of psychiatric panacea. This gross overuse led to a plethora of serious adverse psychological and physical side effects, thereby creating a strong negative public attitude towards the therapy. In 1976, in reaction to public backlash against ECT and similar treatments, the FDA assumed regulatory control over all emerging medical devices. Interestingly, ECT (along with several other brain stimulation devices on the market prior to governmental intercession) today remains out of the purview of FDA regulation. Although ECT is considered by many to be a highly effective treatment for depression,⁹ its use remains impacted by unfavourable public opinion. An important charge for the FDA is to oversee the cautious development and implementation of novel therapies so as to assure efficacy and preclude preventable complications due to practitioner misuse that may substantiate a stigmatisation that can limit their acceptance by patients who

could potentially benefit from their use (as exemplified by ECT misuse in the 40s and 50s).

In 1972, another incident in the annals of brain-stimulation raised relevant therapeutic ethical concerns. Building upon Jose Delgado's work with behaviour modification in animals via deep-brain electrical stimulation, two doctors from Tulane University attempted to 'cure' a patient of his homosexuality. Combining electrical stimulation of *patient B-19's* septum with forced heterosexual interactions (provided by a female prostitute), Drs Moan and Heath reported a 10-month eradication of homosexual behaviour.¹⁰ Here we see what many modern practitioners consider the darkest hour for brain stimulation. When contemplating this event, it is important to remember that our ethical perception is inextricably linked to the often shifting social definitions of the core concepts of health and disease. It is important, therefore, to remain cognisant of the sociological factors that may colour our opinion and, whenever possible, attempt to remain pluralistic when constructing any ethical framework (See Figure 1).

THE EVOLUTION OF TMS

The first reliable transcranial magnetic brain stimulator was developed by Anthony Barker and colleagues and was introduced to the world in 1984–1985. Since that time, TMS has gone through several major stages of development, each defined by unique achievements and concomitant considerations.

Establishing diagnostic utility

In the late 1970s, a handful of clinicians began using transcranial electric stimulation to diagnostically measure motor conduction time in patients suffering from multiple sclerosis. This technique, although efficacious, was limited by the extreme discomfort it elicited in patients and subjects. TMS provided a propitious solution to this problem: via single-pulse stimulation, practitioners could perform similar motor conduction time tests in a much safer, far less-painful manner.¹¹ Over the ensuing years, physician interest in TMS remained largely within the realm of diagnostics.

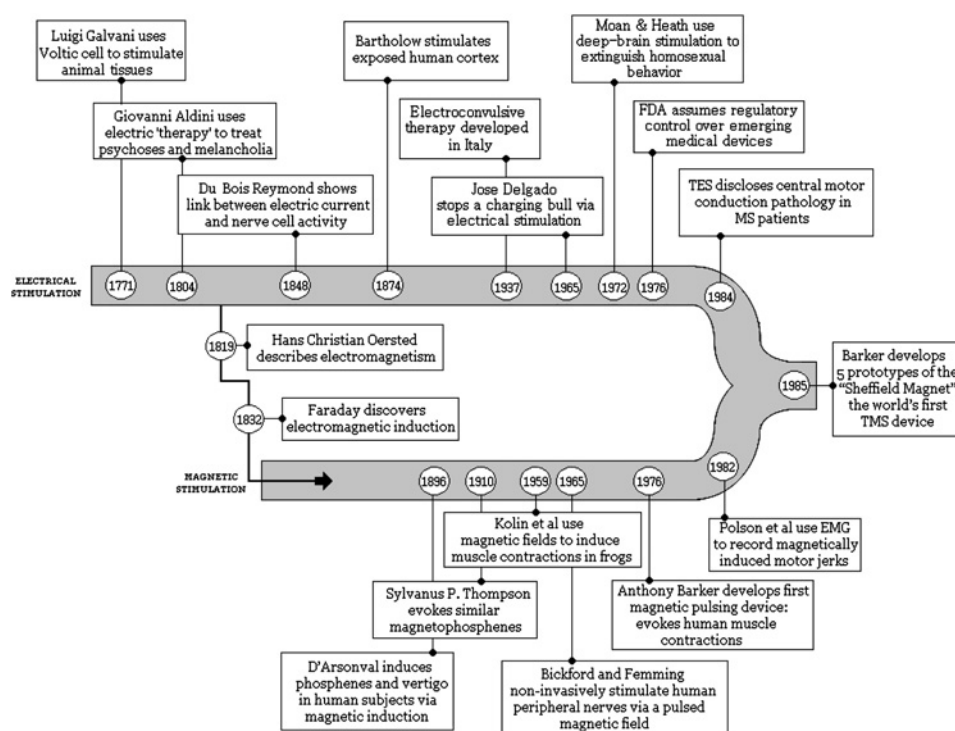
The major ethical considerations during this first stage of TMS concerned overall device safety. Because TMS originated as a diagnostic and investigational device, not many animal models were developed to study short or long-term effects. As such, TMS practitioners promoted the field rather cautiously (as compared with ECT). A keen focus was maintained on patient reported side-effects, especially those related to or resembling seizure activity.

Exploring therapeutic possibilities

In 1991 the journal *Neurology* published an article by Dr Alvaro Pascual-Leone *et al*, entitled *Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation*.¹² This paper was one of the first to use an rTMS paradigm. Qualitatively different from previous single-pulse methodologies, rTMS allowed for a more sustained neurological intervention. This new paradigm opened the door for researchers to conduct more nuanced studies of cognitive function and neural interaction. In 1994, Pascual-Leone *et al* reported that rTMS could generate lasting cortical effects that remained after the cessation of stimulation (lasting between 3 and 4 min).¹³ This ability to induce sustained physiological and cognitive effects made rTMS a tool conducive to the field of therapeutic medicine.

The expansion of TMS from single-pulse indication to repetitive-pulse intervention greatly increased the number of TMS ethical concerns. In addition to lasting matters of safety,

Figure 1 A timeline of notable uses and discoveries in electrical and magnetic stimulation leading up to the development of the first reliable magnetic brain stimulator in 1984–1985.



practitioners and clinicians were suddenly confronted with innumerable clinical considerations, including which disorders might be responsive to stimulatory treatment, issues of patient response patterns, and potential interactions between rTMS and medication. Even as labs elsewhere continued to generate ever increasing numbers of active rTMS studies, practitioners undertook the daunting but necessary task of conducting Phase I research.^{14–16}

The clinical push

One of the first proof-of-principle TMS studies specifically focused on a therapeutic application of repetitive TMS in a neuropsychiatric disease was published by Kolbinger *et al*, who examined the effects of rTMS on 15 patients suffering from drug-resistant depression.¹⁷ Of the 10 patients receiving non-sham stimulation, all showed significant improvement.

This transition to proof-of-principle studies did not eradicate previous ethical concerns; rather, it added new considerations to the ever relevant previous concerns. The inclusion of lengthy and repetitive patient treatment protocols (as opposed to transitory research protocols) raised questions about the long-term cortical effects of TMS. The apprehension felt by many clinicians and scientists was reflected in a letter entitled *Shocking Safety Concerns*,¹⁸ published several months after a successful proof-of-principle trial conducted by Pascual-Leone *et al*.¹⁹ In this missive, Browne gave voice to the fear that history might repeat itself in the later phase realisation of a treatment's detrimental effects (eg, prolonged use of Vioxx, a drug prescribed for the acute treatment of pain, was found to increase the risk of heart-disease only after the drug had been widely used).²⁰ Due in large part to the concerns voiced by Brown and others, TMS practitioners largely agreed that, in order to maintain a circum-spect developmental trajectory, it was imperative to outline universal safety and procedural standards.

To this end, a group of leading TMS authorities convened in 1996 and published the first detailed safety and ethical guidelines for TMS in both the clinical and the laboratory setting.²¹

Perhaps borrowing a lesson from the unchecked stimulation methodologies of the past (eg, ECT), this assemblage set out written standards which would serve to maintain prudence and discretion in a field that could easily be derailed by one or two rogue practitioners. Despite the relative nascence of the TMS device, the International Federation of Clinical neurophysiology demonstrated foresight by adopting and implementing these standards worldwide (although, to be fair, these guidelines did not cover all the aspects of TMS safety, such as long-term effects).

Clinical expansion

With safety guidelines in place and numerous successful proof-of-principle trials affirming potential benefits, TMS became more established. Clinics offering off-label therapies for myriad neurological and psychological pathologies began appearing worldwide.^{22–23}

As is common with novel treatments, initial rTMS patient populations consisted primarily of patients who had exhausted other, more established forms of treatment. As such, for many patients, rTMS became a 'last hope' intervention, which raises an ethical issue relevant to many young technologies: when a treatment population consists of desperate individuals willing to endure potentially unsafe procedures to obtain relief, an objective focus on potential signs of diminished autonomy as a result of neuropsychiatric illness, desperation or both, becomes doubly important. This is especially true when obtaining informed consent.^{24–25} This problem may be further aggravated by patients seeking and receiving misleading information via secondary sources such as the internet. Therefore, additional safeguards may need to be instituted to avoid potential problems or mistakes when exploring novel treatment methods within vulnerable populations.

As rTMS became more widespread, on-label treatment for depression was approved by the regulatory agencies of numerous countries, including Brazil, Israel, Australia and Canada. This swift expansion created an explosion of ethical concerns in the

world of brain stimulation. How are practical guidelines to be enforced with the migration of patients over borders to obtain treatment unavailable in their home countries? How is honesty to remain in side-effect reporting when said reports directly affect business? These questions remain important today and the need to revisit and continually update TMS safety guidelines and recommendations for global clinical implementation is imperative.

In addition to clinical expansion, practitioners developed various new stimulation paradigms impacting the risk-to-benefit profile of TMS. For example, theta-burst stimulation, a high-frequency stimulatory pattern, can induce rapid long-term potentiation and long-term depression effects via the mimicry of powerful brain oscillations. Theta-burst stimulation allows for longer-lasting and more profound modulation of cortical excitability with shorter stimulation duration. Consider also varied coil shapes, varied stimulation pulse characteristics, varied stimulation sites and varied power levels, and a picture of TMS as a broad, permuted methodology begins to emerge. With this breadth, issues of proper technician and practitioner procedural training and certification became important. With increasing numbers of individuals seeking TMS therapy, ensuring patients received the best possible treatment by a doctor well versed in both the appropriate methodology and all relevant device considerations became of paramount concern (and remains so today).

2008 Consensus conference

The guidelines established in 1998 for the application of TMS in research and clinical settings were reviewed in a consensus conference which took place in 2008. The resulting publication updated limits for the combination of rTMS frequencies, intensities and train durations to reduce risk of seizure induction.²⁶ The article provided the scientific community with an up-to-date evaluation of the safety record of research and clinical applications of TMS. In addition, the article introduced several important questions, such as the use of novel parameters, while underscoring several long-standing questions that remained unanswered, such as the risk of TMS in patients with neuropsychiatric disorders.

In the decade spanning the conferences, the uses of TMS expanded exponentially, growing to include new research applications, clinical applications and cross-modality integration (including combining TMS with electroencephalography, positron emission tomography, and functional MRI). Despite these advancements, the initial safety guidelines developed at the 1998 conference were found to have stood the test of a decade's worth of work. While standards must continue to be regularly reviewed and updated, the safety record of TMS to date confirms that potential future ethical problems can often be largely avoided with proper 'preventive ethics' foresight and restraint in the present.²⁷

FDA APPROVAL

In 2007, O'Reardon *et al* published the results of an industry-sponsored, multisite, randomised clinical trial in which 301 patients with major depression, who had previously failed to respond to *at least one* adequate antidepressant treatment trial, underwent either active or sham TMS over the left dorsolateral prefrontal cortex.²⁸ The patients, who were medication-free at the time of the study, received TMS five times per week over 4–6 weeks. The data demonstrated that a sub-population of patients, those who were relatively less resistant to medication (having failed not more than two good pharmacological trials),

showed a statistically significant improvement on several secondary outcome measures. Supported by these results, Neuronetics Inc, the study-sponsoring company, obtained approval from the FDA for the clinical treatment of specific forms of medication-refractory depression (FDA approval K061053).

FDA approval (granted in October 2008) was limited to the NeuroStar TMS device (manufactured by Neuronetics Inc) for the protocol of stimulation employed in the study (high-frequency, 10 Hz—rTMS applied daily for 4–6 weeks at supra-threshold intensity) within a highly specific subpopulation of patients (adults who have failed to achieve satisfactory improvement from one, but no more than one, adequate antidepressant medication trial).

When research studies are sponsored by industries, one must consider scientific rigour and issues of conflicting interest. Ensuring research remains free of undue influence is critical, but there are certain circumstances in which industry sponsorship may not be a detrimental occurrence. For example, with FDA approval granted to Neuronetics, the door has opened for additional companies, devices and treatments to receive serious FDA consideration. More importantly, patients who once lacked an efficacious, safe treatment option now have an alternative with proper risk-to-benefit balance assurances.

Recently, a National Institutes of Health-sponsored, multi-site TMS depression trial was undertaken.²⁹ The researchers were able to successfully reproduce the results from the earlier Neuronetics study. In addition to strengthening the therapeutic profile of TMS, this outcome proved important for three additional reasons: first, with a National Institutes of Health sponsored trial, much of the potential for researcher and patient bias was eliminated. Second, with successful replication, many questions and/or concerns engendered from the earlier industry-sponsored trial were assuaged. Finally, the risk of false positive findings from the initial trial was greatly decreased.

The narrow FDA-approved on-label indication poses ethical questions. The patient criteria leave many potential patients to consider off-label options. Also, studies have revealed that the benefits of rTMS treatment may lapse after 4–6 months.³⁰ Unfortunately, the FDA has not approved long-term TMS maintenance and care. This leaves the issues of prolonged symptom alleviation and continued treatment up for ethical debate. As TMS continues to advance as a therapeutic option, such questions will undoubtedly become increasingly common. As such, we must ensure that naturalistic studies are officially reported so as to increase the pool of analysable safety data.³¹

The existing safety guidelines for TMS differentiate between relative and absolute contraindications, thus providing important guidance in selection of suitable TMS candidates. Patients exhibiting relative contraindications may have, for example, a history of epilepsy or lesions of the brain; they may also be taking medication that lowers the seizure threshold. Patients with an absolute contraindication to TMS are those patients who have implanted metallic hardware in close contact to the discharging coil (eg, cochlear implants). Performing TMS on patients demonstrating an absolute contraindication carries the risk of inducing malfunctioning of such implanted devices.²⁶ Therefore, when it comes to deciding whether a patient is eligible for TMS, the risk-to-benefit ratio is crucial, and the clinician or investigator should carefully weigh the presence of both types of contraindications while assessing whether TMS is appropriate. However, because TMS data is still limited, more concrete recommendations are not possible at this time.

In the USA, FDA approval does not ensure coverage by health insurance companies. Thus, not all patients who meet the FDA guidelines and may benefit from TMS can afford to be treated. Likewise, many patients seeking off-label therapy cannot afford treatment, as neither on or off-label TMS is covered by health insurance in the USA. This leaves payment options to the individual clinics. Is there a way for clinics to set pricing so all patients in need, regardless of socioeconomic status, can access treatment? Although this concern may only be pertinent under the present US healthcare system, as TMS continues to advance as a treatment option, economic questions unique to each country's individual medical structure will undoubtedly become increasingly common and must be addressed.

Another subject worth exploring pertains to TMS advertisements. FDA approval comes with the privilege of therapeutic advertising for on-label application of rTMS for depression. However, advertisement can also attract patients who may want off-label rTMS use. Who should the advertisements target? How should the disclosure of side-effects be dealt with? Surely TMS treatment for depression can be made appealing based on what it *does not* do (eg, it does not cause some of the side-effects associated with other common antidepressant medications), but perhaps it would be more prudent to market TMS for what the literature indicates it *can* do. Even though they would almost certainly be non-binding, consensus standards regarding the content of promotional advertising for TMS would be beneficial before practitioners or companies move forward (See Figure 2).

Present and future ethical considerations for the scientific use of TMS

As the clinical and research utility of TMS grows, questions concerning treatment guidelines must be considered. What criteria should we adopt before recommending TMS as a possible treatment for depression or other neuropsychological diseases? Of course, all pertinent information—small effect sizes

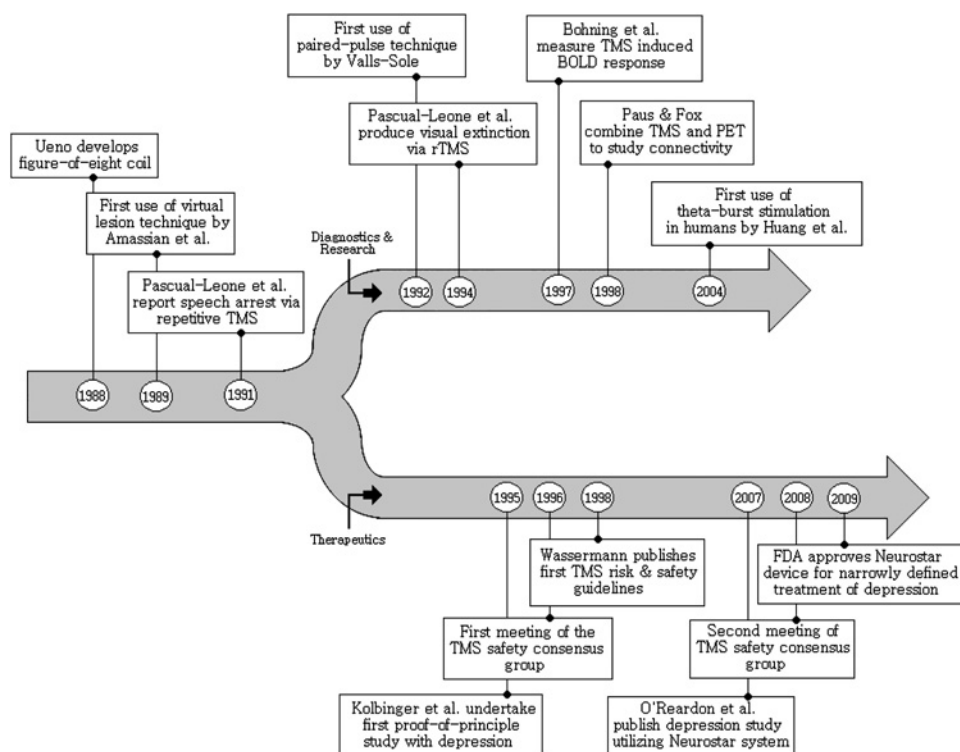
in TMS trials, safety data, alternative treatments, even potential future effects—must be fully disclosed to the patient. The truth about what TMS can and cannot offer must be explicitly stated, and every effort to balance a patient's hopes and expectations with the unpredictable reality of science must be made. Perhaps it would be useful to create an easily-accessible website providing the public with up-to-date TMS information from objective and authoritative sources.

Similarly, as the risk-to-benefit ratio depends on inter-individual differences, practitioners are needed with experience with TMS and with the relevant patient population. Ultimately this requires the development of universal training guidelines and accreditation requirements for TMS clinicians. Who should deliver TMS? How should we ensure practitioners are using TMS correctly and safely? Currently, there are no TMS training requirements, although it is advised that practitioners be well versed in the basics of brain physiology and TMS mechanisms, protocols and safety issues.²⁶ It is apparent, though, that stronger regulations, or at least guidelines, are needed.

In neuroscientific research settings, TMS can occasionally produce seemingly detrimental effects, most typically mild and transient memory deficits. In studies designed to explore these effects on performance tasks, the effects are brief and do not raise particular safety issues.²⁶ Still, these studies challenge the risk-to-benefit ratio. To what extent is it ethical to induce changes in a subjects' brain if the benefit is strictly increased scientific knowledge? Taken one step further, if a therapeutic paradigm is developed that largely mimics one of these research protocols, there is a possibility transient deficits may be produced in the clinic. Although it is not always possible to translate effects generated in healthy populations to clinical patients, the inclusion of cognitive interference on the list of possible treatment side effects is worthy of consideration and discussion.

Finally, recent research combining TMS with genetic testing has revealed that the therapeutic utility of rTMS, particularly in the treatment of drug resistant patients, might be increased by

Figure 2 A timeline of the ethical progression of TMS, highlighting some of the important diagnostic, research, and therapeutic developments in the field.



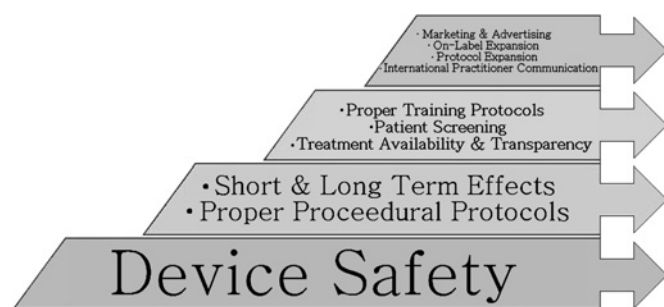


Figure 3 The compiling nature of ethical considerations.

identifying genetic predictors of certain rTMS effects. Combining TMS with genetic testing, though, presents compound ethical challenges: one must keep in mind the ethical considerations applicable to TMS research while evaluating the complex host of issues pertaining to genetic testing. Current research suggests that genetic factors may influence the response to TMS, but is the current evidence strong enough to merit genetic testing on all TMS subjects? The broad range of genetic factors, epigenetic effects and TMS parameters leaves scientists with an intricate array of testing possibilities. Given the postulated role of synaptic plasticity in brain injury and disease, and the epidemiologic evidence concerning the role of BDNF in the synaptic plasticity of the adult brain,³² there does seem to be a potential therapeutic potential for future interventions. However, that potential comes at a cost. Genetic material must first be obtained (and drawing blood certainly poses a discomfort for research participants) and then stored. To address some of these issues, Knoppers and Chadwick highlight the notion of honest and reciprocal exchange between researcher and participant.³³ The autonomy and the contribution of the research participant must be recognised and respected to the fullest in protocols calling for genetic testing. Informed consent and communication with potential participants must be clear, and the objectives transparent. Moreover, participants should fully understand that they have the option to take part in a protocol, and that they can decide whether to have their DNA banked, coded, analysed, even replicated and potentially commercialised.

CONCLUSION

As TMS continues to gain momentum in the field of therapeutic medicine, it is likely to pave the way to additional future non-invasive brain stimulation and neuromodulation techniques. For example, transcranial direct current stimulation is a rapidly expanding non-invasive brain stimulation method that is even easier to apply than TMS and a lot more accessible given much lower device costs. Therefore, we must remain vigilant and use lessons of the past to continually reflect upon current issues of safety and ethics of non-invasive brain stimulation. Our ethical perspective will inevitably evolve with changes in cultural and societal values, but hopefully the issues we have outlined here will provide a strong foundation for approaching the future. As in any discussion, the most essential questions are not those we have the answers to, but rather those which remain uncertain. Should we fail to ask and carefully consider these questions proactively, we risk effecting serious adverse consequences within one or more patients due to future TMS mal-use. If this happens, the entire field may be frozen by outcries of public criticism reminiscent of the overwhelmingly negative perceptions that continue to plague ECT even today. Given the potential of TMS and non-invasive brain stimulation in general, this would be a tragic occurrence—possibly depriving a large

patient population of significant therapeutic benefit. Fortunately, because such a situation is so clearly foreseeable, it is also largely preventable if we act without delay²⁷ (See Figure 3).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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