REVIEW

OPEN

Recent findings on neurofeedback training for auditory hallucinations in schizophrenia

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Purpose of review
To provide recent evidence on real-time neurofeedback (NFB) training for auditory verbal hallucinations (AVH) in schizophrenia patients.

Recent findings
NFB is a promising technique that allows patients to gain control over their AVH by modulating their own speech-related/language-related networks including superior temporal gyrus (STG) and anterior cingulate cortex (ACC) using fMRI, fNIRS and EEG/MEG. A recent limited number of studies showed that while an EEG-based NFB study failed to regulate auditory-evoked potentials and reduce AVH, downregulation of STG hyperactivity and upregulation of ACC activity with fMRI-based NFB appear to alleviate treatment-resistant AVH in schizophrenia patients. A deeper understanding of AVH and development of more effective methodologies are still needed.

Summary
Despite recent innovations in antipsychotics, many schizophrenia patients continue to suffer from treatment-resistant AVH and social dysfunctions. Recent studies suggested that real-time NFB shows promise in enabling patients to gain control over AVH by regulating their own speech-related/language-related networks. Although fMRI-NFB is suitable for regulating localized activity, EEG/MEG-NFB are ideal for regulating the ever-changing AVH. Although there are still many challenges including logistic complexity and burden on patients, we hope that such innovative real-time NFB trainings will help patients to alleviate severe symptoms and improve social functioning.

Keywords
auditory hallucinations, neurofeedback, schizophrenia, treatment-resistant

INTRODUCTION

Among the various functional deficits and symptoms in patients with schizophrenia [1–4], auditory verbal hallucinations (AVH) are one of the most prevalent and devastating features of the disease [5]. AVH is defined by hearing a voice in the absence of an external stimulus, which is often associated with severe distress and social dysfunction and is experienced by more than 70% of patients with schizophrenia [6]. To better understand the functional architecture of this pathognomonic symptom, recent studies have employed computational approaches, which have led to support for hypotheses and conceptual models, such as deficits in self-monitoring, salience, and predictive-coding as the underlying mechanism of AVH in schizophrenia [5,7–9].

Symptomatic remission rate by D2 receptor blockade remains 65% in first-episode schizophrenia) [10], and up to 24% of first-episode schizophrenia patients with additional clozapine treatment still experience residual treatment-resistant symptoms, including AVH [10]. In fact, antipsychotic drugs have little or no effect in about 30% of patients with schizophrenia [11]. Furthermore, clozapine, which is a last resort medication for treatment-resistant schizophrenia, is known to have very low

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KEY POINTS

- Development of innovative treatments, such as NFB, are needed as many schizophrenia patients continue to suffer from severe symptoms, including treatment-resistant AVH.
- Advances in computational neuroscience have enabled real-time NFB using fMRI and EEG/MEG, with fMRI-NFB having the advantage of regulating localized activity and EEG/MEG-NFB having the advantage of fast real-time NFB for regulating the ever-changing AVH in schizophrenia.
- Real-time NFB has shown potential for allowing schizophrenia patients to gain control over their AVH by self-regulating brain function in speech-related/language-related networks.
- Given the limited efficacy of the recent NFB trainings, a deeper understanding of the neural basis of AVH, selecting the optimal AVH-NFB model, standardization of NFB methodologies, and further RCTs to test the efficacy of NFB are necessary.

affinity for dopamine D2 receptors (unlike conventional drugs), which suggests that dopamine antagonism is not necessarily the main treatment target [12]. In line with this, new empirical evidence has shown that neuropathology of schizophrenia involves neural networks beyond the classical dopaminergic subcortical pathway, such as the gamma-aminobutyric acidergic (GABAergic) and glutamatergic systems [11–13]. Currently, the treatment of schizophrenia requires not only symptom relief but also early diagnosis and intervention and restoration of cognitive and social functions to enable patients to return to society [1,14–16]. This necessitates the development of new hypotheses on the pathophysiology of schizophrenia and novel therapies beyond antipsychotics that are based on the dopamine hypothesis. One of the therapeutic challenges in treatment-resistant schizophrenia is the voluntary control of psychotic symptoms, such as AVH [17]. In this regard, neurofeedback (NFB) training has attracted attention as a new therapeutic approach for schizophrenia.

Technological advances in computational neuroscience have made it possible to conduct sophisticated real-time NFB, which is a method in which brain activity is modulated via self-regulation to improve cognitive performance or reduce symptoms of schizophrenia, such as AVH. Historically, electroencephalogram (EEG) had been commonly used for NFB; however, it suffered from low quality because of deficiencies in devices and analysis techniques. There has been dramatic progress with the advent of functional MRI (fMRI), high-performance digital EEG systems, and magnetoencephalography (MEG) [18–20]. Most recent studies using NFB in patients with schizophrenia have predominantly been conducted using fMRI-NFB systems and have shown some degree of effectiveness [21]. However, EEG and MEG have a clear advantage in regard to temporal resolution in the order of milliseconds, which is crucial for real-time NFB [20,22]. Moreover, time–frequency analysis has enabled the evaluation of brain activity in specific frequencies and their corresponding functions during tasks and rest (spontaneous activity) [23,24]. Therefore, given the ever-changing nature of AVH, real-time EEG/MEG-based NFB, in addition to fMRI-NFB, has the potential to be the most suitable NFB system as an alternative treatment approach for AVH in schizophrenia patients.

In order to recommend future directions for NFB training in schizophrenia, it is necessary to clarify the strengths and weaknesses of recent findings. The purpose of this review is to summarize recent evidence (mainly from 2015) on NFB training for AVH in patients with schizophrenia. Summary of recent evidence on NFB training for AVH in patients with schizophrenia is demonstrated in Table 1.

FUNCTIONAL MRI-BASED NEUROFEEDBACK TRAINING FOR AUDITORY VERBAL HALLUCINATIONS

Functional MRI-based neurofeedback training of the superior temporal gyrus

There is consistent evidence that the auditory perception-related areas, such as the superior temporal gyrus (STG) and primary and secondary auditory cortices, are involved in the pathophysiology of schizophrenia [2,23,25]. Recently developed neuroimaging techniques have enabled the identification of functional networks associated with AVH, which include the auditory-related and language-related areas in the STG and inferior parietal gyrus (IPG), speech-related areas in the inferior prefrontal gyrus (IFG), the hippocampus and parahippocampal region, and the anterior cingulate cortex (ACC) [21,26–28]. Several studies and meta-analyses have indicated that when schizophrenia patients are actively experiencing AVH, there is increased activity in the STG and temporoparietal language regions [26–28].

On the basis of this evidence, several studies have attempted to modulate the brain activity of schizophrenia patients who experience AVH, with a specific focus on left STG hyperactivity, which is thought to be linked to severity of AVH

Table 1. Summary of recent findings on NFB training for AVH in schizophrenia

Authors	Participants' characteristics	Stage of illness	Target region and index	Task	Training period	Summary of key findings
fMRI-based NFB training						
Dyck *et al.* [35]	Three SZ with current treatment-resistant AVH (two females) (one unmedicated)	Chronic	BOLD amplitude in ACC	Up-regulation training of ACC activity	Three-day training within 1 week	All patients succeeded in up-regulating the ACC activity during the NFB training. Subjective symptoms of AVH improved after the training in all patients.
Oriov *et al.* [31▪▪]	Twelve SZ or SZAD with current treatment-resistant AVH (two females) (all medicated)	NA[a]	BOLD amplitude in left STG	Down-regulation training of STG activity	3-day training within 2 weeks	The functional connectivity between the brain regions involved in speech production and perception (left STG, left IFG and IPG) increased in accompany with decrease of left STG hyper-activity following the NFB training. The change of functional connectivity was associated with reduction of AVH severity.
Okano *et al.* [32▪▪]	Ten SZ or SZAD with current treatment-resistant AVH (one female) (all medicated)	Chronic	BOLD amplitude in STG	Down-regulation training of STG activity while ignoring a stranger's voice Up-regulation training of STG activity while listening to patients' own voice	1-day training	The decrease of STG activity was observed in 8 out of 10 patients in Task 1 The NFB training resulted in the reduction of the severity of AVH in all patients.
Bauer *et al.* [39▪]	Eleven SZ or SZAD with current treatment-resistant AVH [b] (1 female) (all medicated)	Chronic	Anticorrelation between DMN and CEN	Down-regulation training of DMN and up-regulation training of CEN	One-day training	The reduction of DMN hyperconnectivity was caused by the NFB training. Successful down-regulation of DMN significantly correlated with the improvement of AVH symptoms.
fNIRS-based NFB training						
Storchak *et al.* [44]	A female SZ patient with current treatment-resistant AVH (medicated)	Chronic	O_2Hb amplitude in temporal area	Down-regulation training of temporal area activity when experiencing AVH. Up-regulation training of temporal area activity at the timing of AVH-onset	NA (47 sessions)	The patient was able to up-regulate bilateral temporal area activities in task 2 (but fail to down-regulate bilateral temporal area activities in task 1) The patient's subjective AVH decreased during the NFB training.
EEG-based NFB training						
Rieger *et al.* [47▪]	10 SZ or SZAD with current treatment-resistant AVH [c] (4 females) (unknown medication status)[d]	NA	N1 amplitude P2 amplitude (control condition)	Up-regulation training of N1 (P2) amplitude while listening to beep tones	Four-day training within 2 weeks	Auditory-evoked potentials were not modulated by the NFB training. There was no significant effect of the training on AVH severity (only the learning 'pattern' of NFB training was correlated with change in AVH severity).

ACC, anterior cingulate cortex; AVH, auditory verbal hallucinations; CEN, central executive network; DMN, default mode network; IFG, the inferior prefrontal gyrus; IPG, inferior parietal gyrus; NFB, neurofeedback; SZ, schizophrenia; SZAD, schizoaffective disorder.

[a]Only mean of duration of illness is presented: 10.8 years (SD 8.4).

[b]Ten out of 11 patients performed the NFB training of this study after that of Okano *et al.* [32▪▪].

[c]Participants were randomly assigned to treatment or control condition.

[d]Only mean of medication doses are presented. treatment condition: 333.3 (SD 245.0); control condition: 616.5 (SD 389.1) (chlorpromazine equivalents: mg).

[26,27,29,30]. Oriov *et al.* [31▪▪] reported that patients with schizophrenia successfully downregulated left STG hyperactivity over four sessions during a 2-week fMRI-NFB training period. In addition, the downregulation of left STG activity was accompanied by an increase in functional connectivity between the left STG, left IFG, and IPG (frontal and temporal language regions), and this increase was associated with a reduction in AVH severity. More recently, Okano *et al.* [32▪▪] conducted a 21-min fMRI-NFB training session with schizophrenia patients with treatment-resistant AVH to upregulate STG activity while listening to the patient's own prerecorded voice and downregulate STG activity while ignoring a stranger's voice. This training induced significant reductions in STG (but not motor cortex) activation while ignoring a stranger's voice in 8 out of 10 patients and also decreased the severity of AVH in all patients.

Functional MRI-based neurofeedback training of other regions

Some researchers have suggested that AVH is a result of source misattribution during self-generated thought and inner speech [33,34]. On the basis of this self-monitoring (inner speech) theory of AVH, Dyck *et al.* [35] targeted the ACC using fMRI-NFB training, based on its involvement in differentiating between inner and external speech [36]. After 3 days of fMRI-NFB training, all three schizophrenia patients with treatment-resistant AVH showed significant upregulation of ACC activity and reported subjective improvement in AVH symptoms. However, the small number of patients ($n = 3$) does not allow generalization of these findings for fMRI-NFB of the ACC.

The default-mode network (DMN) has also attracted attention as a neurophysiological marker for fMRI-NFB treatment for AVH; DMN abnormalities (hyperconnectivity of the DMN) have been shown to be associated with the positive symptoms of schizophrenia [37,38]. Bauer *et al.* [39▪] conducted fMRI-NFB training as part of an fMRI-NFB AVH treatment series [32▪▪] to reduce hyperconnectivity of the DMN, centering on the middle prefrontal cortex (MPFC). Results showed that reductions in functional connectivity between the MPFC and STG were accompanied by a decrease in AVH severity.

As described above, the modulation of brain activity centering on the STG using fMRI-NFB training may be a promising treatment for patients with schizophrenia and treatment-resistant AVH. These findings are consistent with repetitive transcranial magnetic stimulation (rTMS) studies that have shown that reducing cortical excitability of the left temporoparietal region improves AVH [40–42]. Although fMRI-NFB and rTMS appear to induce similar effects on AVH, fMRI-NFB may be superior to rTMS because of its ability to visualize the activity that is linked with AVH without the intrusiveness of rTMS.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY-BASED NEUROFEEDBACK TRAINING FOR AUDITORY VERBAL HALLUCINATIONS

Functional near-infrared spectroscopy (fNIRS) has also been employed to assess brain function alterations in schizophrenia [43], although there is only one fNIRS-based NFB study attempt to regulate AVH. Storchak *et al.* [44] reported a single-case study applying a novel fNIRS-based NFB training (instructed to upregulate when expecting and downregulate when experiencing AVH) with a treatment-resistant schizophrenia patient. During the NFB training, the patient only succeeded to upregulate bilateral temporal area activities at the timing of the AVH onset, which was accompanied by the significant reduction of subjective AVH. The authors argued that the constant successful increase of the O_2H amplitude in the target temporal area before the AVH onset may have led to a compensation of neural activity and prevented the emergence of AVH.

ELECTROENCEPHALOGRAPHY/ MAGNETOENCEPHALOGRAPHY-BASED NEUROFEEDBACK TRAINING FOR AUDITORY VERBAL HALLUCINATIONS

Historically, EEG and MEG have been used to identify the neural bases of AVH and language-related functional deficits in schizophrenia because of their superior temporal resolution [45,46]. The fMRI-NFB has an inherent delay in feedback because of the hemodynamic response (approximately 6 s), whereas EEG/MEG-NFB training has no such delay, owing to its excellent temporal resolution. Therefore, EEG/MEG-NFB system is suitable for providing real-time neural dynamics information that underlies AVH. However, to our knowledge, there has only been one study that has used EEG/MEG-NFB training for AVH treatment. Rieger *et al.* [47▪] hypothesized that decreases in the amplitude of the auditory-evoked N1 is related to AVH in schizophrenia and investigated whether modulating the N1 component using EEG-NFB training affects AVH. Despite the intensive 4-day training within 2 weeks, they found no significant effects of EEG-NFB training on either the N1 amplitude or AVH severity.

Instead, they found that the learning pattern of NFB training was correlated with change in AVH severity.

Although the previous study focused on the N1 amplitude, based on the knowledge that the N1 amplitude is attenuated in schizophrenia and is further deteriorated during AVH, there are other promising neurophysiological markers for EEG/MEG-NFB treatment of AVH. The first promising marker is N1 suppression, which is the suppression of auditory cortical activity during vocalization. N1 suppression is thought to reflect the efferent copy/corollary discharge function of the auditory system, which plays a role in the self-monitoring of speech [48,49▪▪]. Therefore, it is conceivable that based on the self-monitoring theory of AVH, N1 suppression abnormalities are closely related to AVH. A previous study supported this hypothesis by showing less N1 suppression in schizophrenia patients with AVH than in non-AVH patients [50]. Therefore, EEG/MEG-NFB training to modulate N1 suppression by targeting the efferent copy/corollary discharge function has potential as a new treatment for treatment-resistant AVH. In addition, a recent study [51▪] showed improvements in abnormal N1 suppression in schizophrenia patients following 40 h of targeted auditory training (TAT) designed to improve brain function for higher order auditory and cognitive processes. The integration of EEG/MEG-NFB training with TAT may improve the efferent copy/corollary discharge function more effectively than TAT alone.

The second promising marker is the increased spontaneous gamma oscillation obtained using EEG, which has been shown to occur during AVH in schizophrenia patients [23]. This phenomenon has been hypothesized to be caused by hypofunction of the N-methyl-D-aspartate receptor of inhibitory GABAergic interneurons [13,52]. There is an underlying assumption that the excitation and inhibition (E/I) imbalance that is predominantly driven by glutamatergic and GABAergic input causes cortical hyperexcitation, which contributes to psychotic symptoms, such as AVH and delusions. Thus, it would be valuable to develop novel treatments that normalize E/I. Although not without challenges, there is potential for tuning neural alterations as an alternative adjunct treatment to alleviate AVH in schizophrenia by regulating and suppressing the increased spontaneous gamma oscillations using EEG/MEG-NFB. Recently, Molina *et al.* [53▪] revealed that the malleability of gamma oscillatory power in response to auditory steady-state stimulation after 1 h of TAT predicts improvement of positive and negative symptoms after 30 h of TAT. Given that gamma oscillations that are evoked by an external input interact with spontaneous gamma oscillations, TAT would be expected to drive the plasticity of spontaneous gamma oscillations. Therefore, it is conceivable that combining TAT and EEG/MEG-NFB training would be an effective method to modulate spontaneous gamma oscillations that are related to AVH severity in patients with schizophrenia.

CAVEATS AND FUTURE DIRECTIONS

Although the discussed NFB treatments have been shown to have promising effects on treatment-resistant AVH in patients with schizophrenia, some caveats should be noted. First, selection of the appropriate AVH model is crucial as there are several models of perceptual disturbances (e.g. bottom-up theory, sensory-gating theory, salience misattribution theory, and predictive-coding theory) [5,9] and AVH (e.g. self-monitoring hypothesis, reduced sense of control, executive and inhibitory control, unstable memories, source monitoring hypothesis, interhemispheric miscommunication, top-down effect and bottom-up prediction deficits, and a hybrid model of spontaneous activations and self-monitoring deficits) in schizophrenia [7,9,54]. The lack of a definitive model of AVH remains a major concern. Of these models, a noteworthy theory-driven approach is the predictive-coding theory, where the brain is defined as a prediction machine that is based on an internal model of the world and interacts with the world using a computational rule of prediction-error minimization [9,55]. Failures in this predictive processing (because of an altered prediction machine) is thought to lead to psychotic symptoms, such as AVH [9]. Next, appropriate selection of device (e.g. fMRI, EEG, or MEG), index (e.g. BOLD signal, event-related potential/field, and components and/or frequency domains), and activity status (evoked or spontaneous/resting) are crucial as they can impact the overall direction of the NFB strategy and its effectiveness. In particular, spontaneous oscillatory activity (EEG/MEG) and connectivity (EEG/MEG/fMRI) that are related to AVH seem to be new targets for suppressing AVH [21,23,24]. The design of the NFB experiment (e.g. symptom-capture design or upregulation/downregulation design) is another notable issue as the appropriate method differs for each AVH model. It is also necessary to consider whether to target a localized area (e.g. STG, IPG, IFG, or ACC) or a network across a wider area related to AVH. Although targeting the STG seems to be a promising localized NFB strategy [31▪▪,32▪▪], targeting the connectivity between the speech motor and speech perception regions of the language network may also be an effective global network approach (e.g.

STG-IFG-IFG) [31▪▪]. In addition, the immediacy of the NFB system and its time lag should be noted. If strict immediacy is required, the delay because of the hemodynamic response of fMRI-NFB training will be problematic. In such cases, EEG/MEG-based NFB training would be more suitable for providing real-time NFB, which has no such delays. Another important factor for real-time NFB is the development of state-of-the-art software that is capable of instantaneous and simultaneous computations of large amounts of data. Novel computational neuroscience approaches may shed light on such real-time computations of complex brain networks [9,56,57]. Furthermore, given the limited efficacy of the above small sample studies as well as some negative findings in NFB trainings [21,47▪,58▪], additional randomized controlled trials (RCTs) with larger samples are essential to ensure the effectiveness of NFB as a widely implemented therapeutic intervention for treatment-resistant AVH [58▪]. There is also the issue of cost-effectiveness. Overall, fMRI-NFB training appears to have a temporal effect for AVH reductions. However, inconveniences and high burden on patients because of high equipment costs, discomfort of the MRI scanner environment, and the high sound volume of the scanner, currently preclude its use in clinical settings. In contrast, EEG is available in many hospitals and institutions at a lower cost. Because of the portability of EEG and new wearable MEG [optically pumped magnetometer (OPM)] [19,59], they are more suitable for NFB approaches that require complex behavioral changes. Moreover, the lack of scanner noise in EEG/MEG makes them ideal methods for targeting AVH. Finally, logistic complexities because of the number of devices (fMRI, fNIRS, EEG, and MEG), modalities (e.g. visual, auditory, and proprioceptive), undefined reinforcement schedule (e.g. continuous or periodic, proportional or binary), undefined reward (e.g. percentage or amplitude), complicated online data processing and artifact rejection/correction [e.g. ocular and muscular artifacts (EEG, MEG), and cardiorespiratory and movement artifacts (fMRI)], the lack of uniformity in NFB systems are the critical issues that need to be solved [60▪▪].

CONCLUSION

Despite recent innovations in antipsychotics, many schizophrenia patients continue to suffer from severe symptoms, including treatment-resistant AVH and social functioning problems. Despite the small number of RCTs conducted to date, with limited efficacy and most studies constituting small sample sizes or case studies, recent research in schizophrenia patients with treatment-resistant AVH has demonstrated that NFB may be useful in helping patients gain control over AVH through self-regulation of brain function. Further larger sample RCTs to test the efficacy of NFB are required to confirm these encouraging findings. Moreover, although fMRI-NFB may be advantageous for regulating localized neuronal activity related to AVH, EEG/MEG-NFB training may be favorable for fast, real-time NFB for regulating ever-changing AVH in schizophrenia. Although various concerns remain, such as optimal model selection, standardized NFB methodologies, logistic complexities in NFB procedures and high burden on patients, NFB is likely to become a new alternative treatment for schizophrenia in the near future. It is our hope that such innovations in NFB training will help to alleviate severe AVH symptoms and improve social functioning in treatment-resistant schizophrenia patients.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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This study demonstrated that schizophrenia patients with treatment-resistant AVH successfully learned to downregulate activity of their left STG following fMRI-NFB training. Patients also showed increased functional connectivity between the left STG, left IFG and IPG (auditory and language-related/speech-related regions) and a reduction in AVH symptoms over the training period.

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This article found that schizophrenia patients with treatment-resistant AVH, who received NFB training to upregulate STG activity while listening to a recording of their own voice and downregulate STG activity while ignoring a recording of a stranger's voice, showed a significant reduction in STG (but not motor cortex) activation while ignoring a stranger's voice and a decrease in AVH scores following the NFB session.

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This is the first study to show a direct causal relationship between meditation-enhanced fMRI-NFB modulation of DMN-CEN activity and postintervention modulation of resting state networks, which resulted in reductions in the frequency and severity of AVH.

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