believe that research from LMICs also allows further understanding of emotional, behavioral, and intellectual abilities in a variety of risk and protective contexts, thus leading to a deeper understanding of the biological and psychosocial processes underlying mental illness and health in general. This will require an expansion in the output of high-quality research focused on those most vulnerable in areas where it is most needed.

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Repetitive Transcranial Magnetic Stimulation to Treat Early-Onset Auditory Hallucinations

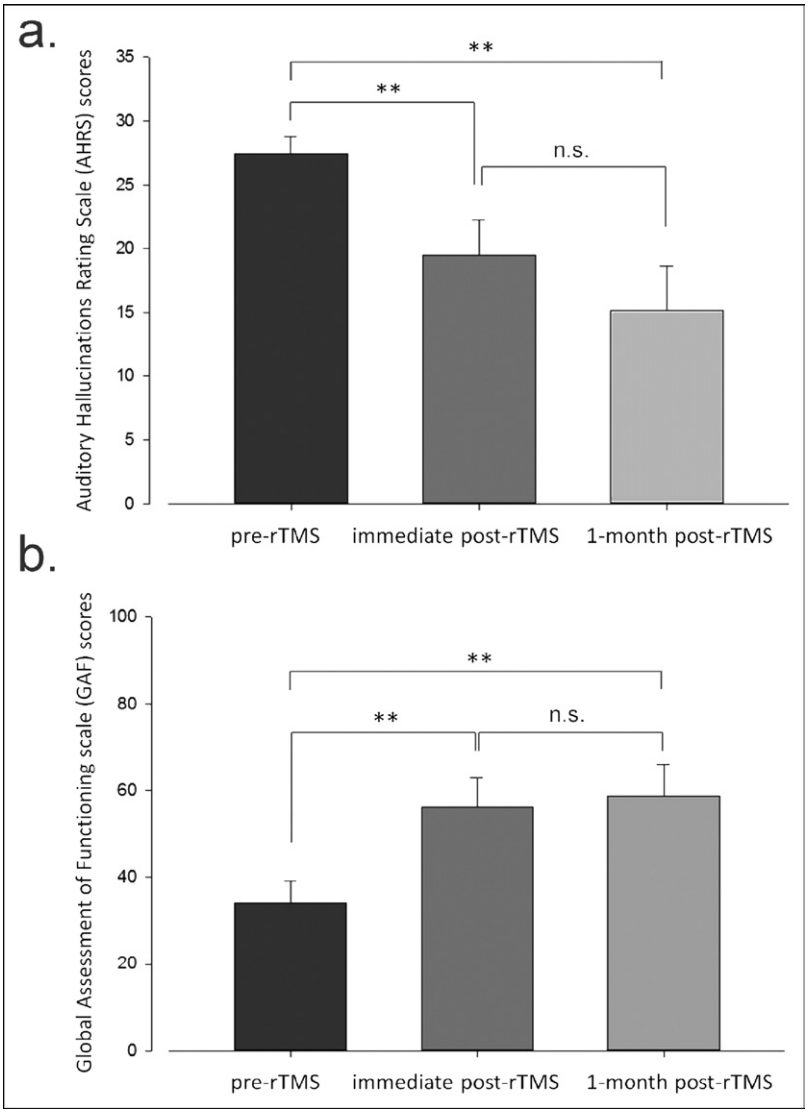
To the Editor:

Hallucinations are defined as unsolicited percepts in the absence of exteroceptive stimuli. These experiences can be far below the threshold for clinical disorders and sometimes are described as a part of normal human development. In contrast, hallucinations may predispose a patient to or be an indicator of early psychosis. Auditory hallucinations (AHs) have been reported in most patients with adult- and childhood-onset schizophrenia (COS). In approximately 25% of patients, conventional antipsychotics are unsuccessful at relieving these symptoms. Recently, noninvasive neuromodulation technologies have been shown to be effective add-on therapies for adults with refractory hallucinations. In particular, 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied over the left temporoparietal junction has been found to be effective.[1]

Repetitive TMS also appears to be a promising therapeutic tool in the pediatric population because it may help avoid the adverse developmental consequences of polypharmacy and frequent suboptimal clinical responses.[2] Using TMS in patients younger than 18 years has been shown to be safe,[3] and French guidelines recently have extended the therapeutic indications for rTMS to children and adolescents.[4] Although pilot studies investigating the efficacy of rTMS in patients with depressive, attention-deficit/hyperactivity, or autistic disorders have been conducted,[2] little is known about the efficacy of rTMS on early-onset AHs. To the best of the authors' knowledge, only a few case reports have described significant clinical improvements in the severity of AH in patients with COS after low-frequency rTMS.[5-7] The replication of these very preliminary findings at the group level is critical.

To achieve this objective, the authors established a case series of adolescents diagnosed with COS according to the Schedule for Affective Disorders and Schizophrenia for School-Age Children (n = 10; 15.5 ± 2.3 years old; male/female ratio, 7/3). Informed consent was obtained from each enrolled patient and the patient's parents. All participants had frequent and drug-resistant AHs. The only exclusion criterion was a medical history of seizures. They received a stable dosing of antipsychotic drugs for 8

FIGURE 1 Mean changes from baseline to 1 month in (A) severity of hallucinations and (B) global functioning after 10 sessions of 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied over the left temporoparietal junction in 10 adolescents with childhood-onset schizophrenia. Note: n.s. = not significant. $^{**}p \leq .01$.



weeks before enrollment (18.5 ± 11.6 mg Olanzapine-Equivalent).[8] Refractoriness was defined by the failure of two consecutive 8-week regimens of antipsychotics in the therapeutic range (confirmed by plasma concentration) to relieve AHs. Each enrolled patient received 1,200 1-Hz TMS pulses at 90% of the motor threshold twice daily for 5 consecutive days. Stimulation was targeted to the T3-P3 site (according to the international 10-20 EEG system), similar to the procedures validated in adults. Each patient wore hearing protection during treatment. The authors assessed scalp discomfort clinically and determined there was only minor discomfort.

The authors used a before-and-after design. Severity of symptoms was assessed using the Auditory Hallucinations Rating Scale (AHRS), and the impact of AHs on daily activities was measured using the Global Assessment of Functioning Scale (GAF). Assessments were repeated at baseline, immediately after treatment, and after 1 month. Paired *t* tests were used to explore differences in the AHRS and GAF scores before and after rTMS. The assumption of normality was confirmed by the Shapiro-Wilk test. The findings are synthesized in Figure 1. The AHRS scores decreased significantly from the baseline to the immediate post-treatment assessment (t_9 =

3.4; $p = .007$) and from the baseline to the 1-month assessment ($t_9 = 4,1$; $p = .004$). Furthermore, the GAF scores improved significantly from the baseline to the immediate post-treatment assessment ($t_9 = -4.2$; $p = .002$) and from the baseline to the 1-month assessment ($t_9 = -3.4$; $p = .009$). There were no significant changes in the AHRS and GAF scores between the two post-treatment measurements ($p > .4$).

In summary, this case series highlights the potential beneficial effects of low-frequency rTMS on alleviating early-onset refractory hallucinations. Although these findings are preliminary, this study provides the first evidence for a significant improvement in the severity of AHs and global functioning after 10 sessions of 1-Hz rTMS over the left temporoparietal junction in a group of adolescents with COS. Moreover, the therapeutic effect was sustained, as demonstrated by persistent improvements at the 1-month follow-up. No specific adverse effects were observed, and treatment did not need to be interrupted for discomfort. These promising results constitute a first step toward developing evidence-based interventions using rTMS in pediatric patients with drug-resistant hallucinations. Implementing larger controlled trials is required to validate 1-Hz rTMS against placebo in this population, determine optimized stimulation parameters in developmental periods, and evaluate the long-term duration of the therapeutic effect. The best strategy to define the targeted stimulation site, such as using functional magnetic resonance imaging-guided rTMS, will also have to be determined.[7]

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Could Repetitive Transcranial Magnetic Stimulation Improve Neurocognition in Early-Onset Schizophrenia Spectrum Disorders?

To the Editor:

We read the recent report by Frazier and colleagues with great interest.[1] These investigators should be commended for the landmark Treatment of Early-Onset Schizophrenia Study and this recent examination of neu-