As this technology evolves, new diagnostic and therapeutic applications are emerging. Here’s a preview of how it could eventually fit into clinical practice.

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The treatment of illnesses with magnetized iron-containing stones was practiced in ancient Egyptian and Greek medicine. In 18th century Europe, Franz Mesmer claimed to heal the sick with magnetism, believing that magnetic forces held a special power over human behavior. Magnetic fields were then applied in the treatment of neurologic disorders. Various reports in 20th century European medical literature indicate the use of electromagnetism in the treatment of peripheral neuropathies and neuromuscular disorders. In the 1990s, considerable publicity was given to claims that magnets promoted the healing of various disorders of the body. Rarely, however, were these claims supported by controlled studies. It was in this atmosphere, one of popular interest in magnetic therapy, that transcranial magnetic stimulation (TMS) of the cerebral cortex evolved as a scientific tool and gained acceptance in neuropsychiatry.

Transcranial magnetic stimulation is capable of producing the same effect as electrical stimulation of the cortex. Yet, contrary to the conditions of electrical stimulation, TMS achieves its ends by using painless means. This device was adopted by neurologists for measuring nerve conduction time. Single-pulse transcranial magnetic stimulation has moved into the routine clinical neurophysiology laboratory.

This article reviews the applications of TMS in the diagnosis and treatment of neurologic disorders as distinct from electrical stimulation of the brain, as well as from the uses of magnetic fields over the whole body for healing of various diseases including neurologic disorders.

Scientific Basis & Physiological Effects

The effects of magnetic energy on the nervous system have been investigated extensively, and the physiological effects of transcranial magnetic stimulation have been well documented. Transcranial magnetic stimulation may be applied in either a single-pulse or paired-pulse protocol. Single pulses affect brain function for just a few milliseconds. Repeated rhythmic application is called repetitive transcranial magnetic stimulation (rTMS). If the stimulation occurs faster than once per second (1 Hz), it is referred to as fast-repetitive transcranial magnetic stimulation.

Changes may be induced in the electrochemical properties of the neurons by rTMS; these persist for some time after the termination of the stimulation. A rapid method of conditioning the human motor cortex using low intensity rTMS at 50 Hz produces a long-lasting effect on motor cortex in healthy people after an application period of only 20 to 190 seconds. This is a version of the classic theta burst stimulation protocol and has implications for the development of clinical applications of rTMS.

Cortical excitability increases with higher frequency pulses and decreases with lower frequency pulses. With the ability to increase or decrease cerebral activity, repetitive transcranial magnetic stimulation can partially correct overactivity or underactivity and has the potential to “tune” the cortex. Preliminary evidence from positron emission tomography scans suggests that higher frequency (20 Hz) stimulation may increase brain glucose metabolism in a trans-synaptic fashion, whereas lower frequency (1 Hz) stimulation may decrease it.

Mechanisms of action of transcranial magnetic stimulation. Transcranial magnetic stimulation-evoked motor responses result from direct excitation of corticospinal neurons at or close to the axon hillock. Repetitive transcranial magnetic stimulation has been reported to induce the following changes that can be exploited for therapeutic purposes:

• Changes in brain monoamines.
• Reduction of the detrimental effects of oxidative stress in neurons that may have a neuroprotective effect.
• Changes in beta-adrenergic receptor binding.
• Gene induction.
• Changes in cerebral blood flow.

Transcranial magnetic stimulation preferentially activates different structures than transcranial electrical stimulation. These differences occur because different structures in the motor cortex have a differential threshold to the different techniques of stimulation.

Technology. A typical magnetic stimulator is capable of discharging 3000 to 8000 amperes through a hand-held wire coil. When the current is rapidly turned on and off in the coil, through the discharge of capacitors, a magnetic field lasting for about 100 to 200 microseconds is produced. The magnetic field created around the coil has a strength of 2-tesla to 3-tesla. When the coil is held against the skull, a secondary current is induced in the underlying cortical neurons which serves to trigger action potentials. With current technology, the area of depolarization is limited to a depth of about 2cm below the brain’s surface. Stimulation of one hemisphere can inhibit or facilitate responses elicited in the opposite hemisphere, indicating interhemispheric modulatory effects.

Cortical mapping by stimulation. A single transcranial magnetic stimulation pulse of sufficient intensity over the motor cortex can cause involuntary movement. Placing the coil over different areas of the motor cortex causes contralateral movement in different muscles, corresponding to the well-known homunculus. Transcranial magnetic stimulation can then be used to map the representation of body parts in the motor cortex on an individual basis.

Applied over the primary visual cortex, transcranial magnetic stimulation can produce the perception of flashes of light. No reports of the elicitation of memories, smells, or other complex psychological phenomena like those reported during direct cortical stimulation in epilepsy surgery have been
advanced. Possible explanations include the lack of TMS usage as an adjunct of epilepsy surgery and the spread of electric current beyond the point of direct cortical stimulation.

TMS has been applied to study plasticity following amputation and cortical excitability in patients with dystonia.\(^\text{10}\) This approach can also be used for mapping clinically relevant plasticity after stroke.

**Three-dimensional cerebral mapping.** The TMS-compatible multichannel EEG system makes it possible to locate TMS-evoked electric activity for the purpose of brain mapping. Association of the 3-D positions of the transcranial magnetic stimulation probe on the scalp enables a 3-D brain reconstruction. Besides EEG, neuroimaging techniques (e.g., PET and MRI) can be combined with repetitive transcranial magnetic stimulation to assess connectivity and excitability in the cerebral cortex.\(^\text{11}\)

**Investigation of central motor conduction.** Transcranial magnetic stimulation has been used for testing central motor conduction in patients with amyotrophic lateral sclerosis, and also provides evidence for motor cortex dysfunction in movement disorders such as Parkinson disease or dystonia.\(^\text{12}\) TMS-induced motor-evoked potentials can be used to detect spinal cord ischemia during surgery for thoracoabdominal aneurysms.

Transcranial magnetic stimulation has been used as a prognostic tool in stroke patients. Presence of motor-evoked potentials following a stroke is usually considered a sign of good outcome. Absence of response to transcranial magnetic stimulation during the first hours following stroke indicates a poor outcome for motor recovery of the hand.\(^\text{13}\) TMS along with EEG and brain imaging has led to the identification of mechanisms underlying recovery of motor function after stroke, which have enabled novel strategies for rehabilitation of stroke patients.\(^\text{14}\)

**Study of brain-behavior relations.** TMS can create virtual lesions, thereby enabling determination of the contribution of a given cortical region to a specific behavior.\(^\text{15}\) PET studies done during transcranial magnetic stimulation might identify the area of the brain activated.\(^\text{16}\) When combined with functional neuroimaging, transcranial magnetic stimulation can be used to study the neural networks involved in a given behavior.\(^\text{17}\) Thus, TMS is a tool for cognitive neuroscience and can be used to map the functional connectivity between brain regions.

**TMS has been used as a prognostic tool in stroke patients. The presence of motor-evoked potentials is considered a good sign.**

**Combination of TMS with fMRI.** A reflective tag, which can be tracked by an optical sensor, is attached to the coil, allowing the coil’s position to be displayed on the MRI scan. This and similar methods should allow the neural connections within the brain to be mapped out. This can enable the investigation of how tasks such as learning change neural connections.

**Investigation of pathomechanism of cerebellar tremor.** Tremor can be induced by repetitive transcranial magnetic stimulation at 10 Hz to 30 Hz and intensities above motor threshold when applied over the motor cortex. This is similar to cerebellar tremor, suggesting that cerebellar tremor is caused by interference with adaptive cerebellar afferent inflow to motor cortex. Further, rTMS-induced tremor may be a model of some cerebellar tremor.\(^\text{18}\) Repetitive transcranial magnetic stimulation has been shown to reset orthostatic tremor due to cerebellar atrophy, but not primary orthostatic tremor.\(^\text{19}\)

**Peripheral nerve conduction studies.** Although transcranial magnetic stimulation can be used to stimulate the peripheral nerves, it is not suitable for routine nerve conduction studies because the site of stimulation is uncertain. It is useful in situations where location of the exact site of stimulation is not important and electrical stimulation is painful. One example of a useful application in the peripheral nervous system is the evaluation of the conduction in the cauda equina.\(^\text{20}\)

**Diagnostic Applications**

Navigated transcranial magnetic stimulation is a reliable alternative for localizing cortical functions and may be a useful adjunct to other functional neuroimaging methods.\(^\text{21}\)

The latency of motor responses evoked by single-pulse transcranial magnetic stimulation conveys information about conduction velocity. The difference in latency for responses evoked with cortical and cervical spinal transcranial magnetic stimulation assesses the central motor conduction time. This method is useful in the following conditions:

**Amyotrophic lateral sclerosis.** A high rate of central motor conduction abnormalities has been found in patients with amyotrophic lateral sclerosis who do not have definite upper motor neuron signs. Transcranial magnetic stimulation can contribute to a more reliable diagnosis in these patients.

**Multiple sclerosis.** Central motor conduction time has been found to be abnormal in 72 percent of patients with multiple
sclerosis. Central motor conduction was also delayed in other disorders associated with white matter hypomyelination.

**Evaluation of pharmaceutical prophylaxis of migraine.** Transcranial magnetic stimulation has been used to measure occipital cortex excitability as a noninvasive adjunct to assessment of migraine prophylaxis with sodium valproate.

**Therapeutic Applications**

Although many successes have been reported concerning treatment of neurologic disorders by transcranial magnetic stimulation, the results of blinded, sham-controlled trials do not provide clear evidence of beneficial effects that replace or even match the effectiveness of conventional treatments in any disorder. The use of repetitive transcranial magnetic stimulation has been explored in the following conditions:

**Epilepsy.** Low-frequency repetitive transcranial magnetic stimulation leads to 70 percent reduction in the frequency of seizures and a 77 percent reduction in the frequency of interictal spikes. This finding supports the concept of cortical inhibition induced by low-frequency repetitive transcranial magnetic stimulation.

Paired-pulse inhibition is reduced in focal epilepsy and enhanced by gamma-aminobutyric-acid agents. Pharmacological manipulations suggest that intracortical paired-pulse inhibition reflects the activation of inhibitory gamma-aminobutyric-acid-ergic and dopaminergic interneurons, whereas paired-pulse facilitation reflects excitatory N-methyl-D-aspartate-mediated interneurons, and ion channel conductivity modulates motor threshold. These profiles provide novel methods for investigating local alterations in neurochemical systems in epilepsy.

Transcranial magnetic stimulation can be used for assessing the efficacy of a particular drug in an epilepsy patient and for monitoring antiepileptic drugs levels. Changes in threshold intensity of transcranial magnetic stimulation in response to anticonvulsant treatment may prove useful in guiding therapy. Paired-pulse transcranial magnetic stimulation can be used as an in vivo method in the assessment of the transcranial magnetic stimulation of drug effects on cortical facilitatory, as well as inhibitory phenomena. Single-pulse transcranial magnetic stimulation can be used to evaluate the effect of an antiepileptic drug in patients with seizures using motor threshold, motor-evoked potential amplitude, cortical silent period, and peripheral conduction velocity as parameters. Loading doses of lamotrigine, administered as monotherapy for complex partial seizures, were demonstrated to progressively increase patients’ motor thresholds over short periods while using this method.

The incidence of seizure in a subject with epilepsy during single pulse transcranial magnetic stimulation and paired pulse transcranial magnetic stimulation appears to be small and not associated with long-term adverse outcome. Such seizures may be coincidental occurrence but the patient should be informed about this possibility prior to the procedure.

**Depression.** Repetitive transcranial magnetic stimulation is used for the care of treatment-resistant depression. This has been investigated in several open as well as controlled clinical trials. In an open study, rTMS was as effective as electroconvulsive therapy in the treatment of major depressive disorders. In contrast to electroconvulsive therapy, repetitive transcranial magnetic stimulation does not require the generation of a major motor seizure to achieve therapeutic efficacy. Therefore, it obviates the need for general anesthesia and avoids side effects such as transient memory loss, which is seen following electroconvulsive therapy. Several randomized studies have compared electroconvulsive therapy and repetitive transcranial magnetic stimulation but the current belief is that the two therapies are complementary rather than competitive.

**Table 1. Indications for Transcranial Magnetic Stimulation**

| Diagnostic (single-pulse TMS): |
| Measuring speed of conduction in the central motor pathways (e.g., multiple sclerosis). |
| Measuring nerve conduction in cauda equina. |
| Mapping cerebral cortical functional. |
| Evaluating the efficacy of drug action on the brain. |
| Determining location of the motor cortex during neurosurgical procedures. |
| Determining prognosis in post-stroke hand palsy. |

| Therapeutic (repetitive TMS): |
| Depression and other psychiatric disorders |
| Epilepsy |
| Parkinson’s disease |
| Multiple sclerosis |
| Stroke rehabilitation |
| Chronic pain |
Retticulocentric magnetic stimulation treatment can be useful in the treatment of depression associated with Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. 31

**Parkinson's disease.** Dose dependency between the applied electromagnetic field in repetitive transcranial magnetic stimulation and parkinsonian symptoms has been demonstrated with long-term maintenance of the improvement. Daily application of repetitive transcranial magnetic stimulation in patients with Parkinson's disease causes significant improvements beyond the maximal benefit obtained from drug therapy. 32 Therapeutic efficacy by application of pulsed electromagnetic fields in the picotesla flux density in PD involves the activation of dopamine D2 receptor sites, which are the principle sites of action in dopaminergic pharmacotherapy. Transcranial magnetic stimulation at 7 Hz frequency has been reported effective in improving olfactory loss in Parkinson's disease for dopamine released into the synapses of the olfactory bulb during magnetic stimulation may cause activation of these supersensitive receptors resulting in an enhanced sense of smell. 33

Another explanation is that rTMS increases the responsivity of the motor cortex in Parkinson's disease. A study on unmedicated patients with Parkinson disease showed that 5 Hz repetitive transcranial magnetic stimulation over the motor hand area could improve bradykinesia beyond the time of magnetic stimulation. 34 Isolated case reports of improvement of olfactory loss in Parkinson's disease for dopamine released into the synapses of the olfactory bulb during magnetic stimulation may cause activation of these supersensitive receptors resulting in an enhanced sense of smell. 35

**Huntington's disease.** Repetitive transcranial magnetic stimulation can improve choreic movements in Huntington’s disease patients. 36

**Multiple sclerosis.** Transcranial magnetic stimulation, with pulsed electromagnetic fields in the picotesla flux density, has been useful in the symptomatic treatment of multiple sclerosis. One case report exists of visual acuity improvement and visual-evoked response following transcranial magnetic stimulation treatment in a multiple sclerosis patient who developed optic atrophy following optic neuritis. 37 The explanation offered was that there was an enhancement of neurotransmitter functions in the retina and central optic pathways. No controlled studies of transcranial magnetic stimulation have been done in such patients.

**Essential tremor.** An exploratory study of the potential therapeutic properties of repetitive transcranial magnetic stimulation on essential tremor showed an acute antitremor effect. 38 Further investigation in search of a more lasting benefit is warranted.

**Neurologic rehabilitation.** Paired-pulse transcranial magnetic stimulation techniques have been used for identification of the mechanisms underlying neuroplasticity. Cortical function can be modulated with rTMS to influence behavior and guide plasticity. 39 Mapping the central representation of muscles provides a method for investigating the cortical reorganization that follows training, amputation and injury to the central nervous system. Such studies of human plasticity may have important implications for neurologic rehabilitation. By increasing the activation threshold of the cortical neurons, repetitive transcranial magnetic stimulation may increase the speed at which the cortex acquires a new function, and may facilitate poststroke rehabilitation.

Transcranial magnetic stimulation can be used to treat hemispatial neglect due to damage the parietal cortex on one side. This is based on the concept that when parietal cortex is damaged on one side, the other side becomes hyperactive to compensate for this. Transcranial magnetic stimulation might be able to balance the activity by creating a virtual lesion in the undamaged side and initial results are promising, with the patients showing improved awareness during stimulation. 40

By increasing the activation threshold of the cortical neurons, repetitive transcranial magnetic stimulation may increase the speed at which the cortex acquires a new function, and may facilitate poststroke rehabilitation. In a controlled trial on stroke patients within 12 months of onset, repetitive transcranial magnetic stimulation of the unaffected hemisphere decreased interhemispheric inhibition of the affected hemisphere and improved motor function. 41

**Stroke management.** By increasing the activation threshold of the cortical neurons, repetitive transcranial magnetic stimulation may increase the speed at which the cortex acquires a new function, and may facilitate poststroke rehabilitation. In a controlled trial on stroke patients within 12 months of onset, repetitive transcranial magnetic stimulation of the unaffected hemisphere decreased interhemispheric inhibition of the affected hemisphere and improved motor function. 42

**Chronic pain.** Use of transcranial magnetic stimulation for management of chronic pain has been suggested based on the success of electrical stimulation of the cerebral cortex in relieving pain. The mechanism of this analgesic effect is unknown. Transcranial magnetic stimulation might influence the affec-
tive-emotional component of chronic pain by means of cingu-
late and orbitofrontal activation, which leads to descending
inhibition of pain impulses by activation of the upper brain-
stem. In a pilot study with 12 patients, no significant differ-
ences could be demonstrated between active and sham treat-
ment, although some patients had a remarkable benefit from
the treatment. Transient but significant relief of drug resistant
neurogenic pain has been achieved by repetitive transcranial
magnetic stimulation in another study.

Migraine. It may be possible to assess long lasting metabol-
ic effects of repetitive transcranial magnetic stimulation on the
cortex and subcortical structures with functional imaging
methods and to explore novel therapeutic strategies for
migraine.

ADVERSE EFFECTS
Risk and safety of repetitive transcranial magnetic stimulation
and suggested guidelines for use of this technique have been doc-
umented in a publication based on an international workshop
on this topic. Single-pulse transcranial magnetic stimulation is
considered to be safe and provide no adverse effects. Although
tissue damage is unlikely following transcranial magnetic stimu-
lation, adverse effects have been observed following repeated
stimulations and the possibility of unintended long-term
changes in brain function are theoretically possible. The follow-
ing are examples of events that may occur following repetitive
transcranial magnetic stimulation:

Headache. Low-intensity transcranial magnetic stimulation
is usually painless; but stimulation at higher intensities and fre-
cuencies is generally more painful. The pain is most likely due to
the repetitive stimulation of peripheral facial and scalp muscles.
As a result, muscle tension headaches are reported in 5-20 per-
cent of patients in various studies. These headaches respond to
treatment with acetaminophen or aspirin.

Seizures. Low-frequency repetitive transcranial magnetic
stimulation has been used for inhibition of seizure activity.
Alternatively, high-frequency repetitive transcranial magnetic
stimulation, used for the treatment of depression, may provoke
seizure activity. This is rare because only a few patients with
repetitive transcranial magnetic stimulation-induced seizures
have been reported to date. In one patient with depression, a
complex partial seizure was observed following repetitive tran-
Transcranial Magnetic Stimulation

Scien
tal magnetic stimulation over the left dorsolateral-pre
tfrontal cortex. A few cases have also been reported in normal volunteers. The transcranial magnetic stimulation-induced seizures are usually self-limiting and do not seem to leave permanent sequelae. The risk of seizure induction is related to the parameters of stimulation. No seizures have been reported with single-pulse transcranial magnetic stimulation or repetitive transcranial magnetic stimulation delivered at a low frequency.

Working memory impairment. Verbal memory and reaction performance are usually not impaired after repetitive transcranial magnetic stimulation. Evidence exists, however, of transient working memory impairment associated with reduction in regional cerebral blood flow as shown by positron emission tomography during right or left dorsolateral prefrontal cortex stimulation by repetitive transcranial magnetic stimulation. This is important because these areas are stimulated for the treatment of depression.

Conclusion

Although transcranial magnetic stimulation is unlikely to replace the more conventional treatment modalities for its multifarious indications, it is emerging as a viable alternative and/or complement, as well as a diagnostic imaging tool of high specificity. At present, cost and accessibility issues limit acceptance of TMS in general neurology practice. However, as the body of research on TMS applications continues to grow, it is reasonable to expect more widespread integration of the technology into clinical practice in the future. PN

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