Transcranial Magnetic Stimulation and Schizophrenia

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This article describes challenges for psychiatrists striving to ensure informed consent for, and for patients who may lack full appreciation of the risks and benefits of, neurostimulation.

Electrical current flowing through a coil induces a magnetic field. This is the basis for MRI, a technology that has been groundbreaking in furthering our understanding of the human brain with respect to structure and function. Correspondingly, changes in magnetic fields can also induce electrical currents. When applied in proximity to live brain tissue, alternating magnetic fields can induce electrical currents that will lead to depolarization in neurons, causing them to fire. Thus, we can use electromagnetism not only to image the brain, but to probe it.

Transcranial magnetic stimulation (TMS) uses coils of various shapes and sizes held near the scalp to stimulate the brain beneath the skull; a figure-8 coil is commonly used (Figure). Electric current flows through the coil, quickly reversing the direction of flow and inducing alternating magnetic fields. Magnetic fields easily cross the scalp and skull and induce electrical current in the underlying cortex, with downstream effects in functionally connected brain regions. The depth of penetration of the magnetic field is approximately 2 centimeters, reaching the junction between gray and white matter, at which point it is dissipated to about half of its initial strength. Interneurons and GABA fibers are more amenable to TMS as they are parallel to this induced electrical field, whereas pyramidal neurons are less so, because they are more perpendicular in orientation with respect to the scalp. The cerebral cortex is excitable and responds to electrical and magnetic stimulation. The excitability of the cortex is influenced by many factors, including medications, caffeine, sleep deprivation, and even expectancy of response. When the motor cortex is stimulated with TMS pulses, motor responses can be evoked. Think back to the homunculus you learned about in medical school that lies along the motor cortex, which begins inferiorly with the mouth, then rises to the face, then hands and arms, then torso, with the feet dangling from the top of the homunculus into the interhemispheric medial longitudinal fissure that separates the 2 hemispheres. When you stimulate the area that corresponds to the thumb, the thumb will move. In doing so, you can estimate a person’s cortical excitability at a certain point by calculating the resting motor threshold —the minimum pulse strength necessary to elicit a twitch in at least 6 of 10 stimulation pulses. TMS is an important tool in brain mapping, as direct activation of circuits can immediately elicit or disrupt observable responses; it can be particularly informative when used with brain imaging and electrophysiology. With respect to therapeutics, the delivery of a series of repetitive pulses (rTMS) has more lasting modulatory effects on neuroplasticity and functional connectivity of the brain and has been developed to treat neuropsychiatric disorders. When pulses are delivered at a high frequency, more than once per second, the result is excitation (increased firing) of the target neural tissue. When pulses are delivered at a low frequency, fewer than 1 per 10 seconds, the result is inhibition (decreased firing) of the target neural tissue (see Figure).

Safety

TMS has an excellent safety profile —in low-risk patients. Therefore, it is essential to adequately screen for risk factors such as a personal or familial history of seizures. The use of medications that alter the seizure threshold, history of head injury, and extent of sleep deprivation must also be assessed. The dose of TMS pulses is tailored to an individual’s resting motor threshold, which also promotes safety. When planning the use of TMS, a protocol to manage any emergent seizures must be in place —practice the protocol in advance of initiating TMS. TMS pulses are louder than they seem, given that they are so brief. Although reports of hearing damage are rare, patients who receive TMS must wear ear plugs. More commonly, muscle pain and headache can occur as TMS leads to repeated muscle contraction underneath the coil. These symptoms generally respond to nonsteroidal anti-inflammatory agents or acetaminophen. Overall, it is recommended that you read the article by Rossi and colleagues,1 “Safety, Ethical Considerations,
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TMS can be used to identify brain circuits affected by injury or disease, and then to modulate activity in these circuits to improve function. This strategy has been applied to many different neurological and psychiatric disorders. In some disorders, activity in essential brain circuits needs to be upregulated to restore function. In other disorders, activity in essential brain circuits requires downregulation to restore function. Repetitive TMS can be selectively applied to inhibit or excite brain regions in a variety of disorders.

For example, with respect to neurological disorders, TMS was used to map motor plasticity to demonstrate the specific effects of structured skill training compared with unstructured practice on hand use and dexterity in children with unilateral spastic cerebral palsy. The findings suggested increases in the hand motor map and in amplitudes of motor evoked potentials, correlates of improved hand function and indices of motor cortex plasticity. TMS can also be used to facilitate recovery from aphasia due to stroke. The proposed mechanism for this is that TMS releases language networks undamaged by the stroke in the left hemisphere with right hemisphere transcortical inhibition.

TMS and schizophrenia

The use of rTMS for schizophrenia is considered off-label —there has not been a definitive multisite randomized controlled clinical trial similar to the one that supported FDA approval for MDD. The primary use of rTMS in schizophrenia has been for the reduction of otherwise treatment-refractory auditory hallucinations, specifically inhibitory low-frequency 1-Hz stimulation to the left temporoparietal regions. These areas have abnormally increased activity or metabolism associated with hallucination severity. Another treatment strategy for schizophrenia is high-frequency stimulation of the left DLPFC to reduce the negative symptoms of schizophrenia, such as low motivation. Finally, there have been efforts to use rTMS, and non-invasive brain stimulation (NIBS) more broadly, to characterize and remediate cognitive deficits in schizophrenia.

The research on TMS for each of these indications is described below, with supporting evidence from other NIBS strategies, including transcranial direct current stimulation (tDCS), which is the flow of low electrical current from the surface anode to cathode electrodes through the brain. The putative mechanism of action of tDCS is that it is neuromodulatory; it alters the responsivity of neurons by creating electric fields that change the voltage across neuronal membranes, which leads to increased neuromodulation that can facilitate cognitive activities and motor training and remediating.

Low-frequency 1-Hz rTMS to left temporoparietal regions to reduce treatment-refractory auditory hallucinations in schizophrenia. Hoffman and colleagues published the results of a randomized controlled trial of 50 patients who received 9 days of active 1-Hz rTMS to the left temporoparietal cortex, at 90% resting motor threshold, for up to 16 minutes daily compared with sham stimulation. The rationale was that increased activity in these regions was associated with auditory hallucinations and that 1-Hz rTMS could produce sustained reduction in cortical activation, and thereby reduce hallucination severity. Active rTMS was well-tolerated and led to a significant reduction in hallucinations, with decreased salience and frequency, and sustained improvement for several weeks. Many patients who participated in the study reported that their “voices” were reduced in intensity and salience and sometimes ceased entirely, at least for days to weeks. These prompted other investigators to replicate the study, with subsequent mixed results. Overall, however, meta-analyses of these studies have found efficacy for 1-Hz left temporoparietal rTMS in the treatment of medication-resistant auditory hallucinations, with moderate effect size.

The research on rTMS for medication-resistant auditory hallucinations was described in a 2015 Cochrane systematic review of randomized controlled trials relevant to TMS and schizophrenia, which found that the evidence was “not yet robust, consistent and standardized enough to make any firm conclusions.” The review described a limited number of studies with various TMS parameters...
In many of the studies, sham and active rTMS treatments were both associated with a reduction in auditory hallucinations over time, which raises questions about placebo effects and whether the tilting of a coil (as in sham stimulation) truly renders it neutral with respect to cortical stimulation.\(^7\) The question has also been raised whether neuronavigation —using MRI to identify targets—improves the spatial precision in targeting TMS and hence shows more consistent efficacy in the improvement of auditory hallucinations.\(^8\)

The rationale for Hoffman’s approach\(^5\) in using NIBS to target temporoparietal regions to reduce auditory hallucinations has been supported by findings of efficacy for cathodal tDCS in decreasing auditory hallucinations. Twice-daily tDCS (20-minute 2-mA cathodal) for 5 days, which targeted the left temporoparietal cortex, led to a reduction in auditory hallucinations that was maintained for 3 months.\(^9\) As with rTMS, this finding has been replicated, although not consistently, and more research is needed.

High-frequency rTMS to the prefrontal cortex to treat negative symptoms in schizophrenia. The 2015 Cochrane review of rTMS and schizophrenia also covered the evidence for high-frequency prefrontal rTMS as a treatment for negative symptoms; the authors noted that meta-analyses have suggested efficacy. Overall, the evidence is less strong than that for low-frequency rTMS for auditory hallucinations, with more methodological variation across studies, which includes:

- Variation in target: left, right, bilateral prefrontal
- Frequency of stimulation: 10 to 20 Hz, and bursts of 50 Hz
- Pulse strength: 90% to 110% resting motor threshold
- Duration of stimulus trains and intertrain intervals
- Target localization: 10 to 20 EEG electrode positions, MRI
- Study duration
- Types of sham
- Rating scales of negative symptoms

A large multicenter trial of 10-Hz rTMS to the left DLPFC for 15 days (vs sham) in 175 schizophrenia patients with predominant negative symptoms showed no difference between active versus sham rTMS in improvement of negative symptoms.\(^10\) However, negative symptoms improved steadily over the 21 days of treatment, which suggests that a longer treatment trial might have shown efficacy for active rTMS.

As with NIBS for auditory hallucinations, the rationale and strategy for stimulating the prefrontal cortex with high-frequency rTMS has recent support from tDCS studies. A randomized controlled trial of 20 patients showed that anodal left/cathodal right prefrontal tDCS (ten 20-minute sessions at 2 mA) was superior to sham in reducing negative symptoms.\(^11\)

TMS and cognitive deficits in schizophrenia. Schizophrenia is characterized by marked deficits across cognitive domains. These deficits account for much of the chronic morbidity associated with schizophrenia; they largely do not respond to medication, although mild to moderate improvement with remediation strategies is possible. NIBS holds promise as a means to improve cognition in schizophrenia, either alone or in conjunction with existing remediation programs. Hasan and colleagues\(^12\) systematically examined the cognitive effects of NIBS in schizophrenia, including rTMS and tDCS. They found 4 studies that had cognitive measures as a primary outcome; 29 had cognitive measures as a secondary outcome. As with the Cochrane review of rTMS for symptoms in schizophrenia, these studies also varied widely in stimulation parameters and outcome measures. Most of the randomized controlled trials reviewed showed no differential effect on cognition between active and sham treatment. However, there was evidence to suggest that rTMS to the left DLPFC might improve working memory in schizophrenia; correspondingly, anodal tDCS to left DLPFC led to improvement in cognition, specifically working memory and attention/vigilance. This is consistent with studies that show that functional MRI-guided TMS can remediate sleep-deprivation-induced working memory in healthy volunteers.\(^13\) Correspondingly, our group has worked to transiently recapitulate the cognitive deficits of schizophrenia in healthy volunteers to identify targets for therapeutic NIBS to augment remediation in patients.\(^14\)

**Conclusion**

NIBS is a relatively safe strategy for the reduction of auditory hallucinations and negative symptoms in patients with schizophrenia —albeit in an “off-label” fashion. NIBS also has the potential for cognitive mapping in schizophrenia and other neuropsychiatric disorders to identify targets for therapeutic remediation of cognitive deficits.
FIGURE. Schematic of transcranial magnetic stimulation (TMS) coil on h...

SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST

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References:


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