The New Ethics of Neuromodulation with Transcranial Magnetic Stimulation: A Critical Appraisal

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Abstract

With over 16 years of experience in clinical, research, and educational activities related to transcranial magnetic stimulation (TMS), I have written this article exploring the ethical dimensions of TMS. This article aims to provide valuable and informative content for those unfamiliar with TMS as well as those just starting in the field. Specifically, this article elaborates on four principles of medical ethics, including those applicable to TMS therapy, the disparity between public medical insurance coverage and medical indications in private practice for TMS therapy, and issues concerning research ethics in practice. I also provide recommendations regarding roles and strategies for adoption by academia and those in this field dedicated to making TMS therapy accessible to a larger patient population in a suitable manner. Lastly, it is my hope that this article will serve as a contemporary “Ethics of TMS Neuromodulation”, resonating with the inherent human pursuit of “truth, goodness, and beauty” for a sound mind and spirit.

Keywords: TMS therapy; neuromodulation; biomedical ethics; research ethics; psychiatric disorders

1. Introduction

1.1 Preface

First, medicine and healthcare have both conservative aspects, such as respect for traditions and customs, and progressive aspects, such as innovation. In particular, due to the relative infancy of neuromodulation, which includes transcranial magnetic stimulation (TMS)—although it has already been around a quarter of a century—people in the field tend to be divided into two camps: those who resist new things and those who welcome new medical treatments. Moreover, these attitudes can differ in view and approach depending on the country, region, and healthcare system. In North America, especially in the United States (USA), practices in healthcare easily progress rationally based on scientific, medical, and economic judgments. In contrast, people in Japan and other Asian countries tend to take a cautious stance toward new and unprecedented things; thus, suggested changes—even those supported by medical and economic rationale—are often delayed. Therefore, in this article, I propose a way to balance the ethical (ideal) and practical (reality) aspects of advancing TMS therapy that seeks to satisfy the individual interests of each patient while promoting the maximum happiness for the greatest number of people possible in the context of the societies of Japan, Asia, and the world.

1.2 The Major Ethical Issues Associated with TMS Treatment

The following is an introductory summary of 14 issues, including ethics issues and some new concerns (Nos. 13 and 14) central to the future of TMS treatment. The summary highlights the crux of each issue relative to TMS. The subsequent information and discussions provide background and supplemental information to consider in light of these 14 issues.

(1) Marketing issue: Unlike other general branches of medicine, the advertising for some medical facilities that provide TMS is over-hyped, misleading, and perverted and, thus, may be detrimental to the public interest.

(2) Off-label use: The problem of “off-label use” refers to usage that deviates from the medical rationale and indications, as opposed to the problem of the lack of insurance coverage for established medical indications.

(3) Technician Certification: In countries and regions, a certification system for technicians who provide TMS treatment has not yet been firmly established. For example, in Japan, there are academic workshops on TMS and simple, practical training sessions organized by local companies. Still, these are somewhat formalized and cannot be called certificates for acquiring practical knowledge and skills.

(4) Patient Selection and Treatment Response: The proper selection of patients suitable for TMS treatment. Careful screening for contraindications to TMS treatment should first be performed to minimize the risk of iatrogenic adverse events. Additionally, it is important to appropriately select patients who are likely to respond to TMS treatment, and the determination of that likelihood is inextricably associated with psychiatric diagnoses. For example, a TMS protocol that has been proven effective for depres-
sion is likely to be effective for patients with depression but not necessarily for patients with completely different conditions and characteristics. This issue is directly related to the degree of success or failure of the TMS protocol.

(5) Pharmacotherapy Interaction: Although pharmacotherapy is the mainstay treatment for most psychiatric disorders, TMS treatment is often used as an add-on to pharmacotherapy. Therefore, various interactions naturally occur when pharmacotherapy and TMS therapy are combined. For example, when the combination of both therapies provides potential synergistic effects, no particular problem is posed. However, a situation wherein the combination attenuates the effects of both and ultimately diminishes the therapeutic effect can be medically and ethically problematic. For example, if a high dose of benzodiazepine was administered prior to the introduction of TMS, benzodiazepine should be appropriately tapered off before introducing TMS treatment. However, if a patient has been using benzodiazepines for many years and has already developed dependence, it is often challenging to reduce the dosage. Therefore, the excessive pursuit of benzodiazepine reduction may lead to withdrawal symptoms, making the introduction of TMS treatment difficult. A potential risk for psychiatrists is that medication adjustments made with the best intention for the patient may worsen the patient’s condition and even impede the introduction of TMS treatment. Such clinical issues related to TMS treatment can also lead to ethical issues.

(6) Patient Autonomy: Some patients with depression and other psychiatric disorders have tried conventional therapies, such as pharmacotherapy and psychotherapy, with limited or no effect. Thus, they seek TMS treatment as a straw that will bring them back to life. Furthermore, some patients are not well-versed in medical knowledge and do not fully understand the details of TMS treatment, such as its advantages and disadvantages. In this situation, the medical side may take advantage of the patient’s weaknesses and force the patient to undergo TMS treatment irrationally or at an unreasonably high price. In the unlikely event that such a situation occurs, it would be a direct violation of the ethical principles of medicine and, in particular, could be an affront to the autonomy of the patient.

(7) Informed Consent: Related to the medical literacy issue mentioned above, shared decision-making is important in today’s medical practice, in which patients and medical professionals share necessary medical information in advance and decide on treatment options together. This process is equally important not only in clinical research but also in usual clinical practice. These procedures are routinely practiced as explanations and consent forms for examinations and therapeutic interventions in all medical departments.

(8) Regulation of Health Information: Today, with the spread of the Internet and social networking services, anyone can freely disseminate information related to medicine. In a democratic society, it is natural to allow “freedom of speech”; on the other hand, the world is now flooded with fake information. Consequently, those lacking sufficient information as well as scientific and medical literacy may be at the mercy of malicious information. Thus, there is a medical and ethical danger that unscrupulous medical agencies with business purposes will take advantage of this and prey on the underinformed. In this sense, constant efforts to disseminate accurate medical knowledge and education to the general public are extremely important.

(9) Perception of Invasiveness: There is an issue regarding the perception of invasiveness of TMS and other neuromodulations. TMS is considered a non-invasive intervention by customary definition; however, when potential unknown risks and other factors are considered, it is defined as minimally invasive stimulation. Perceptions are also influenced by how people feel about new medical technologies and the cultural affinity for new technologies in the society to which they belong.

(10) Social Acceptability: A background factor that indirectly influences the ethics involved in TMS is the social acceptability of new medical technologies. This is a common aspect of the perception of invasiveness mentioned above. If the culture and atmosphere of a society actively accept new medical technology, the introduction of TMS treatment can occur and spread easily without much resistance from, for example, regulatory authorities, academic societies, and the general public. Conversely, in countries and regions with few social conventions around readily accepting new medical technologies, introducing TMS treatments into the medical field may take much longer. In addition, depending on (a) a new medical technology’s mechanism of action on the target disease and (b) the intended use of the technology, the acceptability of the technology will vary greatly in each society in accordance with the perception of invasiveness mentioned above. If the clinical application is for patients with medical problems such as treatment-resistant depression, social acceptability is naturally high. However, if the purpose of its use is primarily for recreation and amenity, far from the original medical care, it may be perceived as a hobby of the rich or exploitation of the socially vulnerable and, thus, could be subjected to social criticism.

(11) Balancing Risks and Benefits: This issue is not limited to TMS treatment; even when TMS is administered, the balance between risks and benefits must be carefully considered for each patient. It is often possible to offer TMS within the framework of private practice, especially in cases that are not covered by public insurance but have medical indications. However, in such cases, the physician in charge should coordinate the treatment in a way that minimizes the risks to the patient while increasing the benefits as much as possible.

(12) Limitations of Insurance Coverage: The dilemma of striving to deliver TMS treatments that have not
yet been approved by regulatory authorities to patients in front of us in a timely manner to the extent possible. Specifically, the ethical question of whether to provide TMS treatment for special situations in which medical necessity compels some action but does not meet the coverage and requirements of public insurance or the reimbursement conditions stipulated by private insurance companies. One unrealistic response might be to submit an ethics application as a pure research study, obtain approval, and then conduct a trial intervention. However, the review process takes more than a year for some research institutions, and it is unrealistic to impose such a complicated and burdensome procedure on physicians who are busy with their clinical work. In addition, if such a lengthy ethical review were to be required in each case, the patient in front of us would not be saved, and such a requirement would be unethical in another sense for both the patient and physician concerned. Thus, an ethical dilemma arises regarding the extent to which it is permissible to use unapproved TMS treatments for clinical purposes; however, the final ethical decision is likely to rest in Section 37 of the Declaration of Helsinki (see below).

Unproven Interventions in Clinical Practice

§37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy, in all cases, new information must be recorded and, where appropriate, made publicly available (Excerpt from Declaration of Helsinki 2013 [section 37]).

(13) Artificial Modification of Brain Function: At present, TMS neuromodulation is used clinically mainly for the treatment of depression and other psychiatric disorders; in the future, it may be used not only for such medical needs but also for artificial modification of brain functions in healthy people or for pure curiosity. As this momentum grows, society needs to consider and decide on the pros, cons, and conditions of such indications, including public comments.

(14) Limitation of Safety Data and Guidelines: This issue is limited to TMS neuromodulation treatment; however, the collection and evaluation of associated safety data are very important, especially in the development of new TMS protocols, because safety data for relatively new medical technologies are relatively limited. Furthermore, because basic and clinical research on TMS neuromodulation is constantly evolving, it is necessary for experts to revise the guidelines for the clinical application of TMS as needed and stay up-to-date with the latest evidence.

2. History of the Development of TMS Therapy and Its Current Situation

2.1 The Present Status of TMS Therapy and Its Potential Problems

Since its prototype was developed in 1985, TMS has gained attention as an effective treatment for major depressive disorder, central pain, and obsessive-compulsive disorder. In 2008, a repetitive TMS (rTMS) therapy device (NeuroStar TMS Therapy Device®) that provides high-frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of medication-resistant depression, and since then, several types of TMS therapy devices have also been approved. In the past, ethical considerations in TMS therapy primarily focused on the safety of the subjects in clinical trials. The FDA approval of rTMS as a medical device in 2008 raised a new ethical issue that was different from the traditional issues associated with the approval of new drugs. Specifically, these issues include marketing, off-label use, and technician certification, none of which have been discussed extensively. Ethical issues will continue to increase rapidly, especially as the potential of TMS therapy, especially when patients have few alternative treatment options, expands to include a variety of psychiatric disorders [1].

2.2 Establishment of Diagnostic Utility of TMS Examination

Single-pulse stimulation with TMS allows physicians and researchers to perform nerve conduction time testing in a safer and less painful manner. An ethical consideration during the initial stages of TMS is the safety of the entire device. Since TMS was developed as a diagnostic and research device, few animal studies have assessed the mid- to long-term effects of TMS interventions. Therefore, TMS researchers and practitioners have promoted this field with caution compared with electroconvulsive therapy (ECT). Specifically, TMS studies have placed the greatest emphasis on side effects, especially those related to seizure induction [1].

2.3 Potential Issues Involved in the Clinical Application of rTMS

In 1991, Dr. Pascual-Leone [2], a neurologist, applied the rTMS paradigm to six adult patients with epilepsy for the first time and reported the first virtual lesion study in which high-frequency rTMS of a region corresponding to Broca’s area temporarily suppressed brain function, resulting in loss of speech. This study was qualitatively different from previous single-pulse TMS studies that showed rTMS could provide a more continuous neurological intervention [2]. This new rTMS paradigm provided a scientific means for neurologists to study the interplay between cognitive function and neural circuits in a non-invasive manner. Furthermore, in 1994, Pascual-Leone [3] showed that rTMS...
can produce cortical effects that persist for several minutes after the completion of stimulation. The ability of rTMS to induce lasting neurophysiological and neurocognitive effects has led to its potential as a new therapeutic modality that can non-invasively neuromodulate the central nervous system externally.

As TMS developed from a single-pulse device to a machine capable of repetitive pulses, the potential for ethical problems caused by TMS increased. In addition to the medical safety issues related to rTMS, clinicians and researchers seeking to apply rTMS clinically have encountered a variety of clinical considerations, including conditions and patients potentially responsive to rTMS therapy, treatment response patterns for each patient, and the interactions between rTMS therapy and pharmacotherapy. While various rTMS clinical studies have been conducted at the laboratory level, in pursuit of approval from the FDA and other authorities, the companies and researchers involved needed to conduct formal clinical trials from Phase I to Phase III, which met the Good Clinical Practice (GCP) criteria. Thus, medical device rTMS has faced a large gap between academia-driven research-based advanced rTMS research and regulatory science aimed at obtaining approval from authorities, which has led to confusion in the rTMS industry and among patients [1]. In this regard, the “confusion” was not limited to that period; it continues today. The confusion comes from the vast differences in purposes and goals between “medical science”, which is primarily academia-driven research and development of novel TMS neuromodulation treatments for innovation, and “regulatory science”, which focuses on conservative clinical trial procedures conducted under regulatory control to make these findings available for clinical application in the field. The public and patients, particularly those who are unfamiliar with the details of these differences, cannot immediately understand that the latest TMS treatment protocols are not immediately available in the medical field and that such new treatments are not covered by their regular medical insurance, causing frustration for healthcare providers in the field as well.

2.4 Early Attempts at Clinical Application of rTMS Therapy and Development of Safety Guidelines

In 1995, Kolbinger and colleagues [4], neurologists, performed rTMS for the first time in the world on 15 patients with depression for a total of five consecutive days for therapeutic application. This trial is the earliest clinical study to suggest a possible antidepressant effect of rTMS. In 1996, Pascual-Leone et al. [5] conducted an rTMS interventional study on the left prefrontal cortex in a randomized controlled trial (RCT) crossover design in 17 patients with medication-resistant depression and reported the possibility that rTMS could produce antidepressant effects. However, the success of these early demonstrations of rTMS has raised concerns among some researchers regarding its long-term effects on the cerebral cortex, including potential adverse events. In 1996, TMS experts met at the National Institute of Mental Health (NIMH) to develop the first detailed guidelines on the safety and ethics of TMS research and clinical use, which were published in 1998 in the official journal of the International Federation of Clinical Neurophysiology, headed by Wassermann [6].

2.5 Expansion of Clinical Application of rTMS Therapy

With the development of safety guidelines for TMS and the confirmation of the potential benefits of rTMS therapy for depression, rTMS gradually became established worldwide. However, the majority of patients with depression who sought rTMS therapy in the early days were those who had not responded to other more established treatments, including pharmacotherapy, making rTMS therapy their “last resort”. Such a situation could lead to the “loss of patient autonomy” among participants and patients and, thus, pose some potential ethical issues. These issues could arise in the process of obtaining informed consent, especially because rTMS treatment is a possible “next-step” treatment option for patients who have failed to respond to conventional antidepressants and other medications. The ethical problem would stem from the fact that such patients—those who are resistant to medication—are in a persistent state of depression and need help; thus, some may visit TMS clinics seeking rTMS treatment as their only hope. At that point, such patients may not be willing to consider other non-rTMS treatment options like psychotherapy; they also cannot calmly and rationally consider the merits and demerits of rTMS or judge the appropriateness of the price of rTMS treatment. Being in this disadvantageous situation may lead such patients to deviate from medical care that respects patient autonomy. Furthermore, this problem was caused by an information gap regarding TMS expertise and medical knowledge, including psychiatry, which prevented participants and patients from obtaining the minimum necessary information, leading to false perceptions and judgments regarding rTMS therapy. Therefore, professionals need to be more careful and meticulous when considering novel therapeutic options for vulnerable populations (i.e., patients with mental illness and those who lack sufficient knowledge and information necessary to make medical decisions) to avoid potential problems and misconceptions [1].

In the 2000s, with the spread of rTMS therapy, regulatory authorities in many countries, including Brazil, Israel, Australia, and Canada, granted regulatory approval, recognizing rTMS treatment equipment as a medical device and permitting the use of rTMS therapy for depression. In addition, industry-sponsored clinical trials funded by NeuroNetics Inc. were conducted by O’Reardon et al. in 2007 [7]. Based on these trials, which demonstrated the effectiveness of the NeuroStar TMS device in treating patients with treatment-resistant depression [7], the U.S. FDA ap-
proved the NeuroStar TMS device in 2008 for the treatment of adult patients with treatment-resistant depression who did not respond to at least one antidepressant medication.

The subsequent rapid spread of rTMS treatments led to dramatic increases in ethical issues in the rTMS industry. For example, if a patient moves across borders because rTMS treatment is not available in their home country, how do the actual guidelines apply? Ultimately, it would be determined that such patients are subject to the guidelines of the jurisdiction in which they are seeking medical care, not their country of origin. However, when considering this issue as a thought experiment, ethical questions arise. For example, a patient with obsessive-compulsive disorder (OCD) living in Japan may be forced to engage in medical tourism, traveling to the USA or another foreign country to seek TMS treatment for OCD because the treatment is not approved by public insurance in Japan. Japan has a national health insurance system based on the premise that the nations should provide for the welfare of the people, including medical care. However, if the approval process for new TMS technologies in Japan is too slow, not only “device lag” but even “device loss” could occur, resulting in a situation in which some Japanese people are forced to go abroad to receive necessary medical care. This situation could arise as a possible negative consequence of the stringency of the regulations in Japan, which is often extremely burdensome for the people concerned. Furthermore, such a medical structure is not healthy and is unethical.

The opposite of this case also presents a dilemma. For example, if a patient with OCD living in the USA moves to Japan, the patient would not be able to receive TMS treatment in Japan, where the patient has moved, although some TMS devices and protocols for OCD have been approved by the FDA in the USA, because they are not yet covered by public insurance in Japan. In such a case, the ethical dilemma is the loss of access to medical care that should be, but is not, medically and scientifically available in the home country because of the local rules of the country or region in which the patient is staying (e.g., the country or region of jurisdiction). This example demonstrates that because TMS treatment is a scientific medical technology, guidelines should be formulated based on scientific evidence, even though cultural and customary differences exist among countries and regions. In other words, ideally, there will be no major differences between the USA and Japan or between any countries, regions, and societies in terms of the framework of guidelines. Additionally, how can medical and ethical integrity be maintained when a new adverse event report directly affects the medical business of rTMS treatment? Such possibilities should be constantly considered, and TMS safety guidelines and appropriate rTMS use guidelines should be revised and updated continuously.

Furthermore, because knowledge and medical technology related to TMS therapy are constantly developing and evolving, appropriate training courses for TMS practitioners and technicians, as well as certification issues for them, are crucial for becoming proficient in the details and procedures of the latest TMS therapies. Given the current relative increase in the number of patients seeking TMS therapy, it is of utmost importance that patients be treated by psychiatrists familiar with (1) medically appropriate patient selection for TMS therapy, (2) operating techniques for various TMS treatment devices, and (3) overall knowledge and procedures for selecting and implementing various TMS treatment protocols as much as possible [1].

3. Ethics of Neuromodulation

3.1 Lessons to be Learned from the Negative History of Neuromodulation in Psychiatry

ECT, developed in 1937 by Dr. Ugo Cerletti, an Italian neurologist, and Dr. Lucio Bini, an Italian psychiatrist, transformed the history of “brain stimulation” dating back to ancient times into the modern era of “medical devices” as if it were a medical renaissance. Initially, ECT was intended to reduce agitation symptoms in hospitalized patients with schizophrenia; however, as the device’s inexplicable popularity increased, ECT became a panacea or ultimate weapon in the psychiatric armamentarium. As a result, in the 1940s and 1950s, the inappropriate abuse of ECT caused a number of serious adverse psychiatric and physical side effects that were perceived negatively by society. This public backlash against ECT and other invasive therapies led the FDA to establish regulations for all new medical devices beginning in 1976. Ironically, however, because ECT was already on the market before the FDA intervened, along with several other brain stimulators, it remains a medical device that is not regulated by the FDA [8]. However, the current ECT has been improved into a modified ECT, which is more effective and safer than the old one [9]. In 1972, an infamous incident occurred in the history of brain stimulation, raising serious ethical issues regarding treatment. Around 1970, Dr. José Delgado, a Spanish neuroscientist, successfully experimented with implanting electrodes into an animal’s brain and applying a weak electric current to change the animal’s behavior. Dr. Robert Heath, an American psychiatrist, and his colleagues at Tulane University, New Orleans, attempted to use the findings to cure patients of their sexual orientation (homosexuality) [10]. They implanted electrodes in the septum of patient B-19 and successfully suppressed the patient’s homosexual behavior for 10 months by combining electrical stimulation at the same site with forced heterosexual intercourse with a female prostitute. At the time, this research report was fiercely opposed not only by academia but also by the media as a “mad scientist’s folly” [11]. The criticism of this event was not directed at the deep brain stimulation research method itself, which was too advanced for its time, but rather was closely related to the fact that people’s views and social perceptions of the fundamental con-
cepts of “normal and abnormal” or “healthy and ill” had changed drastically [12,13]. Therefore, when developing an ethical framework for clinical research, it is necessary to consider the impact of such research on society from as many different perspectives as possible, including not only the viewpoints of researchers but also those of the patients involved [1].

3.2 Ethical Considerations for Clinical Application of TMS Therapy

TMS therapy has been progressively developed, and the research and clinical utility of TMS are steadily increasing. Therefore, it is necessary to review and revise the guidelines for the appropriate use of TMS therapy and other guidelines in a timely manner. Specifically, it is necessary to include and disclose sufficient information based on the latest evidence regarding the efficacy and safety of TMS therapy to the public. It is also necessary to explain in an easy-to-understand manner what TMS therapy at the present stage can and cannot provide to patients, and while accommodating patients’ wishes and expectations to some extent, it is also necessary to clearly state in advance the inherent unpredictability of individual treatment responsiveness as a limitation of medicine. TMS therapy is a treatment technique that is still in its developmental stages and, like other therapies, is not a panacea or magic cure. Therefore, with regard to TMS therapy, relevant academic societies and research groups need to continue to provide the latest TMS information from objective and legitimate sources and improve the information environment for easy access by the general public. Furthermore, as with any specialty treatment, since the risk-benefit ratio regarding TMS therapy varies from person to person, it is essential that the administrator of TMS therapy should have not only a certain level of experience in treating depression (e.g., years of experience at the level of a board-certified psychiatrist) but also a certain level of experience with TMS therapy (e.g., a minimum of one year of training under an expert in TMS therapy, as well as, more specifically, a minimum of 2–3 years and dozens of cases of experience with this therapy). Eventually, those involved in TMS therapy will be encouraged to participate not only in the current one-day academic and industry sessions but also in training courses developed by TMS experts that meet the certification requirements for the mastery of TMS therapy. During their training course, clinicians who intend to specialize in TMS should acquire basic knowledge of TMS neurophysiology, operating principles, typical TMS protocols, and their safety [14].

3.3 Four Principles of Ethics

The use of neuromodulation technology for psychiatric disorders is also subject to the pillars of medical and bioethics: (1) Respect for Autonomy (respect for the patient as an individual and his or her right to self-determination; the patient has the right to refuse or choose his or her own treatment), (2) Beneficence (the medical practitioner should act in the best interest of the patient), (3) Non-maleficence (the patient should be treated in a way that does not harm him or her), and (4) Justice (the principle of fairness in the distribution of scarce medical resources and the right of the patient to a fair trial). These principles apply not only to clinical research but also to usual medical care; however, adherence to ethical guidelines in clinical research will result in the full compliance of healthcare professionals and researchers [15]. These four principles were applied to the ethics of TMS treatment as follows:

(1) Respect for Autonomy: The patient has the right to refuse or choose his or her own treatment, and the sharing of information about TMS treatment is essential for healthcare providers and patients to make such decisions together (i.e., shared decision making). Conversely, the worst scenario would be for the healthcare provider to try to guide and introduce only TMS treatment to the patient without presenting other possible treatment options from the outset. Today, the public uses the Internet and other media to obtain medical and health information. While there are issues of media literacy, scientific literacy, and medical literacy among the general public, the reliability and accuracy of the information sources in the first place, as well as the intentions and speculations of the people who are disseminating the information, also have a significant impact on the information [16]. In this sense, it is ethically important to have a certain level of regulation at the democratic level over a flood of information and provide sufficient information to subjects through informed consent in clinical research. These attitudes and activities are based on the ethical principles mentioned above [17].

(2) Beneficence: When TMS treatment is provided in the context of usual medical practice rather than purely clinical research, it is essential to pursue best practices whenever possible and to act rationally in a professional and attentive manner to the needs and concerns of the patient.

(3) Non-maleficence: It is imperative that TMS treatment is provided to patients in a form that causes as few adverse events as possible. Fortunately, TMS treatment is characterized by far fewer side effects and adverse events than other pharmacotherapy or electroconvulsive therapy. However, careful screening before TMS treatment, close monitoring after the start of treatment, and follow-up for a certain period are necessary.

(4) Justice: As TMS is a relatively new treatment that requires manpower, minimal cost, and a certain amount of time, we need to consider distributing the limited medical resources for TMS treatment as equitably as possible. Therefore, reasonable pricing for TMS treatment is crucial. In Japan, the cost of one TMS treatment is currently 12,000 yen (~US$80) under the public insurance system but is scheduled to be raised to 20,000 yen (~US$132) in the 2024 revision of reimbursement. This revision was made to resolve the structural problem in Japan: the more TMS
3.4 Regulation and Reimbursement Issues

This section discusses regulatory and reimbursement issues related to TMS treatment. One aim of this article is to highlight the ways in which TMS treatment under the private insurance reimbursement system used in the USA and many other developed countries differs from the public insurance reimbursement system used in Japan and a few other countries. Moreover, we must consider how a balance or compromise between two systems could be achieved. Regulations regarding the use of TMS differ from country to country and region to region. In general, neuromodulation is not currently considered a first-line treatment for psychiatric disorders, and most of the potential indications for TMS are still in the research phase. In the USA, rTMS has been approved by the U.S. FDA, but FDA approval is a separate process for each device manufacturer, indication, and treatment protocol; thus, at present, only a few rTMS treatment devices, indications, and treatment protocols have been approved. Nevertheless, the USA has granted the most approval for rTMS among developed countries [14], although it is difficult to make a general statement because insurance systems differ from country to country and region to region, at least in Japan. TMS therapy using the Neuronetics NeuroStar TMS System® [18] is currently publicly covered in Japan only for adult patients with depression and moderate or severe symptoms who have not responded to one or more antidepressant medications. Therefore, it should be noted that any other use would be off-label use under the public insurance treatment category. Additionally, when clinical research is conducted using medical devices and/or treatment protocols that have not been approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, it must be conducted within the framework of specific clinical research after appropriate review and approval by a Certified Review Board.

On the other hand, when a device that has not been approved by the regulatory authority (PMDA) or TMS treatment that is not covered by public medical insurance is applied clinically as “usual medical care”, it is performed within the framework of private practice in Japan according to an individual contract (Quasi-Assignment Contract) between the patient and the medical institution (facility director or physician in charge) that provides the care. The term “usual medical care” refers to the routine care provided to patients for the prevention or treatment of a disease. The definition of usual medical care is not standardized but depends on the type and severity of the disease, the department from which the patient receives care, the healthcare system, and the individual physician [19]. In other words, usual medical care is a complex concept that encompasses a wide range of activities and practices in the medical field, which vary widely depending on the context, particular medical environment, and needs of individual patients. For example, a medical institution that specializes in TMS routinely provides a variety of TMS treatments that are assured of a certain level of efficacy and safety and thus fall under the category of usual medical care in the above context.

Furthermore, to implement a particular TMS treatment as a medical practice intended to treat a patient based on the physician’s bona fides and discretion rather than purely for clinical research, and if no established intervention exists for individual patient treatment or if an established intervention has been ineffective when implemented, physicians could implement as-yet unproven therapeutic interventions after providing appropriate informed consent to the patient and seeking expert consultation (Declaration of Helsinki 2013 [section 37]) [20]. In Japan, the meaning and scope of public medical insurance coverage and medical indications differ greatly; thus, when referring to the coverage and indications, it is important to clearly distinguish whether we are talking about public medical insurance “coverage” or medical “indications”. I believe that this is a major factor causing unnecessary confusion and controversy in Japan.

3.5 Views on Side Effects

The cliché that “drugs without side effects are ineffective” applies to many non-pharmacological reinforcement interventions. In the original medical context, invasiveness has a more or less clear meaning, such as physically cutting the skin or entering deep into the body, such as the gastrointestinal tract, through external openings, but with regard to artificial cognitive enhancement through brain stimulation and neuromodulation, it is difficult to explicitly determine whether and to what extent it is invasive. However, both nutritional supplements and pharmaceuticals are medically invasive in the narrow sense of the term as they involve artificial substances entering the body. Therefore, brain stimulation that does not directly injure the skin has conventionally been classified as noninvasive [21].
However, in addition to the known risks of brain stimulation methods, such as scalp burns from transcranial direct current stimulation and seizure induction by TMS, there are “known unknown risks” for which there is a need to know and an understanding of the possibility of a certain potential risk, but not enough information is available to make it known. For example, there are unknown risks regarding the cumulative effects of multiple TMS sessions and the potential spillover effects of TMS on non-target areas. Thus, in contrast to the strict medical definition of invasiveness in general, the presence or absence and degree of invasiveness in the field of neuromodulation are often intuitively perceived based on familiarity with public and cultural traditions. Against this background, most people tend to find it less invasive to change their diet or exercise, regardless of the actual health benefits, but more invasive to take pharmaceuticals or stimulate their brains. In other words, it could be said that it depends on whether the intervention act feels more natural to many people [22].

3.6 Social Acceptability

The social acceptability of interventions, such as antidepressant effects and cognitive enhancement, depends largely on societal conventions, the nature of the intervention’s content, and the rationality of its mode of action. In general, natural interventions with thousands of years of tradition, such as meditation, nutritional therapy, sleep, and exercise, are overwhelmingly accepted by society compared to many of the recently discussed strategies for enhancing function, such as brain stimulation and pharmaceuticals. This is probably due to the customary cognitive biases of humans. Thus, ethical issues in terms of social acceptability could be related to the question of whether mechanical medical interventions such as brain stimulation are related to general concerns about benefits and side effects for patients or are due to their modality or mechanism of action being clearly different from conventional and more natural approaches [21].

In empirical studies on the artificial modification of brain function, safety, coerciveness, and fairness are the most common concerns. Those who have never used the technology tend to express more concerns about medical safety and fairness than their users. Another aspect that influences the social acceptability of the modification of brain function is the purpose of the intervention. In empirical medicine, philosophical, and sociopolitical contexts, the idea of modifying brain function varies considerably depending on the specific objectives of the intervention. Many people tend to be relatively tolerant, especially when it comes to modifying and enhancing functions and abilities that are not directly related to their self-identity. Additionally, brain function enhancement in individuals with cognitive impairment or low baseline performance is likely to be more permissive than interventions in individuals with normal brain function or high cognitive performance [23].

In summary, there are at least four issues related to the artificial enhancement of brain function through neuromodulation, and the ethical evaluation of each differs. (1) The first is a neuromodification aimed at preventing normal age-related cognitive decline or delaying the aging process. For example, reinforcement strategies aimed at improving cognitive function in healthy individuals are partially acceptable at this time but are still limited to improving cognitive function within the normal range. (2) The second and currently the greatest ethical concern is the attempt to further enhance normal brain function in healthy individuals to elicit high performance in a manner that exceeds the original human capacity. (3) Neuromodulation for therapeutic purposes in certain brain dysfunctions. This is considered ethically acceptable because it is consistent with the objectives of conventional medicine. (4) Fourth, apart from the presence or absence of brain dysfunction and the purpose of the intervention, we aimed to determine whether the neuromodulation technique itself was safe as an intervention method for human subjects. This is also a concern shared by 1–3 listed above. In addition, because there are many methods of intervening and modifying brain functions, including those that are latent or customarily accepted by society, it can be difficult in practice to rigorously examine the differences in their usefulness, the interactions, and the synergistic effects of their combinations, and their individual ethical issues. However, it is possible to resolve or avoid confusion and disagreement in ethical arguments by adhering to the principles of ethics regarding neuromodulation or neuroenhancement [24]. Specifically, for healthy adults, there is very limited evidence that non-invasive neuromodulation improves long-term cognitive function; thus, there may be no major problems or concerns. However, in the case of children and other minors, the ability to make their own judgments about the advantages and disadvantages of neuromodulation is limited; therefore, in principle, practice should be discouraged unless there are special reasons to do so. In children, the implementation of neuromodulation therapy should be postponed until the individual is mature and able to make informed personal decisions. Opinions from neuromodulation specialists could play an important role in addressing these issues. Therefore, clinical research in this field, which is continuously evolving, must continue. In addition, the International Federation of Clinical Neurophysiology has issued an official statement that, as a minimum rule, “neuromodulation is not a do-it-yourself technique for non-professionals and should only be performed under the supervision of a physician.” [25,26].

3.7 Ethics of TMS Interventions in Clinical Research

Interventional research includes clinical research on interventions aimed at either preventing or treating diseases or alleviating disease symptoms. The participants have the potential to benefit individually. Placebo-controlled trials, of course, may result in some of the participants gaining

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**Note:** The image contains a page from a document with text that is partially obscured or cut off, particularly at the bottom. The text is mostly readable, but some parts are not fully visible. The natural text above is a transcription of the visible content. If you need the complete or exact content, please refer to the original document or use the provided bounding box information to extract the text more accurately.
medical benefit from a valid intervention; however, empirical studies have shown that subjects assigned to the sham stimulation group may also benefit to some extent from the placebo effect and enhanced monitoring and care. In neuromodulation treatment research, acceptable burdens and risks also depend on the burden and risk of the disease and the anticipated benefits. Novel experimental therapeutic interventions, such as no one has yet employed, are usually implemented when approved treatments are inadequate or unacceptable or no approved treatments exist. The proposed therapeutic research is reviewed and approved by a Certified Review Board, which ensures that the safety and interests of the participants are adequately protected. In particular, clinical research that prospectively examines the effectiveness of non-standard treatment protocols is considered specific clinical research and must comply with the provisions of the Clinical Trials Act in Japan. The submission of evidence for adequate, relevant training, reporting of adverse events, and long-term follow-up evaluations are examples of procedures often required by clinical research review committees to oversee clinical research. Specifically, the standard treatment of rTMS procedures is essentially determined based on materials and evidence obtained from medical devices and related product inserts, guidelines developed primarily by professional societies, research groups, other expert groups, and other legitimate sources that are widely accepted by experts (e.g., PubMed). However, it should be noted that the term “standard” also has a kind of misnomer: it just refers to the “standard” treatment at present and does not necessarily mean that the old-generation treatment methods covered by public medical insurance are the standard treatment as they are.

In contrast, studies that retrospectively analyze clinical data on standard rTMS therapy or other TMS therapies usually administered under the guidance of experts in the context of usual medical care may also be conducted as observational studies. However, because most medical care in Japan is covered by the national public medical insurance system, it is often implemented within the framework of private practice. In such cases, it can be handled within the framework of the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Japan and does not need to be conducted specifically within the framework of specific clinical research.

Notably, there is also some divergence in the scope and concept of what is meant by “usual medical care” in Japan, depending on the specialty of the physician and the customary practices of the medical institution to which the physician belongs. For example, for physicians specializing in TMS practice, it is natural to perform clinical assessments related to the evaluation of depressive symptoms, including routine examinations using the Montgomery–Åsberg Depression Rating Scale and Hamilton Rating Scale for Depression, on a regular basis. This is similar to the manner in which diabetologists perform monthly HbA1C and other diabetes-related blood tests on their patients. Regarding TMS treatment techniques, it is relatively natural for TMS experts to consider low-frequency rTMS therapy for the right DLPFC or other TMS treatment methods when the so-called standard high-frequency rTMS therapy for the left DLPFC is ineffective within the framework of private practice.

Currently, because rTMS therapy is not yet widely available in Japan and is in its early stages, it is premature to consider it in cases for which there is no medical indication. However, TMS should be performed on a limited basis under the guidance and supervision of TMS experts when medically indicated, even for diseases, conditions, and procedures not covered by public medical insurance (see Declaration of Helsinki [section 37]) [20]. The publicly uncovered (off-label use) or experimental (off-medical indication) use of rTMS therapy is often evaluated and determined based on peer-reviewed data showing possible benefits and associated safety profiles, considering the available treatment options. In Japan, this may be the case with some rTMS therapies provided by private practice; however, even in such cases, the decision should be made based on medical evidence and after carefully weighing the clinical benefits to patients. In such cases, the administrator or practitioner of rTMS therapy is still ethically obligated to explain the risks and benefits of the non-standard treatment to the patient and obtain written informed consent from the patient using explanatory and consent documents for in-hospital use.

3.8 Practicalities to Mitigate Risk in Clinical Research Using TMS

In TMS research, factors that may generate possible risks or noise should be avoided in advance, not only from a safety risk management perspective but also for scientific reasons, to reduce extreme variability and bias in clinical and biological indices. Specifically, patients with a history of epilepsy or intracranial implantation of ferromagnetic metals were excluded. However, such cases do not necessarily represent an absolute contraindication if the research is justified by ethics or medical necessity. For example, if the specific symptoms that are the target of the intervention can be better modified by rTMS and there are no therapeutic alternatives other than rTMS, it may be acceptable to implement rTMS, even with the associated relative risks, if sufficient steps are taken beforehand. In such cases, the physician in charge must consult relevant experts in advance. In addition, there is an unknown risk of unintentionally including cases that are unsuitable for treatment or potentially high-risk because the efficacy and safety of new TMS protocols are unknown in the early stages of the development of new therapies. Preventive measures to reduce such risks may include a more rigorous screening of subjects, neurophysiological monitoring during TMS administration, use of the medical environment and external resources to sup-
port compliance with and execution of study procedures, and attendance of medical professionals and other clinical experts [25].

3.9 TMS Interventions for Medically Fragile Populations

Healthcare providers should not prevent medically vulnerable populations from participating in clinical research involving innovative therapies or from having access to relatively new treatments, such as usual medical care in a clinical setting, including private practice, unless there are special reasons to do so. However, minors under the age of 18 years, pregnant women, and cases in which it is difficult to obtain informed consent may be prohibited or restricted from participating in TMS research, not only for medical reasons but also in terms of the ethical principles described above. The potential risks and benefits of TMS therapy need to be comprehensively weighed against the risks associated with alternative treatments other than TMS therapy and the risks associated with vulnerable individuals in society not receiving TMS therapy. For example, special consideration should be paid to studies involving pregnant women, as adverse events associated with TMS therapy may adversely affect both the mother and the fetus. However, in special cases, such as for a pregnant woman with severe depression, consideration of taking such a risk may be justified [27,28].

Furthermore, the application of TMS therapy in children should be undertaken only after the intervention has been adequately studied in adults and its efficacy and safety have been established. Although the legal age of minors is defined as, for example, 18 years, from an ethical point of view, it is important that they reach an age (usually around 12–14 years of age) at which they can understand the research procedures and express their own will. In other words, although, legally, a person under 18 years of age corresponds to a minor, in terms of research ethics, it is possible to conduct a TMS intervention in children as a clinical study if approval is obtained from an ethics review committee, even at the age of 13 years. When conducting TMS research on patients with significant impairments in decision-making due to the presence of psychiatric disorders, additional measures are needed to ensure appropriate informed consent. Clinical studies involving patients with dementia or severe cognitive impairment require the consent of a surrogate at the time of assent. In addition, a one-page summary description may be used as a brief statement to help the participants understand the major risks and potential benefits. Moreover, clinical studies on TMS therapy for depression must also consider the relative risk of requiring discontinuation of certain medications or modification of ongoing treatment as a result of participation in the study, as subjects are often already receiving pharmacotherapy. Although these procedures may decrease the risk of seizure induction, they pose unacceptable risks. For example, discontinuation of antidepressants in patients with depression may increase the risk of suicide, and anticonvulsant medications may decrease cognitive function. Thus, the risks of TMS vary depending on the specific study protocol and participant characteristics.

3.10 Safety Recommendations for Research Use and Clinical Application of TMS

Biological studies using TMS as a tool for neurophysiology and cognitive neuroscience should be conducted in accordance with the research protocols approved by the research ethics review board. Informed consent should, in principle, be obtained by the principal investigator or co-investigator who is authorized to obtain informed consent, as described in the research protocol. The research protocol often includes a description of the degree of risk, assumed risks and benefits, and the role of each member of the research team involved in the TMS study [29].

However, in specific clinical research, the decision to include subjects in intervention studies using novel TMS protocols should always be made by appropriately trained physicians in accordance with the standards of medical practice; additionally, informed consent for the study should, in principle, be obtained from the physicians in charge of the research. TMS should be administered by physicians or appropriately trained personnel under their supervision. Furthermore, TMS interventions should be administered under circumstances in which the anticipated side effects can be adequately managed [25].

3.11 Limitations of the Current Safety Data

In clinical research and practice regarding TMS therapy, research subjects and patients must be informed of possible adverse events associated with TMS interventions; however, a current review of adverse events associated with TMS interventions indicates that TMS is generally safe in most currently applied protocols and that no permanent adverse events associated with TMS have been reported. Nevertheless, just because there have been few reports of serious adverse events associated with TMS in the past, we should not assume that there will be no new adverse events associated with TMS treatment for the foreseeable future. Therefore, researchers and clinicians who employ TMS should always be alert to any unanticipated or unknown risks associated with TMS. Although researchers in the field of TMS and sponsors in the TMS medical device industry have made great efforts to collect safety data, our knowledge of safety remains limited because of the relatively small number of large-scale clinical studies, especially in Japan, where there are currently virtually almost no studies, and the paucity of long-term follow-up data. In particular, the use of TMS equipment that does not comply with the regulatory guidelines may pose an increased relative risk and should be handled with special caution.
3.12 New Negative Consequences Arising from Stringent Medical Coverage Conditions that are not in Accordance with the Realities of Clinical Practice

The narrow application of TMS therapy approved by the U.S. FDA, as well as the application of TMS therapy under extremely limited conditions approved by the Ministry of Health, Labour and Welfare (MHLW) in Japan, may raise other ethical issues. This relatively stringent TMS therapy coverage criterion increases the likelihood that many patients will consider non-covered options. For example, previous studies have reported that the current standard rTMS therapy for patients with treatment-resistant depression only maintains its antidepressant effects for approximately 4 to 6 months, but the FDA has not approved maintenance rTMS strategies for the long-term management of patients at present. Therefore, long-term management with TMS therapy for the prevention of relapse or recurrence of depressive symptoms is not covered by the current public medical insurance coverage, and, consequently, it is an off-label use subject to ethical debate. Therefore, in Japan, there is currently no alternative but to implement TMS for the prevention and management of the recurrence of depression as an advanced medical treatment within the framework of specific clinical research or as a private practice under the guidance and supervision of psychiatrists with expertise in TMS [30].

As rTMS treatment strategies for psychiatric disorders continue to be developed, medical and ethical issues related to such non-covered uses will inevitably increase. Thus, in order to bridge the gap between the application requirements from regulatory authorities and the reality of medical practice, it is essential to revise the guidelines for safety and appropriate use of TMS as necessary to meet the reality through careful and constructive discussions by a group of experts in TMS therapy from related academic societies. It is also important to note that experts and professionals must not become overly conservative and fall into unrealistic empty theories. In this sense, it is critical that experts with extensive case experience and knowledge at the front line of the field take the lead in discussions. It is also important to proactively submit opinions and guidelines prepared by experts to regulatory authorities as reference materials and encourage them to regularly revise the conditions of public medical insurance coverage in a realistic manner. The existing safety guidelines for TMS distinguish between absolute and relative contraindications, which are important considerations in the selection of appropriate candidates for TMS. Patients with absolute contraindications for TMS included those with intracranially implanted metallic devices. In addition, patients with relative contraindications to TMS have a history of epilepsy or intracranial organic lesions, and taking medications that lower the threshold for seizure induction may also be relative contraindications. Therefore, it is important to consider the balance of risks and benefits when deciding whether a patient is eligible for TMS. The attending physician or principal investigator must carefully evaluate the presence and extent of absolute and relative contraindications when determining whether TMS therapy is appropriate for a given patient and subject. However, as safety data on TMS therapy remain limited, more specific and precise risks and benefits for all cases cannot be reliably demonstrated [25].

Currently, in Japan, only rTMS therapy using an FDA-approved standard treatment protocol with the NeuroStar TMS device is covered by national public insurance for adults with moderate to severe depression whose symptoms do not improve with one or more antidepressant medications. Furthermore, facilities that can provide TMS therapy under public medical insurance (i.e., those that meet the criteria for providing TMS therapy as stipulated by the MHLW) are limited to university hospitals and psychiatric hospitals of medium size or larger. In addition, the hurdles for practitioner standards are relatively high in Japan, making it difficult to implement rTMS therapy under public insurance coverage. In other words, the authorities’ carefully considered regulations have become a major obstacle to the widespread use of rTMS therapy under public insurance in Japan, resulting in the serious problem of rTMS therapy not adequately reaching the patients who really need it. Consequently, both patients and medical practitioners are forced to adopt a more realistic approach to TMS therapy based on practical principles, such as the use of off-label therapy or therapy that is not covered by private practice. When offering TMS therapy in private practice, it is important to provide evidence-based justification for the medical indications for a given TMS therapy rather than pricing. Thus, ethical issues of various aspects and at different levels emerge in relation to the structural problems of medicine and the realities of medical care. However, when we reflect on the more fundamental “medical ethics”, such as “medicine is the art of benevolence”, it seems that there is no unique solution as to what way of medical care is truly the right path to take.

4. Conclusion

TMS has shown significant potential for the diagnosis and monitoring of neurological and psychiatric disorders. Furthermore, the therapeutic form of rTMS can induce lasting effects by altering synaptic plasticity, showing promise for the treatment of conditions such as depression, pain, stroke, schizophrenia, and OCD. However, certain challenges in using the treatment remain, such as determining the optimal parameters, accounting for individual variability, and ensuring cost-effectiveness. The clinical application of rTMS presents ethical and regulatory dilemmas, including marketing, off-label use, technician certification, patient selection, treatment response, and pharmacotherapy interactions. Particularly, for patients with depression seeking rTMS therapy as a last resort, there are concerns about a lack of information and autonomy. This necessitates a
multidimensional ethical framework that considers social impacts, stakeholder perspectives, and changing norms and values of health and normality. The principles of respect for autonomy, beneficence, non-maleficence, and justice must be applied to TMS research and practice, emphasizing the need for informed consent and the democratic regulation of health information. Comparisons of FDA approvals, insurance coverage, off-label use, and usual medical care for TMS between the USA and Japan highlight the challenges of evidence-based decision-making.

As TMS continues to evolve with new technologies and applications, the professional community must remain vigilant and cautious regarding potential adverse events and ethical issues. Throughout this process, we must always consider the safety and ethical issues that may arise with these new medical technologies and remain cautious and not overconfident, drawing on lessons learned in the past. In addition, the ethical perspectives that we hold as a collective consciousness inevitably change with the transition of cultural and social values, but medical ethics, including the “four ethical principles” mentioned above, are considered universal in nature and do not change much with the passage of time [31]. Ethical issues are questions that continue to be asked on a case-by-case basis; however, by nature, there is no correct answer. Rather, the answer is uncertain and changes according to the situation, context, and values of the people at that time [16]. Therefore, we must always be on the lookout for potential ethical issues and carefully consider any problems that may arise so that the misuse of TMS does not cause serious harm to an unspecified number of patients. As such, the role and responsibility of the professional community regarding TMS is important. Fortunately, as TMS therapy does not have the stigma and negative public image of tragic treatments that existed in the past, it will continue to be a meaningful treatment for many patients if we continue to focus on scientific evidence and take a sincere attitude toward the ethical issues that may arise.

Author Contributions
YN conceived of this work on his own, conducted the literature search, and wrote and discussed this review. The author contributed to editorial changes in the manuscript. The author read and approved the final manuscript. The author had participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate
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