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REVIEW

Auditory verbal hallucinations in schizophrenia: current perspectives in brain stimulation treatments

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Clément Nathou[1,2]
Olivier Etard[2,3]
Sonia Dollfus[1,2]

[1]Normandie Univ, UNICAEN, CHU de Caen, Service de Psychiatrie Adulte, Caen, F-14000, France; [2]Normandie Univ, UNICAEN, ISTS, EA 7466, GIP Cyceron, Caen 14000, France; [3]Normandie Univ, UNICAEN, CHU de Caen, Service des Explorations Fonctionnelles du Système Nerveux, CHU de Caen, Caen, F-14000, France

Purpose: This review reports the current perspectives of brain stimulation techniques in the treatment of auditory verbal hallucinations (AVH) in schizophrenia.

Methods: A systematic search of the literature in the PubMed database revealed that the most studied techniques are noninvasive techniques (NIBS), including electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS).

Results: The results showed that ECT could have great clinical efficacy but is currently underused in practice perhaps due to the costs associated with its limited implementation and potential associated risks. tDCS is still poorly studied and does not demonstrate sufficiently homogeneous or conclusive results yet to prove its efficacy in the treatment of AVH. However, its safe and simple implementation allows us to recommend it to patients who are refractory to other stimulation techniques. Finally, rTMS seems to be the most efficacious NIBS to offer patients with persistent AVH as an add-on therapeutic strategy. Its implementation has a non negligible cost but can be performed by a single practitioner. Great evolution in these techniques with technological progress, robotics and computer science are currently being tested and will undoubtedly improve the clinical efficacy of these procedures, particularly towards more personalized treatments such as individual rTMS targets and intensities. There are also new techniques for deep brain stimulation based on focused ultrasound that could provide much insight into the treatment of AVH in schizophrenia.

Conclusion: This review suggests that add-on brain stimulation treatments could play a key role among the therapeutic strategies for auditory hallucinations reduction in schizophrenia.

Keywords: electroconvulsive therapy, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, auditory hallucinations, schizophrenia

Introduction

The treatment of auditory hallucinations with brain stimulation techniques has been continuously growing in recent years, with the need to help the large number of patients with schizophrenia who persistently experience this debilitating symptom despite well-conducted pharmacological treatments regimens.[1] Up to 30% of patients using antipsychotic medications still experience auditory verbal hallucinations (AVH), and although clozapine is considered the most efficacious antipsychotic agent in refractory patients, 40–70% of these patients achieve only poor or partial response to it.[2] Practitioners can then decide to attempt alternative solutions such as an add-on strategy or a complementary treatment. Therefore, the development of alternative approaches to

Correspondence: Clément Nathou
GIP Cyceron – EA ISTS, Boulevard Henri Becquerel, BP 5229-14074 Caen Cedex 5, France
Tel +33 23 106 5018
Fax +33 23 106 4987
Email nathou-c@chu-caen.fr

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alleviate these treatment-resistant/persistent symptoms is crucial. The present review aims to summarize the current clinical use of brain stimulation techniques in the treatment of auditory hallucinations in schizophrenia and to propose some perspectives of use to improve the techniques efficacy. Here, we will focus on electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) techniques as they represent the largest use of brain stimulation in schizophrenia.

Understanding auditory hallucinations

Auditory hallucinations (AVH) have been described since antiquity, but have been identified as pathological only for the last 3 centuries. The hallucinatory phenomenon is to be distinguished from the illusion which is a misinterpretation of an existing external stimulus. In schizophrenia, the presence of hallucinations would largely drain patients' attention and thus mobilize cognitive resources in a less productive manner.[3] AVH are characterized by the perception of voices without external stimuli, typically located outside of themselves by patients but also, and more and more described, from within of the subject's head. The content of voices is frequently accompanied by a negative emotional valence and often with a lived experience described as distressing.[4]

Neuropsychological theories consider that hallucinations may arise from a mismatch between inner speech and its attribution. The inner speech is considered as a mental simulation of speech without articulatory motor performance can be. The mismatch can either be seen as a defect in the production of the inner speech or in its perception/comprehension.[5]

The pathophysiology underlying AVH is far from fully understood. The techniques of brain imaging allow us to observe their neural correlates. Studies in schizophrenia have essentially found a number of morphological[6] and functional markers.[7,8] Morphological markers associated with AVH have been localized in numerous cerebral structures, including gray matter volume reductions, particularly in the left superior temporal and Heschl's gyrus.[9–11] Some white matter modifications have also been demonstrated[12] within the arcuate fasciculus.[13] Several functional markers have mostly been located in language-related areas as shown by functional cerebral imaging studies. In 1995, a PET study found activity in subcortical nuclei (thalamus and striatum), limbic structures (hippocampus), paralimbic (cingular and parahippocampal gyrus) and orbitofrontal cortex contemporaneous with AVH in a group of 5 patients. In functional MRI, two types of paradigms are used in the protocols. Some teams use a "symptom capture" protocol, which compares brain activity at rest versus perception of AVH in patients. In those studies, increases in cerebral blood flow at the time of AVH perception have been found in the Broca area,[14] bilateral superior temporal gyrus[15] but predominant on the left middle and upper temporal gyri,[16] and more precisely in the Heschl gyrus.[17,18] A meta-analysis of 10 functional MRI studies focusing on the regions activated during AVH perception confirms the involvement of a language-related network associating the left and upper temporal, precentral and supramarginal temporal gyri, the Broca area, the anterior insula and the frontal operculum bilaterally.[7] Other teams compared the functional imaging of patients with AVH to a group of patients or healthy subjects free of this symptom during tasks activating the language networks. There seems to be a hyperfunction of language-related areas in patients with AVH compared to healthy subjects in the absence of external stimuli, whereas a decrease in the functioning of these areas, still compared to healthy subjects when external language stimuli are present. An explanatory hypothesis for this result is that spontaneous activation of auditory areas may be evidence of brain activity that may compete with the processes required to engage with external stimuli[19] and report maladaptive abnormalities in the processing of auditory information at a central level. In summary, morphological and functional studies of AVH primarily report modifications in the temporal cortex, making this brain area a potential target for brain stimulation to reduce AVH.

Studying brain stimulation treatments

Before the twentieth century, there are historical descriptions of the supposed therapeutic power of "shocks", denoting a variety of phenomena such as seizure or hypoglycemic coma. The idea seemed to be "shocking," "shaking," or "frightening" the mind to allow it to come out of alienating thought patterns. The term "shock therapy" was introduced by the Romanian psychiatrist Constance Pascal in 1926, who conceptualized mental illnesses as "cerebral anaphylactic reactions", which could be interrupted by a "shock" that restores the balance of the brain and vegetative nervous system. These include malaria therapy, which involved inoculating patients with syphilitic dementia with malaria. Another author, Dr. Manfred Sakel, an Austro-Hungarian neuropsychiatrist, used the "Sakel cure" that consisted of inducing a hypoglycemic coma through

the injection of insulin in the treatment of patients with schizophrenia or in state of agitation during opioid withdrawal. However, many substances have been used to provoke seizures. The use of electricity for therapeutic purposes dates back to 47 Before Christ when Scribonius Largus applied torpedo fish to certain parts of the body to treat migraines and gout attacks. In the sixteenth century, Jesuit missionaries reported among Ethiopians a belief that the electric catfish can "expel" the demon and bring men back to their senses. In 1730, an acclaimed doctor administered to a wealthy farmer "possessed by eight evil spirits", which probably today would be considered a psychiatric disorder, eight electric shocks that would have had the effect of dismissing the demons. In the year 1789, Benjamin Franklin encouraged European psychiatrists to try to implement the treatment by "electric shock" that he himself accidentally received twice without serious effect apart from amnesia in cases of melancholy. Wilhelm Erb, considered to be the founding father of electrotherapy (application of low-intensity electric current for therapeutic purposes), reported as early as 1881 the interest of applying low-intensity electrical current to different parts of the body (for enuresis, pain, etc.). In the same vein, Babinski reported in 1902 that a case of delusional melancholy had been improved by the application, on the head, of an electric current of low intensity several times, which also induced vertigo.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the first well-established therapeutic noninvasive brain stimulation technique used in psychiatry. Ugo Cerletti and Lucio Bini developed the ECT technique for therapeutic use in Italy, 1938, to treat a schizophrenic patient in Rome. ECT consists of delivering short (less than 8 s) and very low intensity (0.8 amperes) electrical stimulation to the brain using electrodes whose placement may differ from one procedure to another (bilateral, unilateral, temporal, frontal, etc.). The stimulations must be repeated 2 or 3 times a week to produce long-term effects. It is almost exclusively used in mood disorders and particularly in treatment-resistant depression and catatonia in most Western countries, although it is still widely used in the treatment of psychotic disorders in Asian[20] and some African countries;[21,22] ECT is probably underused in Western countries for the treatment of psychotic disorders despite its potential significant efficacy as an add-on strategy. The physiological effects of ECT on the brain remain unknown, but two nonexclusive theories can be retained.[23] A neurotrophic theory notes the correlation between the efficacy of ECT and the increase in BDNF concentrations during treatment.[24] The second theory is based on anticonvulsant effect. According to this theory, the therapeutic mechanism of ECT would come as sequels of the inhibitory processes that put an end to the provoked crisis.[25] Possible mechanisms of the antipsychotic effects of ECT have been reviewed by Rosenquist et al.[26] In addition to interesting open-label studies,[27,28] there are few randomized controlled trials comparing ECT and placebo for schizophrenia treatment, and none of them have been published after 2003. Moreover, they come with global results on standard evaluation scales, including auditory hallucinations, but without specifically reporting efficacy results on AVH. A randomized and controlled study published in 2007 by Masoudzadeh and Khalilian[29] enrolled 18 treatment-resistant schizophrenic patients randomly assigned to three groups. One group was treated with clozapine (after first determining the appropriate dose for 8 weeks); another group was treated with 12 sessions of ECT, and a third group was treated with a combination of ECT and clozapine. This study showed that there was a significantly greater reduction in positive symptoms in the combination therapy group than in the other two groups. One major recent study was conducted by Petrides et al[30] in 2015, who performed a prospective randomized single-blind study in patients with ultraresistant schizophrenia, ie clozapine-resistant schizophrenia. In this study, 39 patients were randomly assigned to 2 arms: the first with the maintenance of clozapine treatment alone and the second with an "add-on strategy" of an 8-week ECT (20 ECT sessions) to the clozapine treatment. The response rate, considered a 40% or greater reduction in the BPRS "psychotic" subscale score or a CGI improvement rating of 2 or less, was 50% in the "add-on strategy" group versus 0% (no responder) in the "clozapine alone" group. In a second phase of the study, the same response rate (47%) was obtained in the "clozapine alone" group, who subsequently benefited from the same ECT "add-on strategy". Although there was no placebo condition in this study, implying a possible placebo effect, the global 50% of responders with the ECT "add-on strategy" drew some attention, considering that these were ultraresistant patients. In the same vein, other teams studied an ECT "add-on strategy".[31,32] A systematic Cochrane review by Tharyan and Adams[33] studied the efficacy of ECT for schizophrenia. In this review, they found from 10 randomized controlled trials that there was a superior efficacy of active ECT over sham or placebo (n=392, relative risk 0.71, confidence interval 0.59–0.86). As an add-on strategy to antipsychotic medication, data from 7 of 9 accessible trials

(n=172) were inconsistent, with 4 studies reporting a significant improvement in general outcomes with active ECT over sham (n=86) whereas 3 reported no improvement (n=86). Although this is the oldest NIBS, there is a lack of recent randomized controlled trials to propose clear recommendations of ECT as an "add-on strategy" to antipsychotic treatment or to confirm these interesting studies with positive results.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive technique for brain stimulation involving the application of weak electrical currents (typically 2 mA) that constantly flow through the brain from an anodal to a cathodal scalp electrode.

Applied upon the cortex, cathodal tDCS generally produces a reduction in excitability while an increase with anodal tDCS. These neuromodulation effects of tDCS were initially demonstrated in the primary motor cortex, and may stem from long-term potentiation (LTP) and long-term depression (LTD) –like mechanisms.[34]

The anodal stimulation, with the electrode placed upon the primary motor cortex (and the cathode in the contralateral susorbital position), induces an increase in the excitability of the primary motor cortex. In contrast, cathodal stimulation induces a decrease in cortical excitability.[35]

There are only a few randomized and controlled trials and some case reports, starting with the first from Homan et al[36] who reported a clinical reduction of hallucination symptoms after 10 days of 1 mA tDCS sessions with cathodal stimulation of the posterior part of the left superior temporal gyrus (anode placed over the right supraorbital cortex). The first randomized controlled trial demonstrated the efficacy of tDCS in the treatment of treatment-resistant schizophrenia.[37] The authors demonstrated that add-on tDCS with the anode placed over the left dorsolateral prefrontal cortex (midway between F3 and Fp1 in the EEG 10–20 system) and the cathode over the left temporoparietal cortex (midway between T3 and P3 in the EEG 10–20 system) could improve several treatment-resistant symptoms, including auditory hallucinations. In this study, 30 patients with schizophrenia and treatment-resistant auditory verbal hallucinations were randomly assigned to 2 groups. The first group received 20 mins of active 2-mA tDCS twice a day on 5 consecutive weekdays. The second group received 20 mins of sham stimulation following the same regimen. Active tDCS consisted of delivering a constant current of 2 mA for 20 mins (ramp-in and ramp-out periods, 30 s). The sham tDCS delivered the 2 mA current only during the ramp-in and ramp-out periods of the 20 min stimulation session, mimicking somatosensory artifacts of active tDCS. The negative and positive dimensions, as measured by the Positive and Negative Syndrome Scale (d=0.98, 95% CI=0.22–1.73), were significantly improved. The authors particularly noted that auditory verbal hallucinations were significantly reduced in the active group compared to the sham group, with a mean decrease of 31% (SD=14, d=1.58, 95% CI=0.76–2.40). Moreover, the therapeutic benefit lasted for up to 3 months. There are some replications of this study[38–41] with heterogeneous results, the most recent with the larger population of patients showing significant therapeutic benefit of the technique.[42] In a recent meta-analysis of randomized controlled trials, Kennedy et al[43] analyzed data of 143 patients recruited from 5 studies evaluating auditory hallucinations with a composite hallucinations score. Eighty patients were treated with active tDCS, and 63 patients were treated with a sham procedure.[37,38,44–46] The authors showed great heterogeneity (I2=77.11%) and the lack of a significant effect of active tDCS over sham tDCS (Hedge's g =−0.28, p=0.38). The most recent meta-analysis by Kim et al. did not found overall efficacy for tDCS.[47]

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is another noninvasive brain stimulation technique capable of inducing neuromodulation of cortical excitability. In practice, the stimulation device consists of a coil of copper wires wound in an insulating shell and produces a focused field that is able to cross certain tissues, including the skull and the scalp, without distortion.[48] The penetration depth of the TMS-induced electric field allows the cerebral cortex to be stimulated in a painless and atraumatic way. The effects of rTMS at the neuronal level are not precisely known. They may be related to two phenomena at the cellular level: long-term potentiation (LTP) induced by high frequency stimulation (≥5 Hz), and long-term depression (LTD) induced by low frequency (≤1 Hz) stimulation.[49]

LF-rTMS

Early protocols used low-frequency rTMS of the left temporoparietal cortex to reduce cortical activity in this area and subsequently reduce auditory hallucination symptoms in patients with schizophrenia.[50] The most frequently used treatment protocol is at least twenty sessions over

2– 3 weeks, at a rate of 2 sessions per day, using a frequency of 1 Hz. Following the promising results from a replication of this study, some randomized controlled trials studied the efficacy of 1-Hz rTMS versus placebo. In 2005, the same pioneering group recruited 50 patients in two parallel groups (active versus placebo) in which patients received 15-min daily rTMS for a total of 9 days over the temporoparietal junction. In this study, more than 1 of 2 of the patients in the active group had a significantly reduced severity of auditory hallucinations (evaluated with the "Hallucination Change Score") compared to less than 1 of 5 patients in the placebo group.[51] Among the dozen replications of this study, some demonstrated positive effects of the active treatment.[52–56] However, other replication studies did not demonstrate the same efficacy,[57–61] in particular the large study by Slotema et al[62] in 2011 where no significant difference was found comparing active to sham rTMS. Several meta-analyses have confirmed these heterogeneous effects of low-frequency rTMS, with a moderate favor of an efficacy in the reduction of auditory hallucinations. The most recent meta-analysis,[63] taking into account 19 monocentric studies with a total of 536 patients, found an effect size of 0.45. This confirmed the interest in the use of rTMS in this indication and supported a recommendation of use of rank C.[64] Nevertheless, taken together, the effect sizes in the meta-analyses that have tested the therapeutic efficacy of low frequency rTMS on auditory hallucinations seem to diminish with the years. In fact, when looking at more recent meta-analyses, they indicate that it may be effective, with a moderate effect size,[63,65] while the initial meta-analyses indicated higher effect sizes (eg, 0.76 in 2007).[66] This apparent decline in efficacy of low-frequency rTMS could call the use of low-frequency stimulation into question, but nevertheless could revive the interest of using higher frequency stimulation in further research protocols.

HF-rTMS

Some studies have reported an interest in high-frequency rTMS (HF-rTMS) in the reduction of auditory hallucinations. Montagne-Larmurier et al[67] in our group was the first to propose high-frequency rTMS to reduce AVH in patients with schizophrenia in 2007, thanks to an open-label study (n=13) demonstrating a drastic decrease in auditory hallucinations that was maintained for 6 months in two patients; further, it was demonstrated that low- and high-frequency rTMS applied to the temporal lobe can exert the same cortical inhibitory neuromodulation effect over the temporal cortex,[68] unlike stimulation in the primary motor cortex, and that high-frequency rTMS would produce more remote effects than low-frequency rTMS.[69] A randomized study [70] also found a decrease in AVH in the group of patients who received the active rTMS versus those that received placebo. In 18 patients, they tested two treatment paradigms, low frequency (20 mins of 1-Hz rTMS) and high frequency (13 trains of 20-Hz rTMS), daily over 1 week versus placebo. The effect of high-frequency rTMS was similar to low-frequency rTMS in AVH reductions.

Kim et al[71] conducted a trial to investigate the efficacy of 1-Hz rTMS over 20-Hz rTMS applied to the temporoparietal region and to Broca's area or sham stimulation in 23 patients. They found that patients allocated across the 4 groups significantly improved hallucination scores with no superiority of one active paradigm compared to sham. Kimura et al[72] stimulated 30 patients enrolled in a double-blind randomized sham-controlled study with active 20-Hz rTMS of the left temporoparietal cortex in 4 sessions over 2 days (n=16) compared to sham (n=14). They found no significant superiority of active treatment over sham.

A larger, recent, multicenter, randomized and double-blind study involving 59 patients[73] replicated this study with an innovative target. The treatment target was anatomically defined at the intersection between the projection of the ascending branch of the left lateral sulcus and the left superior temporal sulcus. This anatomical target area is located near both the epicenter of the language as defined by the cluster with maximal activation in a language task contrasting a native and an incomprehensible foreign language[74,75] and the Heschl gyrus. This study demonstrated a significant greater clinical improvement on overall AVH severity in the arm of actively treated patients than in the placebo arm two weeks after the end of the treatment, whereas there was no difference on AVH frequency.

cTBS

Theta-burst stimulation is a patterned form of rTMS consisting of delivering bursts at a high frequency of 5 Hz, corresponding to theta brain oscillations. Each burst consists of three electromagnetic stimulation pulses at 50 Hz. Continuous TBS (cTBS) with uninterrupted triplets of pulses was shown to reduce cortical excitability,[76] in contrast to intermittent TBS where trains of bursts are delivered in 2 s alternating with 8 s of a stimulation-free interval that increases the cortical excitability. Only

a few studies, mostly case reports, have investigated the efficacy of TBS for AVH. The first randomized controlled trial was conducted by Kindler et al.[77] In this study, the authors compared the classic 1-Hz rTMS procedure (n=12) to cTBS (n=12) delivered over 10 consecutive days. The cTBS paradigm consisted of delivering 10 Hz bursts of 3 pulses at 30 Hz during 44 s in double trains (3204 pulses per day for the first 3 days and 1602 pulses per day for the 7 following days). The 1-Hz rTMS paradigm consisted of 1 session per day. In this study, the authors did not find differences between the two procedures regarding efficacy in reducing auditory hallucinations. In another study, the same authors[78] compared 30 patients allocated across 3 groups: the first group received 1-Hz rTMS (n=8), the second group received cTBS (n=7), and the third group (control) received pharmacological treatment as usual (n=15). In this study, TMS-treated patients were significantly improved with a reduction in auditory hallucinations compared to the control group, but there was no difference between the 2 TMS paradigms. To date, the largest study was conducted by Plewnia et al[79] who recruited 86 patients in a sham-controlled double-blind trial. Patients randomly received either active or sham cTBS targeting both the left and right temporoparietal cortex for 3 consecutive weeks (5 sessions per week, once a day). In each session, both hemispheres were sequentially stimulated. In this study, the authors did not demonstrate the superiority of this bilateral cTBS paradigm over sham, but it is important to note that there was a trend in favor of the active treatment. Another large randomized and controlled trial was from Koops et al[80] in which 71 patients blindly received, over the left temporoparietal cortex, either 10 sessions of active (n=37) or sham (n=34) cTBS during 5 consecutive days (2 sessions per day). The cTBS paradigm consisted of delivering uninterrupted triplets of pulses in 60 s, corresponding to 900 pulses, at 80% of the individual resting motor threshold. In this study, there was no significant efficacy of active cTBS over sham, despite a significant clinical amelioration of auditory hallucinations in both groups. More recently, a study by Tikka et al[81] recruited 20 patients and examined the same paradigm as Koops et al[80] but targeting the right inferior parietal lobe; the results led to the same conclusion of a lack of superiority of active cTBS over sham.

A meta-analysis of randomized controlled trials by Kennedy et al[43] analyzed data from 14 studies using a composite hallucination score derived from 340 patients allocated to an active rTMS condition and 238 patients allocated to a sham condition. They found a significant effect of treatment (Hedge's g =−0.51, p=0.0001) but underlined the existence of moderate heterogeneity (I2=58.81%).

Practicing brain stimulation techniques

Despite impressive results, ECT seems to be underused in Western countries, perhaps because of its cartoonish representation in most media. In practice, the procedure is indeed heavy in terms of infrastructure and staff since it mobilizes the presence of a nurse, a psychiatrist and an anesthesia team for brief general anesthesia. If the ECT device is in itself affordable, the global cost of the procedure, frequently involving hospitalization of the patient, is substantial. Each session must take place in a room equipped for monitoring and reanimation if necessary and requires a period of continuous monitoring in the wake, requiring the attention of a nurse. This procedure, although cumbersome, is necessary because the risks involved are sometimes realized, although rare. During stimulation, there is a risk of asystolia and status epilepticus among other associated risks.[82] After the treatment, one could cite the memory impairment in the foreground as the most commonly encountered debilitating, yet not mandatory, side effect.[83]

In tDCS studies, authors have reported an overall very good tolerance of the technique. The most commonly reported side effects are burning sensations in the scalp, if there is too much impedance between the electrodes. It does not induce pain, but only a tingling sensation in the scalp during the initiation and at the end of the session. The implementation of the technique is simple and accessible to all practitioners for a low cost of hardware investment and can be easily conducted by a single person.

Authors of rTMS studies also report a good overall tolerance for the technique. Side effect (squeezing, local pain, clenched jaw, or blepharospasm) percentage increases with the stimulation frequency but remains at very tolerable levels, even with high-frequency rTMS or TBS. The major adverse effect is seizure, but this is rare when safety recommendations are correctly followed.[84] Similar to tDCS, the treatment procedure is also achievable by a single practitioner but can require the use (and the cost) of associated devices, such as a neuronavigation system. Its utilization requires an expertise in using neuronavigation, whereas the rTMS machine itself is easy to use.

Improving brain stimulation techniques

Although with promising results for treating medication-resistant AVH in schizophrenia, brain stimulation techniques are struggling to establish themselves as among first-lines therapeutic interventions. This may be due to the lack of unambiguous efficacy results in the even recent literature. On the one hand, this inconstancy may be linked with the fact that there is no consensual method on how to stimulate the brain with the available techniques. On the other hand, this could at least partly be due to the great clinical heterogeneity in hallucinatory syndrome and even in schizophrenia illness. About this latter point, a general comment could be made about better evaluation scales for AVH, which need to be standardized and shared to allow better study comparisons. Another important point to explore could be the phenomenology of AVH and the precise study of the effect of brain stimulation treatments on this complex symptom, for example with the use of several scales that may allow us to take into account this compexity.[85] Concerning tDCS and rTMS studies, the global efficacy results are supported in practice by responders with multiple profiles: early responders, late responders, and nonresponders. This opens the way for studies to determine the profile of the responder to brain stimulation techniques and to develop more personalized treatments. A current field of research is neural plasticity. The effects of brain stimulation at the neuronal level are not known yet. Nevertheless, it seems to be mediated by LTP and LTD-like effects.[49,86] The study of the brain-derived neurotrophic factor (BDNF) as a major regulator of neuroplasticity and dendritic growth[87] and its polymorphism could bring interesting results. Another factor of variability directly linked to the patient's characteristics is its cortical excitability state whose variations should be taken into account with the parameters of the stimulation procedure.

As concerning the method of the application of the brain stimulation techniques that could introduce variability in the results, we could name study design, stimulation phase-timing, stimulation target and stimulation intensity among others. Evolution of these brain stimulation techniques will undoubtedly be visible in the future in connection with technological progress, robotics (issues of miniaturization and increased portability, etc.) and computer science. We further suggest some points we could focus on in the future to improve efficacy of the techniques.

Study design

In addition to the improvements of the techniques, some adjustments could also be made in study designs and methodologies. In ECT studies, there is a lack of controlled trials to determine the appropriate number of sessions, their frequency and a maintenance protocol.[88] In an empirical way, experts have recommended developing protocols for preventing relapse for 12 rather than 6 months.[89] Nevertheless, the advantages of a long cure (12 months) compared with a short cure (6 months) have to be determined. The same questions regarding the maintenance protocol have been raised for tDCS and rTMS and remain without any answer. Still concerning general methodology, the placebo method used in the studies may vary from one to another. Although very good for tDCS, the placebo procedure is not homogeneous for rTMS. In rTMS studies, several placebo conditions have been used, and they do not seem to be equivalent.[90]

Stimulation phase-timing

There are only a few studies that took into account the timing for delivering brain stimulation. Nonetheless, the excitability status of the patient during the treatment procedure could be a major factor of variability in the clinical efficacy.[91] Applied in the case of ECT, the use of EEG monitoring to better determine the right time to stimulate could be relevant. In fact, many anesthetics used in the ECT procedure may interfere with its efficacy because they are anticonvulsant drugs, and few studies have addressed this potential bias in their results. The tDCS technique could be improved with individual adaptation more taken into account. For example, the instantaneous state of cortical excitability of the patient with real-time recording of electrical activity of the target could determine the optimal intensity of the stimulation as well as the optimal timing of stimulation delivery, which could improve both therapeutic efficacy and clinical tolerance.[92] In their study, Brunelin et al[37] noticed that patients who were talking during the tDCS session had a greater reduction in their hallucinations, highlighting the importance of the functional status of the brain during the stimulation. The use of rTMS is particularly related to the evolution of neuronavigation and its precision and its coupling to the use of robotic arms to increase accuracy and reproducibility in the stimulation of the target. The algorithm development could allow us to consider the easy stimulation of several targets during the same session to adapt the intensity of the stimulation to

individual anatomical characteristics (eg, relative depth of the target, detection and stimulation along a cerebral groove).

Stimulation target

There is a wide range of cortical targets in the treatment of AVH, depending on the way they are apprehended in the study, from a phenomenological, neuropsychological or physiological perspective. The language areas seem to be consensually involved, but there are multiple gateways to stimulate those areas. Concerning ECT and its global impact on the brain, focality of the stimulation is a nonsense. But improvements could be made on tolerance. There have been some serious suggestions for decreasing the probability of side effects, for example, with the use of unifrontal or bifrontal stimulation instead of the classic bitemporal stimulation.[93] tDCS and its large electrodes are appropriate to stimulate brain regions as the frontal or temporal cortex, but could not be considered as a focal technique able to stimulate a precise cortical point of interest. Nevertheless, there are new tDCS techniques such as High-Definition tDCS that uses smaller electrodes that could be arranged in arrays to optimize brain current flows and even support multifocal stimulation.[94] The development of this could lead to protocols with a more focal target as already done in rTMS studies. Indeed, if the left temporoparietal junction is the common target area for rTMS, several methods have been used to determine the best location to stimulate. There are classic methods and more personalized ones to determine the target. One could note that recent parallel, randomized, double-blinded and sham-controlled studies reported consistent AVH improvements by using personalized methods to stimulate Wernicke's area.[73,95,96] The classic method uses the standardized T3P3 site according to the international 10–20 system of EEG electrode positioning.[97] This site determination is widely applied for the positioning of the coil in the cognitive neurosciences and in psychiatric treatments but is known to be a rough estimation because of its variable projections on the individual brain.[98] In contrast, there are more personalized methods using magnetic resonance imaging (MRI)[99] and based on the individual structural or functional images to guide target placement.[100] A study from our group[101] using geodesic slicer demonstrated that targets determined with personalized methods were significantly different, approximately 3 centimeters distant, from the classical T3P3 site. The targets determined with personalized methods were located in the left temporal region, whereas T3P3 are mostly part of the left parietal region, which may be the reason why personalized methods with the stimulation of Wernicke's area would lead to more significant results. Interestingly, we developed an easy way to determine a personalized target using an anatomical method either for rTMS or High-Definition tDCS.[73]

Stimulation intensity

The dose of the treatment that is delivered to the patient could also differ from a patient to another. The intensity or dose of the treatment depends on the parameter of the treatment that is delivered, but also on the characteristics of the patients that receive the treatment. The ideal procedure should be able to precisely evaluate the delivered dose upon the targeted cortex. This parameter is very difficult to control in practice. If it could, the parameters of the treatment such as stimulation frequency, treatment duration, current intensity could be individualized to enhance tolerance and avoid side effects such as the convulsion crisis considered as the worst ones. In ECT for example, the use of brief or ultrabrief pulses may diminish side effects.[102] The most recent meta-analysis about tDCS enlights that tDCS may be more effective when delivered twice daily or more than 10 sessions[47] and when is associated with a relevant task.[103] This observation could motivate future studies that implement tDCS with a task or during active AVH. A crucial parameter for rTMS intensity is the scalp-to-cortex distance (SCD). In fact, there are anatomical alterations that have been reported in patients with schizophrenia in the temporoparietal cortex[104] and AVH severity correlates with a decrease in the gray matter volume of the left temporal superior gyrus.[6] Focal cortical temporal atrophy could be responsible for an increase in the distance between the rTMS stimulation coil applied to the scalp and the therapeutic target and/or for modifications in cortical excitability that could lead physicians to underestimate the power of stimulation required to treat the patient.[105] SCD measures may predict the response to rTMS or this measure may allow us to adapt the dose of intensity.[106]

Developing new brain stimulation techniques

Although the idea that partial ablation of the brain could reduce auditory hallucinations dates back to 1888 by Gottlieb Burkhardt, a psychiatrist who operated at that

time on 6 patients with schizophrenia, psychosurgery and stereotactic deep brain stimulation remains very limited in the therapeutic strategy to cure auditory hallucinations, probably due to ethical considerations.[107] There are new and innovative deep noninvasive brain stimulation methods using stereotactic magnetic resonance ultrasound to produce noninvasive thermal brain ablation. There are two methods for ablative brain stimulation. High-intensity focused ultrasound (HIFU) is a stereotactic MRI-based deep-ultrasound ablation method using transducers whose frequency ranges between 650 and 720 kHz to produce precise lesions (0.5–2.5 mm in lower brain areas (eg, thalamic nuclei, striatum, pallidum). This is a monitored procedure as the patient wears a stereotaxic frame embedded in a cap-shaped device filled with water, which is itself embedded in the MRI apparatus. Temperatures at the core of the lesion are up to 48 °C to produce reversible ablation, while at lesion temperatures between 58 and 60 °C, permanent ablation is produced.[108]

Conclusion

This review of the literature suggests that brain stimulation treatments could play a key role among the therapeutic strategies to offer to patients with schizophrenia with treatment-resistant auditory hallucinations, even if, indeed and unfortunately, these techniques have not revolutionize the care for patients suffering from it. Add-on strategies with one of these techniques could provide relief, although temporarily, for the patients, with very few negative impacts compared to antipsychotic polytherapy. ECT studies report outstanding clinical results, but its practical implementation requires the intervention of several practitioners and access to specialized infrastructures for the monitoring of general anesthesia. One with access to these conditions should not deprive their patients of this technique. tDCS studies are growing in number, but there is currently a lack of sufficient conclusive results with appropriate dosing that do not permit conclusions about its clinical efficacy. As it is safe, easy to use and affordable, it is worth attempting to identify patients who are not improved by other methods. rTMS studies currently yield more proof in terms of efficacy for reducing AVH frequency than other techniques. One who wants to specifically propose a NIBS technique to a patient should first suggest rTMS. Finally, there are some ongoing promising studies that could bring great perspectives to the development of new techniques of deep brain stimulation.

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References

1. Horacek J, Bubenikova-Valesova V, Kopecek M, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs*. 2006;20(5):389–409. doi:10.2165/00023210-200620050-00004
2. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry*. 1994;151(12):1744–1752. doi:10.1176/ajp.151.12.1744
3. Hugdahl K. "Hearing voices": auditory hallucinations as failure of top-down control of bottom-up perceptual processes. *Scand J Psychol*. 2009;50(6):553–560. doi:10.1111/j.1467-9450.2009.00775.x
4. McCarthy-Jones S, Thomas N, Strauss C, et al. Better than mermaids and stray dogs? Subtyping auditory verbal hallucinations and its implications for research and practice. *Schizophr Bull*. 2014;40 Suppl 4:S275–S284. doi:10.1093/schbul/sbu018
5. Waters F, Allen P, Aleman A, et al. Auditory hallucinations in schizophrenia and nonschizophrenia populations: a review and integrated model of cognitive mechanisms. *Schizophr Bull*. 2012;38(4):683–693. doi:10.1093/schbul/sbs045
6. Modinos G, Costafreda SG, van Tol M-J, McGuire PK, Aleman A, Allen P. Neuroanatomy of auditory verbal hallucinations in schizophrenia: a quantitative meta-analysis of voxel-based morphometry studies. *Cortex J Devoted Study Nerv Syst Behav*. 2013;49(4):1046–1055. doi:10.1016/j.cortex.2012.01.009
7. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry*. 2011;168(1):73–81. doi:10.1176/appi.ajp.2010.09101522
8. Ford JM, Dierks T, Fisher DJ, et al. Neurophysiological studies of auditory verbal hallucinations. *Schizophr Bull*. 2012;38(4):715–723. doi:10.1093/schbul/sbs009
9. Gaser C, Nenadic I, Volz H-P, Büchel C, Sauer H. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cereb Cortex N Y N 1991*. 2004;14(1):91–96.
10. Palaniyappan L, Balain V, Radua J, Liddle PF. Structural correlates of auditory hallucinations in schizophrenia: a meta-analysis. *Schizophr Res*. 2012;137(1–3):169–173. doi:10.1016/j.schres.2012.01.038

11. Maïza O, Hervé P-Y, Etard O, Razafimandimby A, Montagne-Larmurier A, Dollfus S. Impact of Repetitive Transcranial Magnetic Stimulation (rTMS) on brain functional marker of auditory hallucinations in schizophrenia patients. *Brain Sci*. 2013;3(2):728–743. doi:10.3390/brainsci3020728
12. Steinmann S, Leicht G, Mulert C. Interhemispheric auditory connectivity: structure and function related to auditory verbal hallucinations. *Front Hum Neurosci*. 2014;8:55. doi:10.3389/fnhum.2014.00055
13. Leroux E, Delcroix N, Dollfus S. Left fronto-temporal dysconnectivity within the language network in schizophrenia: an fMRI and DTI study. *Psychiatry Res*. 2014;223(3):261–267. doi:10.1016/j.pscychresns.2014.06.002
14. McGuire PK, Shah GM, Murray RM. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet Lond Engl*. 1993;342(8873):703–706. doi:10.1016/0140-6736(93)91707-S
15. Jardri R, Pins D, Delmaire C, Goeb J-L, Thomas P. Activation of bilateral auditory cortex during verbal hallucinations in a child with schizophrenia. *Mol Psychiatry*. 2007;12(4):319. doi:10.1038/sj.mp.4001980
16. Weiss AP, Heckers S. Neuroimaging of hallucinations: a review of the literature. *Psychiatry Res*. 1999;92(2–3):61–74.
17. Dierks T, Linden DE, Jandl M, et al. Activation of Heschl's gyrus during auditory hallucinations. *Neuron*. 1999;22(3):615–621.
18. Lennox BR, Park SB, Jones PB, Morris PG, Park G. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet*. 1999;353(9153):644. doi:10.1016/S0140-6736(98)09449-5
19. Hugdahl K. Auditory hallucinations: a review of the ERC "VOICE" project. *World J Psychiatry*. 2015;5(2):193–209. doi:10.5498/wjp.v5.i2.193
20. Leiknes KA, Jarosh-von Schweder L, Høie B. Contemporary use and practice of electroconvulsive therapy worldwide. *Brain Behav*. 2012;2(3):283–344. doi:10.1002/brb3.37
21. Mugisha RX, Ovuga EB. The use of electroconvulsive therapy in the treatment of psychiatric illness at Umzimkulu Hospital in Transkei. A retrospective study. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd*. 1991;79(7):391–393.
22. Selis MA, Kauye F, Leentjens AFG. The practice of electroconvulsive therapy in Malawi. *J ECT*. 2008;24(2):137–140. doi:10.1097/YCT.0b013e31815dcfd7
23. Bolwig TG. How does electroconvulsive therapy work? Theories on its mechanism. *Can J Psychiatry Rev Can Psychiatr*. 2011;56(1):13–18. doi:10.1177/070674371105600104
24. Piccinni A, Del Debbio A, Medda P, et al. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2009;19(5):349–355. doi:10.1016/j.euroneuro.2009.01.002
25. Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *J ECT*. 1999;15(1):5–26.
26. Rosenquist PB, Miller B, Pillai A. The antipsychotic effects of ECT: a review of possible mechanisms. *J ECT*. 2014;30(2):125–131. doi:10.1097/YCT.0000000000000131
27. Kho KH, Blansjaar BA, de Vries S, Babuskova D, Zwinderman AH, Linszen DH. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia–an open label study. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(6):372–379. doi:10.1007/s00406-004-0517-y
28. Chanpattana W, Sackeim HA. Electroconvulsive therapy in treatment-resistant schizophrenia: prediction of response and the nature of symptomatic improvement. *J ECT*. 2010;26(4):289–298. doi:10.1097/YCT.0b013e3181cb5e0f
29. Masoudzadeh A, Khalilian AR. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. *Pak J Biol Sci PJBS*. 2007;10(23):4287–4290.
30. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry*. 2015;172(1):52–58. doi:10.1176/appi.ajp.2014.13060787
31. Pawełczyk T, Kołodziej-Kowalska E, Pawełczyk A, Rabe-Jabłońska J. Effectiveness and clinical predictors of response to combined ECT and antipsychotic therapy in patients with treatment-resistant schizophrenia and dominant negative symptoms. *Psychiatry Res*. 2014;220(1–2):175–180. doi:10.1016/j.psychres.2014.07.071
32. Flamarique I, Castro-Fornieles J, Garrido JM, et al. Electroconvulsive therapy and clozapine in adolescents with schizophrenia spectrum disorders: is it a safe and effective combination? *J Clin Psychopharmacol*. 2012;32(6):756–766. doi:10.1097/JCP.0b013e318270e2c7
33. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev*. 2005;2:CD000076. doi:10.1002/14651858.CD000076.pub2
34. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. 2017;10(1):51–58. doi:10.1016/j.brs.2016.10.001
35. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527(Pt 3):633–639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x
36. Homan P, Kindler J, Federspiel A, et al. Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. *Am J Psychiatry*. 2011;168(8):853–854. doi:10.1176/appi.ajp.2011.11030496
37. Brunelin J, Mondino M, Gassab L, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *Am J Psychiatry*. 2012;169(7):719–724. doi:10.1176/appi.ajp.2012.11071091
38. Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. *Brain Stimulat*. 2014;7(6):813–816. doi:10.1016/j.brs.2014.08.002
39. Mondino M, Haesebaert F, Poulet E, Suaud-Chagny M-F, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. *Schizophr Res*. 2015;161(2–3):515–516. doi:10.1016/j.schres.2014.10.054
40. Bose A, Shivakumar V, Agarwal SM, et al. Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: a randomized, double-blind, sham-controlled study. *Schizophr Res*. 2018;195:475–480. doi:10.1016/j.schres.2017.08.047
41. Koops S, Blom JD, Bouachmir O, Slot MI, Neggers B, Sommer IE. Treating auditory hallucinations with transcranial direct current stimulation in a double-blind, randomized trial. *Schizophr Res*. 2018;201:329–336. doi:10.1016/j.schres.2018.06.010
42. Kantrowitz JT, Sehatpour P, Avissar M, et al. Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a replication/extension study. *Brain Stimulat*. 2019. doi:10.1016/j.brs.2019.03.003
43. Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. *Eur Psychiatry J Assoc Eur Psychiatr*. 2018;49:69–77. doi:10.1016/j.eurpsy.2017.12.025

44. Fröhlich F, Burrello TN, Mellin JM, et al. Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia. *Eur Psychiatry J Assoc Eur Psychiatr*. 2016;33:54–60. doi:10.1016/j.eurpsy.2015.11.005
45. Smith RC, Boules S, Mattiuz S, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. *Schizophr Res*. 2015;168(1–2):260–266. doi:10.1016/j.schres.2015.06.011
46. Mondino M, Jardri R, Suaud-Chagny M-F, Saoud M, Poulet E, Brunelin J. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. *Schizophr Bull*. 2016;42(2):318–326. doi:10.1093/schbul/sbv114
47. Kim J, Iwata Y, Plitman E, et al. A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?" *J Psychiatr Res*. 2019;110:117–126. doi:10.1016/j.jpsychires.2018.12.009
48. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet Lond Engl*. 1985;1(8437):1106–1107. doi:10.1016/S0140-6736(85)92413-4
49. Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulat*. 2010;3(2):95–118. doi:10.1016/j.brs.2009.10.005
50. Hoffman RE, Boutros NN, Berman RM, et al. Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated "voices." *Biol Psychiatry*. 1999;46:130–132.
51. Hoffman RE, Gueorguieva R, Hawkins KA, 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. doi:10.1016/j.biopsych.2005.03.041
52. Fitzgerald PB, Benitez J, Daskalakis JZ, et al. A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. *J Clin Psychopharmacol*. 2005;25(4):358–362.
53. Chibbaro G, Daniele M, Alagona G, et al. Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations. *Neurosci Lett*. 2005;383(1–2):54–57. doi:10.1016/j.neulet.2005.03.052
54. Brunelin J, Poulet E, Bediou B, et al. Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. *Schizophr Res*. 2006;81(1):41–45. doi:10.1016/j.schres.2005.10.009
55. Lee S-H, Kim W, Chung Y-C, et al. A double blind study showing that two weeks of daily repetitive TMS over the left or right temporoparietal cortex reduces symptoms in patients with schizophrenia who are having treatment-refractory auditory hallucinations. *Neurosci Lett*. 2005;376(3):177–181. doi:10.1016/j.neulet.2004.11.048
56. Vercammen A, Knegtering H, Bruggeman R, et al. Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: a randomized controlled trial. *Schizophr Res*. 2009;114(1–-3):172–179. doi:10.1016/j.schres.2009.07.013
57. de Jesus DR, Gil A, Barbosa L, et al. A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. *Psychiatry Res*. 2011;188(2):203–207. doi:10.1016/j.psychres.2010.11.022
58. McIntosh AM, Semple D, Tasker K, et al. Transcranial magnetic stimulation for auditory hallucinations in schizophrenia. *Psychiatry Res*. 2004;127(1–2):9–17. doi:10.1016/j.psychres.2004.03.005
59. Rosa MO, Gattaz WF, Rosa MA, et al. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. *J Clin Psychiatry*. 2007;68(10):1528–1532.
60. Blumberger DM, Christensen BK, Zipursky RB, et al. MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory hallucinations. *Brain Stimulat*. 2012;5(4):577–585. doi:10.1016/j.brs.2011.12.002
61. Bais L, Vercammen A, Stewart R, et al. Short and long term effects of left and bilateral repetitive transcranial magnetic stimulation in schizophrenia patients with auditory verbal hallucinations: a randomized controlled trial. *PLoS One*. 2014;9(10):e108828. doi:10.1371/journal.pone.0108828
62. Slotema CW, Blom JD, de Weijer AD, 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. doi:10.1016/j.biopsych.2010.09.051
63. Slotema CW, Blom JD, van Lutterveld R, Hoek HW, Sommer IEC. Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biol Psychiatry*. 2014;76(2):101–110. doi:10.1016/j.biopsych.2013.09.038
64. Lefaucheur J-P, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125(11):2150–2206. doi:10.1016/j.clinph.2014.05.021
65. Demeulemeester M, Amad A, Bubrovszky 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–e16. doi:10.1016/j.biopsych.2011.10.010
66. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *J Clin Psychiatry*. 2007;68(3):416–421.
67. 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. doi:10.1016/j.schres.2009.05.006
68. Nathou C, Etard O, Simon G, Dollfus S. How do high- and low-frequency repetitive transcranial magnetic stimulations modulate the temporal cortex. *Psychophysiology*. 2015;52(2):192–198. doi:10.1111/psyp.12323
69. Nathou C, Duprey E, Simon G, et al. Effects of low- and high-frequency repetitive Transcranial Magnetic Stimulation on long latency auditory evoked potentials. *Neurosci Lett*. 2018;686:198–204. doi:10.1016/j.neulet.2018.09.002
70. de Weijer AD, Sommer IEC, Lotte Meijering A, et al. High frequency rTMS; a more effective treatment for auditory verbal hallucinations? *Psychiatry Res*. 2014;224(3):204–210. doi:10.1016/j.pscychresns.2014.10.007
71. Kim E-J, Yeo S, Hwang I, et al. Bilateral repetitive transcranial magnetic stimulation for auditory hallucinations in patients with schizophrenia: a randomized controlled, cross-over study. *Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol*. 2014;12(3):222–228. doi:10.9758/cpn.2014.12.3.222
72. Kimura H, Kanahara N, Takase M, Yoshida T, Watanabe H, Iyo M. A randomized, sham-controlled study of high frequency rTMS for auditory hallucination in schizophrenia. *Psychiatry Res*. 2016;241:190–194. doi:10.1016/j.psychres.2016.04.119
73. Dollfus S, Jaafari N, Guillin O, et al. High-frequency neuronavigated rTMS in auditory verbal hallucinations: a pilot double-blind controlled study in patients with schizophrenia. *Schizophr Bull*. 2018;44(3):505–514. doi:10.1093/schbul/sbx127
74. Mazoyer BM, Tzourio N, Frak V, et al. The cortical representation of speech. *J Cogn Neurosci*. 1993;5(4):467–479. doi:10.1162/jocn.1993.5.4.467

75. Dollfus S, Razafimandimby A, Delamillieure P, et al. Atypical hemispheric specialization for language in right-handed schizophrenia patients. *Biol Psychiatry*. 2005;57(9):1020–1028. doi:10.1016/j.biopsych.2005.01.009
76. Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45(2):201–206. doi:10.1016/j.neuron.2004.12.033
77. Kindler J, Homan P, Flury R, Strik W, Dierks T, Hubl D. Theta burst transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: results of a randomized controlled study. *Psychiatry Res*. 2013;209(1):114–117. doi:10.1016/j.psychres.2013.03.029
78. Kindler J, Homan P, Jann K, et al. Reduced neuronal activity in language-related regions after transcranial magnetic stimulation therapy for auditory verbal hallucinations. *Biol Psychiatry*. 2013;73(6):518–524. doi:10.1016/j.biopsych.2012.06.019
79. Plewnia C, Zwissler B, Wasserka B, Fallgatter AJ, Klingberg S. Treatment of auditory hallucinations with bilateral theta burst stimulation: a randomized controlled pilot trial. *Brain Stimulat*. 2014;7(2):340–341. doi:10.1016/j.brs.2014.01.001
80. Koops S, van Dellen E, Schutte MJL, Nieuwdorp W, Neggers SFW, Sommer IEC. Theta burst transcranial magnetic stimulation for auditory verbal hallucinations: negative findings from a double-blind-randomized trial. *Schizophr Bull*. 2016;42(1):250–257. doi:10.1093/schbul/sbv100
81. Tikka SK, Nizamie SH, Venkatesh Babu GM, Aggarwal N, Das AK, Goyal N. Safety and efficacy of adjunctive θ burst repetitive transcranial magnetic stimulation to right inferior parietal lobule in schizophrenia patients with first-rank symptoms: a pilot, exploratory study. *J ECT*. 2017;33(1):43–51. doi:10.1097/YCT.0000000000000343
82. Sundsted KK, Burton MC, Shah R, Lapid MI. Preanesthesia medical evaluation for electroconvulsive therapy: a review of the literature. *J ECT*. 2014;30(1):35–42. doi:10.1097/YCT.0b013e3182a3546f
83. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry J Ment Sci*. 2005;186:410–416. doi:10.1192/bjp.186.5.410
84. Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120:2008–2039.
85. Ratcliff K, Farhall J, Shawyer F. Auditory hallucinations: a review of assessment tools. *Clin Psychol Psychother*. 2011;18(6):524–534. doi:10.1002/cpp.729
86. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry*. 2011;17(1):37–53. doi:10.1177/1073858410386614
87. Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2001;2(1):24–32. doi:10.1038/35049004
88. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2016;171(1–3):215–224. doi:10.1016/j.schres.2016.01.024
89. Charlson F, Siskind D, Doi SAR, McCallum E, Broome A, Lie DC. ECT efficacy and treatment course: a systematic review and meta-analysis of twice vs thrice weekly schedules. *J Affect Disord*. 2012;138(1–2):1–8. doi:10.1016/j.jad.2011.03.039
90. Dollfus S, Lecardeur L, Morello R, Etard O. Placebo response in repetitive transcranial magnetic stimulation trials of treatment of auditory hallucinations in schizophrenia: a meta-analysis. *Schizophr Bull*. 2015. doi:10.1093/schbul/sbv076
91. Ziemann U, Siebner HR. Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? *Brain Stimulat*. 2015;8(3):662–663. doi:10.1016/j.brs.2015.01.409
92. Moseley P, Alderson-Day B, Ellison A, Jardri R, Fernyhough C. Non-invasive brain stimulation and auditory verbal hallucinations: new techniques and future directions. *Front Neurosci*. 2015;9:515. doi:10.3389/fnins.2015.00515
93. Bansod A, Sonavane SS, Shah NB, et al. Comparison of efficacy and cognitive outcomes with right unilateral, bifrontal, and bitemporal electroconvulsive therapy in schizophrenia. *J ECT*. 2018;34(1):26–30. doi:10.1097/YCT.0000000000000454
94. Truong DQ, Bikson M. Physics of transcranial direct current stimulation devices and their history. *J ECT*. 2018;34(3):137–143. doi:10.1097/YCT.0000000000000531
95. Hoffman RE, Wu K, Pittman B, 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. doi:10.1016/j.biopsych.2013.01.016
96. M-L P-M, Galinowski A, Plaze M, et al. Active and placebo transcranial magnetic stimulation effects on external and internal auditory hallucinations of schizophrenia. *Acta Psychiatr Scand*. 2017;135(3):228–238. doi:10.1111/acps.12680
97. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;52:3–6.
98. Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr*. 2003;16:95–99.
99. Sommer IE, Kleijer H, Hugdahl K. Toward personalized treatment of hallucinations. *Curr Opin Psychiatry*. 2018;31(3):237–245. doi:10.1097/YCO.0000000000000416
100. Herwig U, Schönfeldt-Lecuona C, Wunderlich AP, et al. The navigation of transcranial magnetic stimulation. *Psychiatry Res*. 2001;108(2):123–131.
101. Briend F, Nathou C, Delcroix N, Dollfus S, Etard O. Repetitive transcranial magnetic stimulation treatment for auditory hallucinations: personalized or standardized targets? *L'Encéphale*. 2019;45:S70. doi:10.1016/j.encep.2019.04.019
102. Youssef NA, Sidhom E. Feasibility, safety, and preliminary efficacy of Low Amplitude Seizure Therapy (LAP-ST): a proof of concept clinical trial in man. *J Affect Disord*. 2017;222:1–6. doi:10.1016/j.jad.2017.06.022
103. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. *Brain Stimulat*. 2015;8(2):253–259. doi:10.1016/j.brs.2014.10.018
104. Sun J, Maller JJ, Guo L, Fitzgerald PB. Superior temporal gyrus volume change in schizophrenia: a review on region of interest volumetric studies. *Brain Res Rev*. 2009;61(1):14–32. doi:10.1016/j.brainresrev.2009.03.004
105. Nathou C, Simon G, Dollfus S, Etard O. Cortical anatomical variations and efficacy of rTMS in the treatment of auditory hallucinations. *Brain Stimulat*. 2015;8(6):1162–1167. doi:10.1016/j.brs.2015.06.002
106. Stokes MG, Barker AT, Dervinis M, et al. Biophysical determinants of transcranial magnetic stimulation: effects of excitability and depth of targeted area. *J Neurophysiol*. 2013;109(2):437–444. doi:10.1152/jn.00510.2012
107. Gault JM, Davis R, Cascella NG, et al. Approaches to neuromodulation for schizophrenia. *J Neurol Neurosurg Psychiatry*. 2018;89(7):777–787. doi:10.1136/jnnp-2017-316946
108. Bretsztajn L, Gedroyc W. Brain-focussed ultrasound: what's the "FUS" all about? A review of current and emerging neurological applications. *Br J Radiol*. 2018;91(1087):20170481. doi:10.1259/bjr.20170481