Generalized anxiety disorder (GAD) is a chronic psychiatric condition defined by excessive and uncontrollable worry, occurring more days than not for at least 6 months, and accompanied by at least 3 of 6 hyperarousal symptoms (restlessness, muscle tension, fatigue, irritability, difficulty in sleeping, concentration problems). Lifetime prevalence in the general population is 5.7%, and rates are higher in treatment-seeking samples such as primary care and psychiatric outpatients. GAD commonly co-occurs with other disorders, most often depression, which further complicates presentation and prognosis. The burden of GAD is substantial. At the individual level, GAD is associated with significant quality-of-life impairments and diminished physical health. At the systems level, GAD is associated with high use of health care services and high costs.

Pharmacotherapy (antidepressants and/or anxiolytics) is the most common treatment for GAD; cognitive-behavioral therapy (CBT) is the method of counseling with the strongest empirical support. Pharmacotherapy and CBT are superior to placebo, but one-third to half of patients do not achieve symptom remission. Since even the best existing treatments leave many GAD patients without relief, alternative treatments are needed.

Neuromodulation is a novel psychiatric treatment that targets specific brain circuits as a means to improve psychopathology. Transcranial magnetic stimulation (TMS) is the neuromodulation therapy with the largest research base and the only one of several such therapies with an FDA-approved indication for treatment-resistant MDD.

In the FDA-approved protocol, the magnet is applied to the scalp over the left dorsolateral prefrontal cortex (DLPFC) to deliver a series of high-frequency pulses intended to stimulate areas implicated in MDD. The efficacy of these stimulation parameters for depression has been supported in numerous clinical trials, and research suggests that anxiety symptoms in patients with MDD also improve. However, there has been far less research on using TMS to treat anxiety disorders and very little is known about use of TMS in GAD. (See Machado and colleagues for an in-depth review.)

**Neurobiology of GAD**

The rationale for considering TMS for GAD is based on neurobiological models of the disorder. GAD is characterized by abnormalities in the frontal and limbic structures as well as in the connectivity between these regions. The frontal regions most often implicated in GAD are the prefrontal cortex and anterior cingulate cortex, and the limbic region most often studied is the amygdala: increased attention has recently been directed toward the hippocampus. Although there are some inconsistencies across studies, structural abnormalities, as well as decreased structural and functional connectivity between frontal and limbic regions, have been documented in GAD patients.

Functional neuroimaging further supports the hypothesis that GAD is characterized by inefficient biological mechanisms associated with emotion regulation. During worry induction, there is increased activation in the prefrontal cortex and decreased activity in the amygdala in both GAD patients and nonanxious control participants; however, unlike nonanxious control participants, GAD patients are not able to normalize this neural activity following worry induction.
The results from studies that use tasks that require conflict monitoring and emotion regulation (although somewhat inconsistent) support a model of GAD characterized by hypoactivation in the prefrontal cortex and anterior cingulate cortex indicative of deficient top down emotional control.8

Although there are many possible neuromodulation targets to improve emotion regulation, this article focuses on the potential role of stimulation of the DLPFC, the region most often targeted in depression and the only region yet tested in patients with GAD. The DLPFC plays a central role in emotion regulation processes as a structure responsible for maintaining task goals and interacting with other brain regions to maximize goal attainment. TMS affects not only the stimulation target but also other cortical and subcortical regions with which it has connections.

Key regions in the regulation of anxiety that may be influenced by cascading effects of DLPFC stimulation are the dorsal anterior cingulate cortex (responsible for threat appraisal and conflict/error monitoring); the inferior frontal gyrus (implicated in risk aversion and selective inhibition); and the ventral anterior cingulate cortex and ventral medial prefrontal cortex, which integrate inputs from cortical regions and suppress limbic activity (through the uncinate fasciculus pathway to the amygdala and bed nucleus of the stria terminalis). Therefore, DLPFC stimulation may improve anxiety via enhanced functioning of and/or improved communication within fronto-limbic networks.

Findings from nonclinical samples indicate that neuromodulation of the DLPFC alters anxiety-related cognitive biases, risk aversion, and cortisol secretions, all of which are implicated in GAD pathology.9-12 These data support a potential role for neuromodulation of the DLPFC in changing emotion regulation of anxiety, but the ways in which the DLFPC exerts an influence are not known. Proposed biological mechanisms of DLPFC stimulation in patients with depression include normalization of neuroendocrine, neurotransmitter, and/or neurotrophic factors, which may also play a role in anxiolytic effects of TMS, given that abnormalities in these systems have been implicated in GAD as well.13,14

Neuromodulation treatment for GAD

The only published study of TMS for GAD was a small open-label trial in adults.15 Treatment consisted of 6 sessions (delivered twice weekly for 3 weeks) of low-frequency (ie, inhibitory) stimulation over the right DLPFC. There was a 60% response rate (defined as a 50% or more improvement in the Hamilton Anxiety Rating Scale [HARS] total score) and a 60% remission rate (defined as HARS score less than 8) at post-treatment; results were largely maintained over a 6-month follow-up.16

A recently published case study used transcranial direct current stimulation (tDCS), another form of neuromodulation, to treat GAD in a 58-year-old woman.17 In tDCS, a direct electrical current is applied to the scalp to alter cortical excitability, with anodal stimulation to excite and cathodal to inhibit. The tDCS parameters were set with the cathode over the right DLPFC and the anode over the contralateral deltoid.

Fifteen treatments were administered (5 sessions weekly for 3 weeks). Self-reported anxiety symptoms were in the nonclinical range at post-treatment and follow-up, indicating acute and sustained remission of symptoms. Clinician-rated symptom changes were not reported, however, which prevented cross-study comparisons. In addition, although the outcomes reported are encouraging, only limited conclusions can be drawn given the absence of a control group.

At the 2014 American Psychiatric Association meeting, preliminary results of a randomized controlled trial (RCT) in GAD patients who received either active TMS or placebo (using a “sham” coil) were presented.18 Low-frequency stimulation was applied to the right DLPFC for a total of 30 sessions (5 sessions weekly for 6 weeks). Preliminary data show that more than two-
thirds (71%) of the active TMS group were treatment responders (50% or greater improvement in HARS score), while only one-quarter of the sham group met this criterion.

At the 3-month follow-up, responder rates were maintained in those who were receiving active repetitive TMS (rTMS). Also, nearly half (43%) of the patients in the active TMS group had symptom remission (HARS score less than 8) at post-treatment, with some additional gains in remission rates over the 3-month follow-up. Remission in the sham group was achieved by only 1 patient and only at post-treatment.

Preliminary analyses from this RCT in patients with GAD suggest that DLPFC activation during a symptom provocation task (used to induce stressful uncertainty) increases following active rTMS stimulation but not following sham stimulation.19 Data from a study with healthy control participants suggest that DLPFC neuromodulation alters activation of, and functional connectivity between, the DLPFC and ventral medial prefrontal cortex during decision making.20 More research is needed to determine the effect of TMS on neurocircuitry in GAD.

Clinical challenges
Currently, there is a limited empirical base to support clinical decision making. There is no FDA-approved indication for neuromodulation therapies for GAD and, thus, any use of TMS to treat GAD is off-label. Optimal stimulation parameters are unknown. In the trials of TMS for GAD, 1-Hz stimulation was applied for 15 minutes to the right DLPFC (900 pulses per session) at an intensity of 90% of the passive motor threshold.15,18 However, the number of sessions differed substantially (6 vs 30 sessions).

It will be important to determine which TMS treatment parameters are best for GAD, including consideration of brain regions other than the DLPFC. When targeting the DLPFC, the standard procedure for coil placement is 5 cm rostrally from the patient’s motor cortex (identified with a motor-evoked potential). However, this procedure results in a minority of patients fitted optimally. Neuronavigation—either structural or functional—allows more individualized precision and improves the efficacy of TMS in treatment of depression. However, this technology is not available in most clinical settings.

There are also no data to identify which GAD patients are most likely to benefit from TMS. Some candidate predictors to explore include enhanced anterior cingulate cortex and attenuated pretreatment amygdala activation, which both predict response to pharmacotherapy and/or CBT for GAD. Cerebral blood flow to the ventral medial prefrontal cortex, which predicts response to low-frequency right DLPFC stimulation in depressed patients, might also be studied as a predictor of TMS response in GAD. Lastly, the only data for TMS in GAD have been from adults. There is evidence that the neurobiology of GAD changes with age; therefore, it will be important to determine whether adjustments are needed when applying TMS across the life span.

Conclusions
Available data suggest that TMS holds promise as a treatment for GAD, but larger and more definitive clinical trials are needed. In addition, it is important for future research to determine the optimal treatment parameters and predictors of treatment response. The mechanisms by which TMS exerts an anxiolytic effect are poorly understood, but hypotheses can be generated and tested based on neurobiological models of GAD and emerging data about the role of TMS in treating this disorder.

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