•Forum•
rTMS for auditory hallucinations

rTMS in the management of auditory hallucinations in patients with schizophrenia

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Schizophrenia spectrum disorders can be accompanied by hallucinations in any of the sensory modalities. They are auditory in nature in 70% of cases, resulting in functional disability and a low quality of life.[1,2] The pathophysiological basis of auditory verbal hallucinations (AVH) remains unclear; functional brain imaging studies suggest the involvement of frontal and temporal cortical regions as well as deep brain structures and the limbic system. The regions associated with the perception and production of speech within the temporoparietal (TP) cortex are of particular interest.[3,4]

As discussed in the Forum by Wang and Xu in the last issue of the journal,[5] repetitive transcranial magnetic stimulation (rTMS) has recently emerged as a possible additional tool in the treatment of medication-resistant AVHs. The rationale for its use is that it is a noninvasive intervention that can have prolonged effects on cortical activity (persisting beyond the stimulation period), making it suitable for therapeutic purposes. The majority of studies to date have examined the effects of low frequency rTMS targeted at the left TP area (Brodmann area 40, which is involved in speech perception).[6] A current hypothesis suggests that the potential clinical benefit of rTMS treatment is associated with its inhibition of cortical activity in the speech-related regions of the brain thought to be pathologically hyperactive during AVH.[2,4,7] Studies published about the use of rTMS to treat AVH have reported both positive and negative results. As pointed out by Slotema and colleagues,[8] most of these studies are underpowered, and those published before 2007 generally had higher effect sizes than those published after 2007. Although larger RCTs published more recently have failed to show a significant effect of rTMS compared to placebo-controlled treatment,[6,9,10] all meta-analyses published to date have concluded that rTMS is more effective than sham treatment.[8,10-16]

There are several gaps in our knowledge about the mechanism of action of rTMS that need to be clarified before its potential application to clinical practice can be fully evaluated. First, the mixed results described above suggest that rTMS does not work equally well for all patients, so it would be useful to identify clinical symptoms or biomarkers that could predict responsiveness to rTMS.[2] To date, little data exists about the individual-based factors associated with responsiveness to rTMS. It has, however, been suggested that responsiveness to rTMS might itself be an indicator of responsiveness to other treatments such as medications.[17] A study by Homan and colleagues[4] assessed changes in resting-brain perfusion in 24 medicated patients with AVH treated with 10 days of 1Hz rTMS (n=12) or theta-burst stimulation (n=12); compared to non-responders the responders had higher regional blood flow (CBF) in the left superior temporal gyrus (STG), suggesting that this is a possible biomarker of responsiveness to rTMS in patients with AVH.

Another issue that remains unresolved is determining the optimal method of administration of rTMS. Most studies using rTMS to treat AVH target the left TP cortex. But more recent fMRI studies show considerable inter-subject variability in the brain regions activated during AVH, so it's possible that the optimal focus for rTMS treatment might vary among different patients.[7,18] However, to date, studies targeting other areas than the left TP cortex (including the brain areas that are most active during AVH) do not show improved outcomes. Vercammen and colleagues[6] raised the possibility that bilateral treatment would be more effective because it would affect aspects of hallucinated content that are more closely associated with the right temporal cortex, such as prosody and emotional salience. They tested this hypothesis in a RCT in which 38 patients with medication-resistant AVH were randomly assigned to 1Hz rTMS treatment of the left TP region, 1Hz rTMS treatment of the bilateral TP regions, or placebo (conducted over 6 days, twice daily for 20 min). They found that the frequency of AVH was only significantly reduced in the left rTMS group, but the bilateral rTMS group showed a significant reduction in self-reported affective responsiveness to AVH. Unfortunately, the

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relatively small samples of such studies makes it impossible to make firm conclusions about the potential benefits of rTMS targeted at brain regions other than the left TP.

Additionally, the duration of rTMS effects and the development of efficient maintenance protocols remain a matter of controversy and concern. Long-term follow-up after rTMS treatment is not commonly reported, and studies that do monitor long-term outcomes have varying results. One recent meta-analysis that identified results for 337 patients found that the effect of rTMS on AVH was no longer significant at one month follow-up. This short duration of the efficacy of rTMS calls into question its potential utility as a treatment for patients troubled with refractory symptoms.[15]

Future research should also focus on further improvement of rTMS treatment paradigms. Given that relatively infrequent sessions with low frequency rTMS is usually well tolerated, it would be valuable to determine whether or not increasing the intensity and/or number of sessions for individuals who do not respond at the initial level would increase the proportion of individuals who benefit from rTMS and the duration of the rTMS effect.

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