Editorial

The positive impact of publishing studies with negative results: transcranial magnetic stimulation in the treatment of auditory hallucinations

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"In order to illustrate the importance of publishing negative results, we have chosen to provide an example from our field of study: transcranial magnetic stimulation..."

Research with results is important in order to canalize and design future study efforts toward other treatment options, as well as to avoid using treatments that are not useful and potentially hazardous. Scientific and medical journals publish studies with positive results more often than they do negative results. This practice is perhaps embedded in human nature as a preference for good news over bad news.

In order to illustrate the importance of publishing negative results, we have chosen to provide an example from our field of study: transcranial magnetic stimulation (TMS) in the treatment of psychiatric disorders and more specifically in the treatment of auditory hallucinations as a symptom of schizophrenia. TMS is a noninvasive tool that stimulates nerve cells in superficial areas of the brain. TMS induces a magnetic field that can produce a substantive electrical field in the brain causing depolarization of nerve cells that results in the stimulation or disruption of local brain activity. TMS can cause either inhibition of brain activity or excitation of brain activity [1].

Since auditory hallucinations are many times refractory to pharmacotherapy, on the one hand, and cause a patient's enormous suffering (to the point of committing suicide) on the other hand, investigators have struggled to develop new treatment strategies.

In March 2011, Slotema *et al.* completed a double-blind study in which 62 patients with medication-resistant auditory hallucinations were randomized over three conditions: repetitive TMS (rTMS) targeted at the area of maximal hallucinatory activation calculated from individual functional MRI scans during auditory hallucinations; rTMS directed at the left temporoparietal cortex; and sham treatment [1]. The effects of functional MRI-guided rTMS and left temporoparietal rTMS on the severity of auditory hallucinations were comparable with those of sham treatment. This study concluded that low-frequency rTMS administered

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to the left temporoparietal cortex, which has been shown to be the site of maximal hallucinatory activation, is no more effective for medication-resistant auditory hallucinations than sham treatment.

"Loo *et al.* enrolled 18 subjects with schizophrenia and frequent auditory hallucinations in a double-blind, crossover trial and found no advantage for left temporal rTMS compared with right temporal and sham stimulation."

The history of brain stimulation using TMS for treatment of auditory hallucinations began with very promising preliminary results.

The first to report positive results (three patients) was Hoffman *et al.* [2], followed by a second positive report (24 patients) [3]. The first negative report appeared 1 year later; McIntosh *et al.* treated 16 patients and found no significant difference between real and sham treatments [4]. At 1 year later, another study of ten patients found real TMS to be superior to sham [5]. In the same year, Hoffman reported results with 26 additional patients [6] and concluded that, "Left temporoparietal 1 Hz rTMS warrants further study as an intervention for auditory hallucinations." However, Lee *et al.* studied 39 patients and concluded that left side rTMS is not superior to right or sham rTMS [7].

In the same year, Chibbaro *et al.* studied 16 schizophrenic patients and found long-term reduction in auditory hallucinations in the active rTMS group, with a return to the baseline in the sham group [8]. In 2005, Fitzgerald *et al.* published a randomized sham-controlled, double-blind trial study of 33 patients with treatment-resistant auditory hallucinations [9]. These researchers concluded that their study did not support the effectiveness of rTMS using the stimulation parameters provided.

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Brunelin and associates published the positive effects of slow TMS in the treatment of resistant auditory hallucinations with a larger group of patients [10]. In 2006, Jandl *et al.*, in a randomized controlled crossover trial involving 16 patients, showed rTMS over the left superior temporal area to be superior to right-sided and sham procedures [11]. Rosa *et al.* studied the therapeutic effects on auditory hallucinations refractory to clozapine with 1 Hz rTMS and found no reduction in hallucination scores in both real and sham groups [12]. In 2009, 38 patients with schizophrenia and medication-resistant AVH were randomly assigned to 1 Hz rTMS treatment of the left temporoparietal region, bilateral temporoparietal regions or placebo [13]. Vercammen *et al.* concluded that, compared with bilateral or sham stimulation, rTMS of the left temporoparietal region appears to be most effective in reducing auditory hallucinations [13].

In another study published by Bagati *et al.*, 40 schizophrenia patients were treated with low-frequency TMS to the left temporoparietal cortex [14]. A significant improvement was found in auditory hallucinations in the experimental group compared with the control group. Loo *et al.* enrolled 18 subjects with schizophrenia and frequent auditory hallucinations in a double-blind, crossover trial and found no advantage for left temporal rTMS compared with right temporal and sham stimulation [15]. Research by de Jesus *et al.* studied 17 right-handed patients with refractory schizophrenia experiencing auditory verbal hallucinations and treated with clozapine [16].

Active rTMS of the left temporoparietal cortex in clozapine-treated patients showed a positive effect on general psychopathology; however, there was no effect on refractory auditory hallucinations compared with sham stimulation.

As we can see, researchers have invested a tremendous amount of time and effort in order to find out whether rTMS is an effective tool in the treatment of auditory hallucinations. Yet, the results are conflicting. If the publication of negative results mentioned above had been rejected or not submitted at all by the authors because of an assumption or belief that it is futile to submit them, then this method of treatment may have already become a standard of care. Is it possible that an investigator will withhold such negative results, mistakenly thinking that they contribute nothing and are not worth the effort required to submit them?

Another question to be considered is whether negative results may deter investigators from continuing their research. This certainly has not happened in the case of rTMS for auditory hallucinations. We all acknowledge that evidence-based medicine should rely on large studies with many more subjects than those presented above. Since, for many reasons (most unrelated to medicine itself), this ideal is not practical, the alternative is many small studies. Therefore, the results of these studies should be statistically combined.

The intention when writing this editorial was to highlight the importance of negative results and to encourage investigators to consider submitting studies with negative results for publication.

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