

Should repetitive Transcranial Magnetic Stimulation (rTMS) be considered an effective adjunctive treatment for auditory hallucinations in patients with schizophrenia?

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The experience of auditory hallucinations, especially verbal hallucinations, is a common psychotic symptom in persons with schizophrenia, but in about 30% of these individuals traditional treatment with antipsychotic medication is not effective in reducing the hallucinations. For this subgroup of patients, alternative forms of treatment need to be assessed. The occurrence of auditory hallucinations has been linked to abnormal activation or inhibition of the neural circuits related to language processing, especially those in the left temporoparietal lobe.^[1] Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive method that adjusts the excitability of the cortex, so rTMS is one type of adjunctive treatment for medication-resistant auditory hallucinations in schizophrenia that researchers have been interested in.

Hoffman and colleagues^[2] first reported the possibility of using rTMS to treat auditory hallucinations in 1999. There have been at least 18 sham-controlled studies that reported the effectiveness and safety of rTMS in the treatment of auditory hallucination; the majority were randomized sham-controlled trials and a minority used a cross-over design. Most participants in these studies had intractable auditory hallucinations. Low stimulation frequencies (e.g., 1Hz) were used with a strength ranging from 80 to 115% of the participant's motor threshold. The most common site of stimulation was the left temporoparietal junction (T3P3); other sites include the right temporoparietal junction (T4P4), the left or right Wernicke areas, and individualized sites determined by fMRI. The total number of pulses ranged from 240 to 4200 for a single treatment session. The duration of rTMS treatment was usually between one and four weeks.^[3] All of these studies were small-scale; only three had 20 or more participants (in each arm of the study) and none of them had more than 30 participants.

Three studies published in *Biological Psychiatry* in 2005, 2011, and 2013, reflect the evolution of scientific thinking about rTMS as an adjunctive treatment for auditory hallucinations in schizophrenia. Hoffman and

colleagues (2005)^[4] conducted a sham-controlled trial with 50 individuals with auditory hallucinations (27 in the rTMS group and 23 in the control group). After nine days of 1Hz-rTMS stimulation to the left temporoparietal area, the rTMS group had significantly greater improvement in auditory hallucinations than the control group. However, another randomized sham-controlled trial by Slotema and colleagues (2011)^[5] did not find any benefit of rTMS treatment and did not find any advantage in using individualized sites for rTMS stimulation guided by fMRI. A follow-up study by the Hoffman's team in 2013^[6] again reported benefits to the adjunctive use of rTMS for auditory hallucinations and found that the effectiveness of rTMS treatment was related to the degree of attention the patient focuses on their hallucinations and the degree of brain lateralization.

There have been six different meta-analyses about the effectiveness of rTMS for auditory hallucinations published since 2007. The meta-analysis by Freitas and colleagues,^[7] which included cross-over studies and open trials, reported an effect size of 1.04 but had substantial heterogeneity across studies. Demeulemeester and colleagues^[8] used stricter criteria, including nine RCT studies published between 2005 and 2011; they reported a pooled effect size of 0.42 (95% CI: 0.13-0.70, $p=0.004$). The most recent meta-analysis^[3] reported an effect size of 0.44 (95% CI, 0.19-0.68) for rTMS stimulation at the left temporoparietal area and an effect size of 0.33 (95% CI: 0.17-0.50) for rTMS stimulation at other areas.

Although the most recent 2013 study by Hoffman and colleagues^[6] was not included in these meta-analyses, all the previous meta-analyses supported the effectiveness and safety of rTMS as an adjunctive treatment for auditory hallucinations. Nevertheless, the effect sizes tend to be smaller in more recent studies. This downward trend is not due to publication bias,^[3,8] but it may be due to the generally higher quality of the more recent studies. Advances in the technique for administering sham rTMS may also have contributed to the reduction of the difference between the intervention and control groups.

(The pseudo-coil designed specifically for these studies can cause a numbing sensation in the scalp of patients.)

Despite the suggestive evidence from meta-analyses, confirmation of the effectiveness of rTMS as an adjunctive treatment for auditory hallucinations will need much larger studies (with 150 patients in each group). Multi-center studies, like those conducted by O'Reardon and colleagues^[9] demonstrating the effectiveness of rTMS in the treatment of depression, are needed. These studies will need to consider the potential relevance of different types of auditory hallucinations. The four commonly recognized types of auditory hallucinations^[10] – persistent commanding or commenting hallucinations, voices of one's own thought, non-verbal auditory hallucinations, and broadcasting auditory hallucinations – may reflect abnormal functioning of different brain circuits and, thus, may respond to rTMS treatment differently. Future studies should also assess the effectiveness of treatment with high-frequency rTMS.^[11]

Conflict of interest

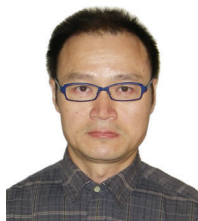
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References

1. Ford JM, Dierks T, Fisher DJ, Herrmann CS, Hubl D, Kindler J, et al. Neurophysiological studies of auditory verbal hallucinations. *Schizophr Bull* 2012; **38**(4): 715-723.
2. Hoffman RE, Boutros NN, Berman RM, Roessler E, Belger A, Krystal JH, et al. Transcranial magnetic stimulation of the left temporoparietal cortex in three patients reporting hallucinated 'voices'. *Biol Psychiatry* 1999; **46**: 130-132.
3. Slotema CW, Aleman A, Daskalakis ZJ, Sommer IE. Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: update and effects after one month. *Schizophr Res* 2012 ; **142**(1-3):40-45.
4. Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT, et al. Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. *Biol Psychiatry* 2005; **58**(2): 97-104.
5. Slotema CW, Blom JD, de Weijer AD, Diederer KM, Goekoop R, Looijestijn J, et al. Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biol Psychiatry* 2011; **69**(5): 450-456.
6. Hoffman RE, Wu K, Pittman B, Cahill JD, Hawkins KA, Fernandez T, et al. Transcranial magnetic stimulation of Wernicke's and right homologous sites to curtail "voices": A randomized trial. *Biol Psychiatry* 2013. **73**(10): 1008-1014
7. Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. *Schizophr Res* 2009; **108**(1-3): 11-24.
8. Demeulemeester M, Amad A, Bubrovsky M, Pins D, Thomas P, Jardri R. What is the real effect of 1-Hz repetitive transcranial magnetic stimulation on hallucinations? Controlling for publication bias in neuromodulation trials. *Biol Psychiatry* 2012; **71**(6): e15-16.
9. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007; **62**(11): 1208-1216.
10. McCarthy-Jones S, Trauer T, Mackinnon A, Sims E, Thomas N, Copolov DL. A new phenomenological survey of auditory hallucinations: evidence for subtypes and implications for theory and practice. *Schizophr Bull* 2012. doi: 10.1093/schbul/sbs156 [Epub ahead of print]
11. Montagne-Larmurier A, Etard O, Razafimandimby A, Morello R, Dollfus S. Two-day treatment of auditory hallucinations by high frequency rTMS guided by cerebral imaging: a 6 month follow-up pilot study. *Schizophr Res* 2009; **113**(1):77-83.



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