Chapter 14

Transcranial magnetic stimulation and the human brain: an ethical evaluation

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Introduction

Transcranial magnetic stimulation (TMS) is a neuroscientific technique that induces an electric current in the brain via application of a localized magnetic field pulse. The pulse penetrates the scalp and skull non-invasively and, depending on the parameters of stimulation, facilitates or depresses the local neuronal response with effects that can be transient or long lasting. While the mechanisms by which TMS acts remain largely unknown, the behavioral effects of the stimulation are reproducible and, in some cases, are highly beneficial. As the applications of and access to this technique become increasingly pervasive, scientific engagement is needed to define the ethical framework in which research with TMS should be translated to application. In this chapter we review the technique in detail and discuss safety as the paramount ethics issue for TMS. We further examine the ethical arguments for and against neuroenhancement with TMS and how the framework for acceptable practice must differ for patient and non-patient populations.

A TMS primer

TMS is a relatively new neurophysiologic technique that allows the safe, non-invasive, and relatively painless stimulation of the human brain (Pascual-Leone *et al.* 2002; Walsh and Pascual-Leone 2003). TMS can be used to complement other neuroscience methods to study the pathways between the brain and the spinal cord and between different neuronal structures. It can be used further to validate the functional significance of neuroimaging studies in determining the causal relationship between focal brain activity and behavior. Most relevant for the present chapter is the way in which modulation of brain activity by repetitive TMS (rTMS) can transiently change brain function and be utilized as a therapeutic tool for treatment of a variety of neurological and psychiatric illnesses.

The principles that underlie TMS were discovered by Faraday in 1831. A pulse of electric current flowing through a coil of wire generates a magnetic field [Fig. 14.1(a)]. The rate of change of this magnetic field determines the induction of a secondary current in a nearby conductor. In TMS, the stimulating coil is held over a subject's head [Fig. 14.1(b)] and, as a brief pulse of current is passed through it, a magnetic field is generated that passes through the subject's scalp and skull without attenuation (only decaying by the square of the distance) [Fig. 14.1(d)]. This time-varying magnetic field induces a current in the subject's brain that depolarizes neurons and generates effects depending on the brain area targeted. Therefore, in TMS, neural elements are not primarily affected by the exposure to a magnetic field, but rather by the current induced in the brain by electrodeless non-invasive electric stimulation.

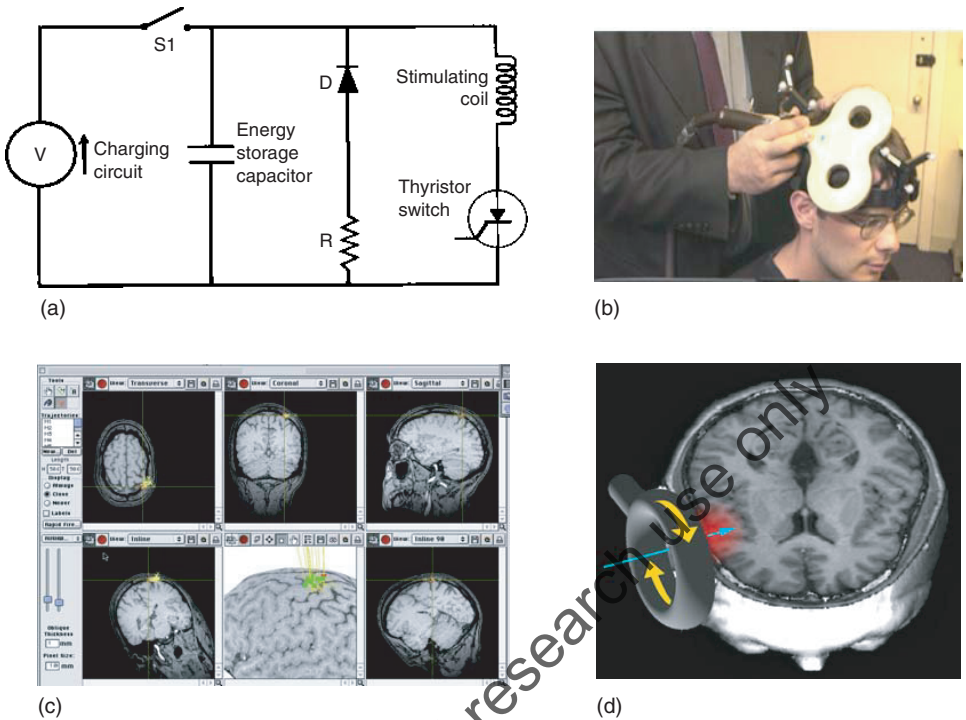

Fig. 14.1 Illustration of the application of TMS. (a) Schematic diagram of the electric circuit used to induce the TMS pulse. (b) The TMS coil being applied by an experimenter. Both the coil and the subject have a tracking device affixed to them so that the head/coil position can be monitored in real time. (c) Illustration of how the subject's MRI can be used, along with the tracking system which monitors head and coil movement, to display the cortical area being targeted in real-time. (d) Depth of effect of the TMS coil on the human cortex.

In the early 1980s, Barker and colleagues developed the first compact magnetic coil stimulator at the University of Sheffield. Soon after, TMS devices became commercially available. The design of magnetic stimulators is relatively simple. Stimulators consist 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 circuits for pulse shaping, energy recovery, and control functions (Fig. 14.2). Different charging systems are possible; the simplest design uses step-up transformers operating at line frequency of 50–60 Hz. Energy storage capacitors can also be of different types. The essential factors in the effectiveness of a magnetic stimulator are the speed of the magnetic field rise time and the maximization of the peak coil energy. Therefore large energy storage capacitors and very efficient energy transfer from the capacitor to the coil are important. Typically, energy storage capacity is around 2000 J and 500 J are transferred from the capacitors into the stimulating coil in less than 100 μs via a thyristor, an electronic device that is capable of switching large currents in a few microseconds. The peak discharge current needs to be several thousand amperes in order to induce currents in the brain of sufficient magnitude to depolarize neural elements (about 10 mA/cm^2).

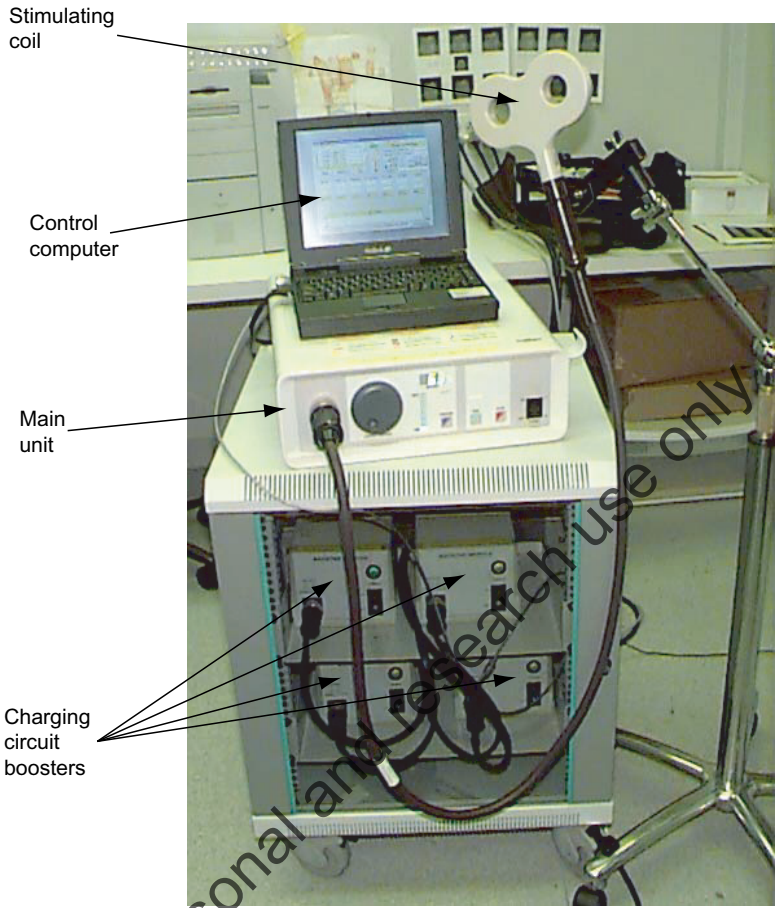

Fig. 14.2 TMS equipment including the charging circuit boosters, the main stimulating unit, the control computer, and the stimulating coil.

During transcranial magnetic brain stimulation only the stimulating coil needs to come into close contact with the subject [Fig. 14.1(b)]. Stimulating coils consist of one or more well-insulated coils of copper wire, frequently housed in a molded plastic cover, and are available in a variety of shapes and sizes. The geometry of the coil determines the focality of brain stimulation. Figure-of-eight coils, also called butterfly or double coils (Fig. 14.2), are constructed with two windings placed side by side and provide the most focal means of brain stimulation with TMS available to date. Current knowledge, largely based on mathematical modeling, suggests that the most focal forms of TMS available today affect an area of 0.5×0.5 cm at the level of the brain cortex (Wagner *et al.* 2004). Stimulation is restricted to rather superficial layers in the convexity of the brain (cortex or gray–white matter junction) and direct effect onto deep brain structures is not yet possible. Digitization of the subject's head and registration of the TMS stimulation sites onto the magnetic resonance image (MRI) of the subject's brain addresses the issue of anatomical specificity of the TMS effects by identifying

the actual brain target in each experimental subject [Fig. 14.1(c)]. The use of optical digitization and frameless stereotactic systems represents a further improvement by providing online information about the brain area targeted by a given coil position on the scalp.

The precise mechanisms underlying the brain effects of TMS remain largely unknown (Pascual-Leone *et al.* 2002; Robertson *et al.* 2003). Currents induced in the brain by TMS primarily flow parallel to the plane of the stimulation coil (approximately parallel to the brain's cortical surface when the stimulation coil is held tangentially to the scalp). Therefore, in contrast with electrical cortical stimulation, TMS preferentially activates neural elements oriented horizontally to the brain surface. Exactly which neural elements are activated by TMS remains unclear and, in fact, might be variable across different brain areas and different subjects. The combination of TMS with other neuroimaging and neurophysiologic techniques provides an enhanced understanding of the mechanisms of action of TMS and a novel approach to the study of functional connectivity between different areas in the human brain.

TMS in clinical neurophysiology and neurobehavioral studies

In clinical neurophysiology, TMS is primarily used to study the integrity of the motor fibers that connect the brain with the spinal cord ('central motor pathways') (Kobayashi and Pascual-Leone 2003). TMS is applied to the motor cortex and motor-evoked potentials are recorded using electromyography and surface electrodes tapped over the belly and tendon of the target muscle(s). Frequently, in order to interpret the results fully, motor cortex TMS has to be combined with peripheral nerve, nerve plexus, or spinal root stimulation. Such studies can provide important diagnostic and prognostic insights in patients with motor neuron disease (e.g. Lou Gehrig's disease), multiple sclerosis, stroke, or spinal cord lesion. The specific sites of stimulation, the recorded muscles, maneuvers used for facilitation of the motor-evoked potentials, and the evaluation of the different response parameters have to be tailored to the specific questions asked.

The development of generalized techniques offers the opportunity of widening the clinical uses of TMS. For example, paired-pulse TMS can be used to study intracortical excitability and to provide insight into the pathophysiology of movement disorders such as Parkinson's disease or the mechanisms of action of different medications. rTMS can be used in the study of higher cortical functions, for example the non-invasive determination of the language-dominant hemisphere. Finally, the integration of TMS with image-guided frameless stereotactic techniques can be used for non-invasive cortical mapping and thus can aid in the presurgical evaluation of neurosurgical patients [see Fig. 14.1(c)]. In addition to such clinical applications, TMS provides a unique tool for the study of causal relationships between brain activity and behavior. TMS delivered appropriately in time and space can transiently block the function of neuronal networks, allowing the creation of a time-dependent 'virtual lesion' in an otherwise healthy brain.

When rTMS trains of stimuli are applied to a given brain area at different stimulation frequencies, modulating the level of excitability of a given cortical area beyond the duration of the stimulation itself is possible (Pascual-Leone *et al.* 1998). Remarkably, depending on the stimulation frequency and intensity, potentiation or depression of cortical excitability can occur (Maeda *et al.* 2000). The possibility of enhancing behavior by applying rTMS at parameters that potentiate cortical excitability is intriguing and could have a profoundly

positive impact on neurorehabilitation and skill acquisition. Since a variety of neuropsychiatric conditions are associated with disturbed cortical activity, as documented by neuroimaging and neurophysiological studies, 'forced normalization' of such disturbed cortical excitability might lead to symptom improvement. However, this potential also raises a number of ethical concerns that warrant attention.

TMS: ethics, clinical research, and therapeutic potential

Guidelines for human subjects research in the United States are articulated in the *Belmont Report* (United States National Commission 1979). This report defines three governing principles that remain the gold standard for human subject research ethics: respect for persons, beneficence, and justice (see also Chapter 9).

The first principle of respect and the third principle of justice are well addressed in the TMS literature, especially with discussion of the basic ethical treatment of subjects [e.g. consent, exclusion and inclusion criteria) (Green 2002; Illes *et al.*, in press). The first clause of the second principle is considered at length in the literature on the guidelines for the safe use of single-pulse TMS as well as rTMS on the normal human brain (Wassermann 1998; Hallett *et al.* 1999). Taking this into account, we focus specifically on the issues of beneficence, and on finding the appropriate balance between benefit and risk of TMS.

The potential benefits of TMS for furthering the understanding of the workings of the human brain and for encouraging neurological enhancement and recovery are significant. By monitoring the effects of TMS on a specific neural node and the time course of those effects, TMS can give us new knowledge about the usage of that particular node (reviewed by Pascual-Leone *et al.* 2000). In the clinical population, TMS has shown promise for treatment of depression (reviewed by Gershon *et al.* 2003; Paus and Barret 2004), Parkinson's disease, writer's cramp (Siebner *et al.* 1999), and chronic pain (Pridmore and Oberoi 2000), as well as rehabilitation for motor neglect, motor stroke (Mansur *et al.*, in press), and aphasia (Martin *et al.* 2004; Naeser *et al.* 2005a,b), among others (Table 14.1).

When conducting new treatment trials with TMS, it is appropriate to recruit patients who have exhausted other less risky forms of treatment, and who have a severe form of a neurological disorder; however, one must also be aware of the potential for diminished individual autonomy in such 'desperate' patients (Miller and Brody 2003; Minogue *et al.* 1995). While

Table 14.1 Clinical applications of TMS research currently being pursued in research laboratories worldwide

Acute mania	Obsessive–compulsive disorder
Aphasia	Pain
Auditory hallucinoses	Visceral pain
Bipolar disorder	Atypical facial pain
Depression	Phantom pain
Epilepsy	Parkinson's disease
Myoclonic epilepsy	Post-traumatic stress disorder
Focal status epilepticus	Schizophrenia
Focal dystonia	Stuttering
Neglect	Tics

such patients might be more likely to participate in clinical trials even when risks are not minimized because the trials represent a last resort, careful oversight by an institutional review board can provide necessary safeguards and advocacy. This idea is utilized in US Food and Drugs Administration (FDA) clinical trials and it would appear reasonable to adapt this to the TMS field.

TMS, especially rTMS, remains an experimental technique. Side effects are possible and strict safety guidelines need to be followed to avoid adverse events. There re relative and absolute contraindications to TMS (Wassermann 1998; Hallet *et al.* 1999). Examples of these contraindications include metal anywhere in the head (excluding the mouth), cardiac pacemakers and implanted medication pumps, intracranial or intracardiac electrodes, raised intracranial pressure, pregnancy, a history of seizures, a family history of epilepsy, and patients taking medications that might increase the risk of seizures. The main safety concern when using TMS is its potential to induce a seizure, even in subjects without any predisposing illness. This risk is low (in the order of ≤ 1 in 1000 studies) and is essentially limited to the application of rTMS. Approximately 10–20 percent of subjects studied with TMS develop a muscle tension headache or a neck ache. These are generally mild discomforts that respond promptly to aspirin, acetaminophen (Tylenol®), or other common analgesics. rTMS can also cause ringing in the ears (tinnitus) or even transient hearing loss if the subjects do not wear earplugs during the studies. Furthermore, TMS can cause mild and very transient memory problems and other cognitive deficits, and mood and hormone changes. These rare adverse effects are usually resolved within hours of cessation of TMS).

The major risk of TMS is the risk of producing a seizure. The likelihood of inducing a seizure is small (only nine seizures induced by rTMS have been reported worldwide) but is increased with increasing frequency and intensity of stimulation and with family history of seizure and/or ingestion of pro-epileptic drugs. The parameters of TMS that have produced seizures during experimentation are well known and documented (Wassermann 1998; Hallett *et al.* 1999), and it is important to note that there are no reports of seizure in subjects who were treated with TMS parameters administered within the safety guidelines (Wassermann 1998). Nonetheless, TMS has only been studied for approximately 20 years and the data on potential long-term effects in humans remain insufficient. Although animal studies using TMS have not indicated any risks of brain damage or long-term injury, caution remains imperative.

Since safety guidelines (Wassermann 1998) were generated from information on TMS of the healthy adult human brain, little is known about the appropriate safety guidelines for patient populations and for the developing brain. Great care must be taken when conducting studies involving such populations, and the fact that there are unknown risks because of incomplete safety data should be appropriately described to patients. For example, patients with infarcts or neurological disorders that cause cortical atrophy should be stimulated with great care as the presence of excess cerebrospinal fluid (CSF) can alter the electromagnetic field properties, and stimulation near CSF could cause adverse effects (Wagner *et al.* 2004).

Only seven pediatric patients are reported in the rTMS literature (reviewed by Walter *et al.* 2001). These patients all had psychiatric disorders and one reported an adverse effect (tension headache). Even though rTMS offers the potential for treating developmental disorders like autism, childhood depression, and obsessive–compulsive disorder among others, it is still not appropriate to carry out research on children until safety parameters are known for the developing brain. Clinical trials on children who have medication-refractory focal epilepsy represent a reasonable entry point given the current state of theart (Thut and Pascual-Leone 2004).

Ethical considerations of TMS in basic neuroscience research

Previously, scientists relied on naturally occurring lesions in the human brain (from stroke or other brain damage) to draw conclusions about the functioning of specific neural regions. However, such data are imprecise, irreversible, and do not always occur in isolation from other neurological disorders. Since TMS (at least single-pulse TMS) has only a transient effect, it can be utilized to investigate the importance of a given brain area in the normal functioning human brain by creating a temporary 'virtual lesion' (Pascual-Leone *et al.* 2000; Walsh and Pascual-Leone 2003). For this reason, TMS is used to investigate a myriad of neuroscientific questions about the functioning of the normal human brain.

Some studies have aimed at understanding the early sensory processing system (Amassian *et al.* 1989; Corthout *et al.* 1999) using single-pulse TMS at different time-points after visual stimulation, while others have investigated higher visual processing (Ashbridge *et al.* 1997) with the same relatively safe parameters. Motor processing is also studied extensively with single-pulse TMS on normal subjects (Robertson *et al.* 2003; De Gennaro *et al.* 2004; Theoret *et al.* 2004).

rTMS studies at rates of repetition well below safety limits are also conducted on normal subjects to investigate phenomena varying from self-recognition (reviewed by Keenan *et al.* 2000) to sequence learning (Robertson and Pascual-Leone 2001). However, some studies utilize rTMS at parameters nearing the limit of safety guidelines. Further ethical consideration is needed here.

For example, researchers have recently begun to investigate the induction of long-term depression (LTD) and long-term potentiation (LTP) (the mechanisms of neuroplasticity) using rTMS protocols in the normal human brain (Iyer *et al.* 2003; Huang *et al.* 2004). These studies, while scientifically worthwhile, challenge the risk–benefit ratio. The benefit of such research is that learning how to induce LTD and LTP could have implications for treatment of diseases like depression, epilepsy, Parkinson's disease, and other neurological disorders. However, the risks are also quite high. As described above, increasing the length and rate of stimulation both contribute to the higher risk of seizure. LTP induction requires only 20–190 s, but must be applied at 50 Hz (in the theta range). The parameters necessary to induce LTD are not of as much concern because they involve stimulation at a relatively low repetitive rate (6 Hz followed by 1 Hz), although it must be applied for a long period of time (20 min). However, the greatest risk is that both forms of stimulation attempt to produce a long-term effect without a priori knowledge of know how long this effect will last and what the outcome will be for the subject.

Is the increased risk of seizure and the unknown transience of the effect an ethically responsible risk to undertake given the lack of benefit for the subjects involved? Would not the same studies on animal models yield appropriate conclusions and a lesser ethical concern? Here, it seems, that the principle of beneficence might well be revisited.

TMS and neuroenhancement

Is neuroenhancement in the non-patient population, i.e. non-therapeutic uses of TMS for enhancing cognitive or affective function, ethical? Does the benefit of increasing mental facility above and beyond natural levels justify an increased risk, as neurorehabilitation benefits might justify increased risk in the patient population?

The idea that targeted brain stimulation (excitatory or inhibitory) can enhance or beneficially alter cognitive function has not been lost on the Hollywood film industry [see *Total Recall*

(1990) or *Eternal Sunshine of the Spotless Mind* (2004)], let alone the scientific community. However, this is not a futuristic issue, as recent studies using TMS and other forms of non-invasive stimulation, such as direct current stimulation, are exploring neuroenhancing applications in the normal population (Antal *et al.* 2004; Kobayashi *et al.* 2004). For instance, Kobayashi *et al.* (2004) discovered that by inhibiting cortical activity in the right motor cortex (which controls the left hand), the reaction time to a sequential finger movement task can be increased in the right hand without affecting the performance in the left hand Similarly, Hilgetag *et al.* (2001) found enhanced attention to the ipsilateral field of a person's spatial environment in normal subjects following suppression of the parietal cortex by rTMS. Others have reported facilitatory behavioral effects of rTMS on working memory, naming, abstract thinking, color perception, motor learning, and perceptual learning (reviewed by Theoret *et al.* 2003).

Snyder *et al.* (2003) reported that latent savant-like qualities could be revealed in normal control subjects following low-frequency rTMS to the left frontotemporal cortex. Subjects (11 right-handed males) performed a battery of tests before, immediately after, and 45 min after rTMS treatment. These tests included drawing animals from memory, drawing novel faces from images provided by the researcher, and proofreading. Of 11 subjects, four showed dramatic stylistic changes in drawing immediately after rTMS compared with the drawings produced before and 45 min after stimulation. This TMS-induced unmasking of increased artistic and language abilities was surprising to the subjects. One subject, who wrote an article about his experiences, commented that he 'could hardly recognize' the drawings as his own even though he had watched himself render each image. He added: 'Somehow over the course of a very few minutes, and with no additional instruction, I had gone from an incompetent draftsman to a very impressive artist of the feline form' (Osborne 2003).

Whether or not savant-like capabilities can be revealed in all persons is a matter of debate. Morrell *et al.* (2000) conducted a study similar to that of Snyder *et al.* (2003) with only minimal success, suggesting that factors like sex, age, genes, and environment might play a role in determining whether or not TMS can induce savant-like responses in the normal population (just as these factors probably play a role in whether or not neurological damage leads to savant symptoms in the patient population). However, it remains a distinct possibility that TMS could soon induce reliable neuroenhancement of motor, attentional, artistic, or language abilities in the normal human brain.

Weighing the dynamic capabilities of the brain and our moral values

In the not too distant future, we could have students using their at-home TMS machines to 'zap' their parietal lobes before taking SATs, or their prefrontal cortices before going to art class. Some believe that enhancement by neurostimulation is no different than enhancement by education, as both are presumably a result of altering neuronal firing and modulating brain plasticity (Pascual-Leone *et al.* 1998). There exist ethicists who argue both for (Caplan 2003) and against (Sandel 2002; Kass 2003) enhancement. Michael Sandel, a member of the President's Council on Bioethics, raises the concern that enhancement poses a threat to human dignity. Sandel believes that '. . . what is troubling about enhancement is that it represents the triumph in our time of wilfulness over giftedness, of dominion over reverence, of molding over beholding' (Sandel 2002). However, the capacity of being molded (plasticity) is an intrinsic property of the human brain and represents evolution's invention to enable the nervous system

to escape the restrictions of its own genome and thus to adapt to environmental pressures, physiological changes, and experiences. Dynamic shifts in the strength of pre-existing connections across distributed neural networks, changes in task-related cortico-cortical and cortico-subcortical coherence, and modifications of the mapping between behavior and neural activity take place continuously in response to any and all changes in afferent input or efferent demand. Such rapid ongoing changes might be followed by the establishment of new connections through dendritic growth and arborization. Plasticity is not an occasional state of the nervous system; instead, it is the normal ongoing state of the nervous system throughout the lifespan. Therefore we should not conceive of the brain as a stationary object capable of activating a cascade of changes that we shall call plasticity, nor as an orderly stream of events driven by plasticity. We might be served better by thinking of the nervous system as a continuously changing structure of which plasticity is an integral property and the obligatory consequence of each sensory input, each motor act, association, reward signal, action plan, or awareness. In this framework, notions of psychological processes as distinct from organic-based functions or dysfunctions cease to be informative. Behavior will lead to changes in brain circuitry, just as changes in brain circuitry will lead to behavioral changes. Therefore all environmental interactions, and certainly educational approaches, represent interventions that mold the brain of the actor. Given this perspective, it is conceivable that neuromodulation with properly controlled and carefully applied neurophysiological methods could be potentially a safer, more effective, and more efficient means of guiding plasticity and thus shaping behavior. Plasticity is a double-edged sword, to be sure, and harbors dangers of evolving patterns of neural activation that might in and of themselves lead to abnormal behavior. Plasticity is the mechanism for development and learning, as much as it can be the cause of pathology.

Therefore the challenge we face as scientists is to learn enough about the mechanisms of plasticity to be able to determine the parameters of TMS that will *optimally* modulate neuronal firing for patients, and perhaps for the non-patient population. Defining 'optimal' is the accompanying immediate ethical challenge. Overcoming inequities of access to the underserved and coercion will follow (Farah *et al.* 2004).

TMS scientists and neuroethicists would do well jointly to take the lead in pursuing these issues further and in ensuring that utilization parameters of TMS for neurorehabilitation and enhancement become clearly defined.

Acknowledgments

The work on this article was supported by K24 RR018875, RO1-EY12091, RO1-DC05672, RO1-NS 47754, RO1-NS 20068, and R01-EB 005047. The authors would like to thank Mark Thivierge for the invaluable administrative support.

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