TITLE: Translating neurocognitive models of auditory verbal hallucinations in schizophrenia into novel therapeutic interventions.

AUTHORS: Orlov N [1 2], Garrison J [3], Allen P [1 2]

AFFILIATIONS

[1] Department of Psychology, University of Roehampton, London United Kingdom (UK)

[2] Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London UK

[3] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK

CORRESPONDING AUTHOR

Paul Allen

Email: paul.allen@roehampton.ac.uk

Tel: 0044 (0)2083925147

ABSTRACT

Neurocognitive models and recent advances in brain imaging allow for a better understanding of the neural underpinnings of auditory verbal hallucinations (AVH). The challenge now for researchers is to use what we have learnt about the neural correlates of AVH and apply these findings as the basis for new and alternative therapeutic interventions. Here we will discuss influential neurocognitive models of AVH, the brain imaging findings that provide support for these models, and how these finding can be used to inform novel interventions using brain stimulation and neurofeedback protocols.

KEYWORDS: Auditory Verbal Hallucinations (AVH), Auditory Cortex, Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), Real-Time Functional Magnetic Resonance Imaging Neurofeedback (rt-fMRI-NF)

INTRODUCTION

Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia, occurring in around 70% of patients with the illness (1) (2). They are associated with high levels of distress and functional disability (3) and approximately a quarter of patients with schizophrenia have made a serious suicide attempt in response to their AVH (4). In around 30% of patients with AVH, traditional antipsychotic drugs have little or no effect (5) meaning novel therapies are needed. Cognitive behavioural therapy (CBT) for AVH has been shown to be effective in some cases (6, 7). However, a recent meta analysis reports that CBT for psychotic symptoms such as AVH has limited efficacy (8) and only short term benefits (7) and other psychological interventions such as Avatar Therapy (9), whilst offering an alternative approach, are still awaiting published randomized control trial data in patients with AVH.

Over the last few decades a number of neurocognitive models have been proposed to account for generation and experience of AVH (10), and recent advances in brain imaging allow for a better understanding of the neural underpinnings of AVH (11, 12). The challenge now for cognitive neuroscientists is to use what we have learnt about the neural correlates of AVH over recent years and apply these findings as the basis for new and alternative therapeutic interventions. Here we will discuss this idea in some detail. Firstly, we will outline potentially useful neurocognitive models so that target brain regions and networks can be identified for therapeutic interventions. Second, we will discuss state-of-the-art technologies that might allow the application of this knowledge to new therapies, and the small number of studies that have utilized these technologies so far.

SELF-MONITORING, PREDICTIVE CODING AND THE AUDITORY CORTEX

Current cognitive models assume that AVH have clear perceptual qualities, are internally generated, but are somehow misrecognised or misattributed to an external source. At a neural level AVH appear to be associated with activity in a distributed network of brain regions (13) although the most robust and replicated finding appears to be elevated and/or aberrant cortical activity in auditory processing areas, particularly the speech-sensitive auditory cortex (14-16). Evidence of increased resting activity (14) and resting cerebral perfusion in the auditory cortex (17) in patients with schizophrenia is consistent with neuroimaging studies employing a 'symptom-capture design' that report increased activation in auditory processing areas when patients are actively experiencing AVH (13). Whilst elevated neural activity in the auditory cortex is likely to underpin the perceptual qualities of AVH, a number of other 'non-sensory' brain regions have also been implicated in AVH including the prefrontal and premotor cortex (PFC), medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and paracingulate sulcus (PCS), as well as subcortical and cerebellar regions (11, 18-20). Thus, AVH and their phenomenological characteristics are likely to emerge from a complex interaction of sensory/cognitive processes and associated neural regions. From a neurocognitive perspective, a particularly difficult phenomenological feature of AVH to understand is the lack of agency that defines the experience (21). Inner-speech models of AVH propose that a loss or lack of agency, and the subsequent misattribution of inner-speech, can come about due to a breakdown in a physiological process known as self-monitoring (22). The self-monitoring model assumes that in patients who experience AVH, inner speech and/or thoughts are not recognized or 'tagged' as self-generated due to a self-monitoring deficit i.e. a dysfunction of the efference copy or corollary discharge mechanism that accompanies a motor action, such as speech or movement (42, 43). Under normal circumstances, an efference copy is generated by motor regions to signal to sensory regions that an action is volitional in nature. In people experiencing AVH, the efference copy produced by inner speech (a presumed motor action) is

defective and does not effectively signal the generation of the accompanying motor action to the corresponding sensory regions. Consequently, this failure can produce confusion regarding the agency between one's own actions/inner-speech and externally generated actions such as perceived voices and speech. At a neuronal level, the model would predict that AVH are associated with greater activity in the auditory cortex when self-generated inner speech is produced (43, 44) because the efference copy signal from speech motor regions fails to attenuate sensory activation in this region. This prediction is broadly consistent with findings from electrophysiological e.g. (23, 24) functional (25, 26) and perfusion neuroimaging studies (27) which reported increased neural activity in auditory sensory regions.

A recent functional Magnetic Resonance Imaging (fMRI) study by Horga and colleagues (28), offers a slightly different theoretical perspective on the observed hyperactivity in auditory cortex seen in patients with schizophrenia and AVH. It is proposed that sensory hyperactivity may arise though sensory learning and predictive coding (PC) deficits in which the influence of *prior* beliefs on sensory input is disrupted. By encoding predictions (priors) and minimizing deviations from these predictions i.e. minimizing prediction errors (PE), neural systems can attenuate response to predictable (sensory) events (28). It is thought that predictive codes drive neural activity in sensory systems such as the auditory cortex (29, 30) and through their role in learning, influence how we form beliefs about sensory input (31).

Horga and colleagues tested the idea that disruption in a system of prediction-based attenuation of sensory activity could explain the elevated cortical activity in auditory cortex reported by imaging studies in patients with AVH. Using a speech-decision task, during which participants' expectations for hearing speech were manipulated, it was reported that patients with AVH displayed a deficit in a PE signaling in the same region of the auditory cortex activated when they were experiencing AVH. Patients with more

severe AVH showed the greater PE deficits and greater activity in the auditory cortex activity during silence. According to Horga and colleagues, these results are consistent with defective PC accounts of schizophrenia *and* with accounts positing defective efference copy signaling, possibly conceived as a type of 'long-range' PC signal between motor and sensory regions. According to Frith's model, efference copies of motor commands convey information about the sensory consequences of self-generated action making them predictable. Defective prediction mechanism, both within sensory regions and/or between motor and sensory regions, would result in a failure in the normal dampening of the auditory cortex response to self-generated speech (23, 28).

It is worth noting however, that whilst at a behavioral level patients with schizophrenia and AVH exhibit difficulty in identifying self-generated information (10), models based on the misattribution of inner speech do not easily account for the observed phenomenology of AVH (48, 49) and it is only an assumption that the cancellation or suppression of re-afference (achieved via the efference copy mechanism) indicates the source of a sensory event i.e. a zero signal is not the same as self-generation (16). On the other hand PC models, although compatible with efference copy models, would argue for a more general impairment in learning and signaling mechanisms in people with schizophrenia, regardless of whether sensory predictions originate from the motor system or within sensory systems (28). It is possible that in sensory systems, shifts towards prior knowledge may provoke anomalous perceptual experiences (32).

Jardri and colleagues have attempted to refine the PC model further still (33). Circular-inference refers to the corruption of sensory data by prior information and vice versa. Recent experimental evidence shows that ascending loops are stronger in people with schizophrenia relative to healthy controls and correlate with the severity of positive symptoms like AVH (33). It is argued that both feed forward and feedback connections

in the brain create strong excitatory loops where top-down influences of priors on sensory regions can easily be misinterpreted as new sensory evidence – making us see (or hear) what we expect. Under normal circumstances such predictable redundant excitatory input however is cancelled by inhibitory signals. Excitatory/inhibitory imbalances in people with schizophrenia are widely reported (34) and are likely to impair this process.

To summarize, defective predictive signaling between motor and sensory regions, and/or within sensory regions could account for increased AC activity widely reported in patients with AVH, and, lead to this misrecognition of internally generated speech and thoughts as external or alien in origin. This raises issues around dysconnectivity *within* auditory sensory regions and *between* auditory and speech motor regions.

REALITY MONITORING DEFICITS AND AVH

In addition to aberrant activity in speech and language regions, deficits in other cognitive and neural mechanisms have been implicated in the experience of AVH, which are also broadly consistent with PC models. A widely researched cognitive ability related to AVH is known as reality monitoring; the ability to discriminate between internally generated and externally perceived memories (35). Hallucinations are thought to result from some impairment in an individual's ability to discriminate information perceived in the outside world from that which has been self-generated (22) so for example, as discussed earlier AVH might arise from a deficit in monitoring the self-generation of inner speech (22, 36). In 1990, Richard Bentall explicitly linked this idea with the source monitoring framework to suggest a specific reality monitoring impairment underlying hallucination generation.

The source monitoring framework (37) suggests that decisions are made about the inner or external nature of information by comparing it with characteristic traces of

perceptual or cognitive content. This is complementary with, and indeed maps at a broad computational level of explanation to the PC account of reality discrimination in hallucinations. In the source monitoring explanation, the concept of priors is replaced by characteristic traces and the emphasis placed on the process by which a decision is made as to the internal or external nature of the information (38). Reality monitoring ability can be tested in the laboratory using a source memory paradigm in which participants recall whether stimuli were previously perceived or had been self-generated, or whether they themselves had performed a task or it had been performed by someone else (39). Using such experimental designs, it has been found that patients with schizophrenia with hallucinations (usually AVH) show reality monitoring impairments compared with healthy individuals and patients without hallucinations (40).

Neuroimaging studies investigating reality monitoring have typically observed activity in a number of brain regions associated with accurate recollection including lateral anterior PFC, dorsolateral PFC, insula/ventrolateral PFC, ACC and lateral parietal cortex (41). However, the brain region that appears to be particularly associated with differentiating between internally and externally generated information is the anterior mPFC (39, 42, 43). This is consistent with previous findings indicating the involvement of anterior mPFC in the retrieval of self-referential information (44) and in other introspective or internally generated processes including day dreaming, evaluating personal attributes or attributing mental states to others (45, 46). Neuroimaging studies have revealed that patients with schizophrenia show dysfunction associated with reality monitoring impairment in the anterior mPFC (42, 47). Notably, the observed reduction in mPFC activity appears specifically related to reality monitoring performance, rather than an element of more general cognitive dysfunction (48). This suggests that reality monitoring might be a distinct neurocognitive deficit in schizophrenia.

Consistent with this neuroimaging evidence, recent work has found that reality

monitoring in healthy individuals is associated with the morphology of the PCS, a structure within the mPFC of the brain (49). The PCS lies adjacent to the ACC, a region that shows significant variation within the population (50), with the relative location and size of its functional regions dependent on local variations in sulcal and gyral anatomy (51). For some individuals there is an extra fold in the ACC, resulting in the tertiary PCS located dorsal and parallel to the more dominant cingulate sulcus (Figure 1). Among the last sulci to develop in utero, the PCS shows significant between subject variation, being completely absent in between 12% and 27% of the brain hemispheres examined from healthy individuals (52, 53), Variability is also seen in the PCS in patients with schizophrenia, with the sulcus absent in 44% of brain hemispheres examined for patients compared with healthy controls (53, 54).

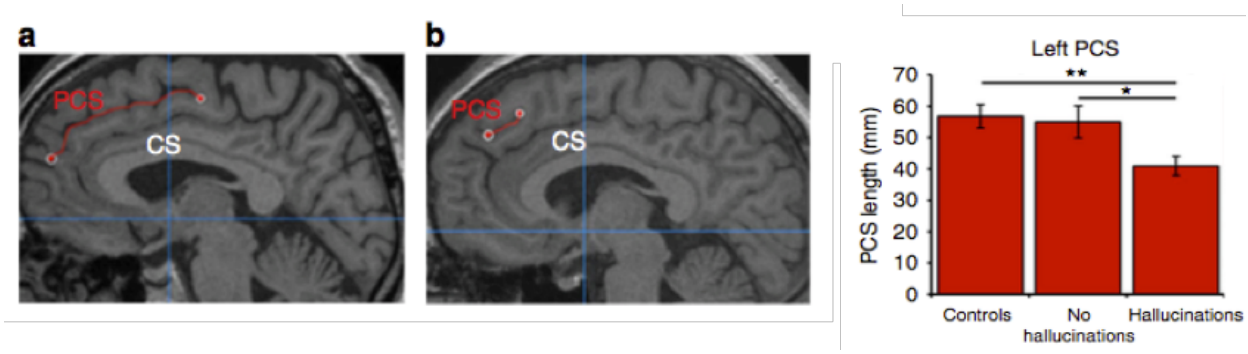

Figure 1. Paracingulate sulcus (PCS) morphology. Left: the PCS, marked in red, lies dorsal and parallel to the cingulate sulcus (CS). (a) the PCS is measured from its origin in the first quadrant to its end. (b) the PCS appears less distinct; it is measured from the point at which it runs in a posterior direction, dorsal to the cingulate sulcus. Right: the chart shows left hemisphere PCS length in patients with schizophrenia with and without hallucinations and healthy controls (55)

In the experimental study by Buda and colleagues (49), it was found that healthy individuals with bilateral absence of the PCS were impaired at reality monitoring judgments, together with the metacognitive ability to introspect about their performance. More recently, in a sample of 113 patients with schizophrenia, we have shown that the length of the PCS is shorter in patients with hallucinations compared to those without (55). These results were not explained by differences in gyrification across the whole

brain, nor by brain volume, and were validated using automated measurement of local gyrification index and voxel-based morphometry analysis. Moreover, there was no difference in PCS length related to the experience of hallucinations in different modalities, consistent with a generalized role for reality monitoring impairment in the formation of hallucinations, regardless of the sensory modality in which they occur. As such, this provides compelling evidence linking brain morphology to the experience of hallucinations in schizophrenia.

Several factors support the role of paracingulate cortex in the generation of hallucinations. The PCS and surrounding anterior cingulate cortex are implicated in a range of functions consistent with reality monitoring, including understanding social interactions, integrating information streams, error detection and monitoring of cognitive processes (56, 57). Furthermore, the significant individual variation seen within the population is known to result in specific functional consequences (50, 58). More specific links to hallucinations come from measurements of metabolic activity within the ACC which are associated with the experience of auditory verbal hallucinations in schizophrenia (59, 60). For example, it is suggested that the experience of an AVH might be initiated with spontaneous random activity in speech sensitive auditory cortex within the superior temporal gyrus (STG) (11). Hunter and colleagues (61) have shown that such spontaneous activity in auditory cortex can be detected in healthy individuals during silence, and correlates with activity in the ACC, consistent with an associated process of reality monitoring. Finally, there are extensive connections between the cingulate region and brain areas which are known to be active during the experience of auditory verbal hallucinations (discussed below).

To summarize, the mPFC, ACC and PCS appear to be important regions for discriminating between internally generated and externally perceived memories and events. There are extensive connections between the cingulate region and brain areas

which are known to be active during the experience of AVH (i.e. sensory regions). Dysconectivity between these regions may results PC in deficits, source confusion and erroneous attribution regarding the origins of internally generated information. Such connectivity studies are discussed in the next section.

CONNECTIVITY AND AVH

It has been established that AVH are associated with the activity in speech and language areas, regions that are involved in self-agency and monitoring, and memory processes (12). Consequently, neurocognitive models of AVH (10, 11, 21, 22, 62) have long emphasised altered interactions and connectivity between neural regions involved in speech and language function e.g.(23, 24), and regions thought to be involved in the monitoring or 'tagging' of internally generated speech and thoughts (46, 63, 64). Consistent with these models, connectivity studies using different methodological approaches report altered structural, functional and effective connectivity in people with schizophrenia (65); several studies have specifically reported altered connectivity in patients with AVH (12). Functional connectivity (FC) is a widely used methodological approach, allowing the assessment of the temporal correlation between blood-oxygenation-level dependent (BOLD) between two or more regions (66). In the context of the neurocognitive models already discussed, efference copy and/or PC deficits in people with schizophrenia would likely manifest in altered functional connectivity between sensory, motor and regions supporting higher level cognitive functioning such as reality monitoring (i.e mPFC/PCS). Broadly consistent with these neurocognitive models, altered functional and structural connectivity between auditory cortex and the inferior frontal gyrus, encompassing speech motor areas, has been widely reported (67-71). For example Curcic-Blake (72), used an inner speech task to investigate connectivity difference in patients with schizophrenia with and without AVH and healthy individuals. They reported reduced connectivity from the posterior STG (Wernicke's

area) to the inferior frontal gyrus (Broca's area) in patients with AVH. Dysconnectivity between these fronto-temporal language regions in patients with schizophrenia and AVH is also seen in electrophysiology studies reporting reduced coherence between these regions (23, 24). Thus, reduced connectivity between speech motor and sensory regions may form the basis of defective efference copy signaling leading to, according the self-monitoring models, a failure to attenuate sensory activity and confusion regarding the source of inner-speech (22). Aberrant functional connectivity in temporal-parietal sensory and language regions, and in primary and secondary auditory cortex in patients with AVH, is also reported (12). These finding may be consistent to some degree with impaired PC signaling in sensory regions. In addition, evidence suggests that AVH are associated with increased connectivity in a cortico-striatal brain network, linking auditory sensory regions, inferior frontal gyrus and the putamen (68). This raises the possibility that altered striatal function in patients with schizophrenia is related to altered connectivity in language and sensory regions. Indeed, theoretical models of PC posit a central mechanistic role for dopaminergic signaling (30, 73) and patients with psychosis exhibit abnormal physiological responses associated with reward prediction error in the dopaminergic midbrain, striatum and limbic system (74).

The involvement of the ACC and other cortical midline regions in reality and source monitoring has been discussed in the previous section. Several studies have investigated connectivity between fronto-temporal speech and language regions and cortical midline regions. Mechelli and colleagues (75) investigate task based interactions between the frontal and temporal language areas and the ACC in patients with and without AVH and healthy controls. For healthy controls and patients without AVH, connectivity from the STG to ACC activity was greater for 'other-person' spoken words compared to self-spoken words; this finding was reversed in patients with AVH. A similar study using a source judgments task of externally presented self/other speech reported similar findings, showing that connectivity between the mPFC and the left STG

was altered in patients with schizophrenia relative to healthy controls (76). To date no studies have directly examined connectivity between the PCS and fronto-temporal language regions but consistent with dysconnectivity theories of schizophrenia (65, 77), it is suggested that variation in paracingulate gyrification, together with the associated change in cortical volume observed in schizophrenia in patients with hallucinations, might result in impaired reality monitoring ability due to weakened functional or structural connectivity with these proximal and distal brain regions (55).

Taken together, connectivity findings in patients with AVH suggest a complex interaction between the language, auditory and monitoring networks that are consistent with neurocognitive models implicating defective efference signaling and predictive coding. Although the literature is not equivocal in this regard, results from connectivity studies point to aberrant connectivity between inferior frontal, temporo-parietal and cortical midline regions in patients with AVH, implicating these regions as key targets for novel interventions that can alter brain activity and connectivity, such as non-invasive brain stimulation and real-time fMRI-neurofeedback (rt-fMRI-NF).

CAN NEUROCOGNITIVE MODELS OF AVH INFORM NEW INTERVENTIONS?

Over the last few decades non-invasive brain stimulation has emerged as a tool with the potential to alter brain activation. The available non-invasive brain stimulation techniques can be divided into those using magnetic stimulation, and those utilising direct currents to modulate neuronal firing. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have recently been utilised for the treatment of AVH in patients with schizophrenia. TMS represents a brain stimulation technique based on the principle of electro-magnetic induction of an electric field that is passed through the skull to the brain (78). The device creates a strong electric field through a coil, which in turn induces a small magnetic field pulse underneath the applied

scalp area. The flow of ions generated by this field alters the electric charge of cell membranes leading to neuronal depolarization or hyperpolarization (79).

TMS can be applied at low frequency (≤1Hz) to decrease cortical excitability. Studies have demonstrated that TMS is able to modulate the activity of a particular cortical region, resulting in trans-synaptic effects on other distant areas (80). A number of studies have utilised TMS for the treatment of AVH and meta-analytic work suggests that TMS induces a reduction of AVH in the small to medium effect size range (81). TMS has been most commonly applied to language production and comprehension regions. Nonetheless, data on the neurophysiological effects of TMS on the AVH networks is still relatively sparse. The available reports suggest that TMS affects not only the stimulated brain regions, but also connected brain networks raising the possibility that this stimulation technique could be used to reconfigure connectivity and communication in networks impaired in patients with AVH. For example, 4-weeks of TMS to the left STG, resulted in reduction of treatment resistant AVH and was associated with decreased activation in the primary auditory cortex (82). Whereas, 10 days of TMS resulted in significant reduction of AVH (at least 50%), but only in those participants who demonstrated a higher regional cerebral blood flow in the STG before treatment (27); possibly due to impaired predictive signaling from motor or cortical midline regions. Indeed, consistent with this notion, TMS applied to the left tempero-parietal junction (TPJ) has been associated with reduced cerebral perfusion in the IFG and cingulate cortex measured with arterial spin labeling, demonstrating wider network effects (83).

Transcranial direct current stimulation (tDCS) is a form of unidirectional current stimulation. Among the low-current stimulation protocols, tDCS represents the most widely explored for the treatment of AVH. tDCS represents a stimulation in which the flow of direct current through two sponge electrodes (cathode and anode) is applied to

the scalp, which results in changes in cortical excitability by influencing spontaneous neural activity (84). Cathodal stimulation reduces spontaneous firing rates, whereas anodal stimulation increases firing rates (85). To date only a small number of studies have investigated the efficacy and neurophysiological effects of tDCS on AVH e.g. (86). One study observed that 10 sessions of tDCS applied to the left TPJ resulted in the reduction of AVH and was accompanied by reduced FC in the left TPJ with left anterior insula, right IFG, and increased FC of the left TPJ with the left angular gyrus and left DLPFC and the precuneus. The reduction of AVH severity was specifically correlated with a reduction of FC between the left TPJ and left anterior insula (83). These reports suggest that both TMS and tDCS are viable treatment option for refractory AVH. However, more and larger studies are needed to confirm the efficacy of stimulation protocols, and to investigate the underlying mechanism of action.

The recent technical improvements in functional Magnetic Resonance Imaging (fMRI) have enabled the development of real-time protocols for the treatment of AVH (87). These fMRI protocols have been developed to provide feedback about brain activation in real time in order that participants can progressively achieve voluntary control over their brain activity. Due to its high spatial resolution Real-time fMRI- neurofeedback (rt-fMRI-NF) allows for the precise targeting of specific brain regions, by using either structural or functional brain region localisers (87). The signal from a chosen brain region(s) is derived by means of blood-oxygen level- depend (BOLD) and is presented through a visual feedback interface, usually through a thermometer display. To date rt-fMRI-NF for the treatment of AVH has only been utilised by two studies. Dyck and colleagues utilized this technique to improve AVH by training three patients to up-regulate neural activity ACC. The ACC was chosen as the key region involved in the generation and intensity of AVH and because its role in source and reality monitoring is well established. Results demonstrated a reduction in AVH, which was accompanied by increased ACC activation and changes in the AVH related networks (88). Indeed, rtf-

MRI-nfb studies have demonstrated that training applied to a single target region can influence and reconfigure network connectivity (89, 90). Our own data (in press) shows that rt-fMRI-NF applied to the left STG, results in deceased activity in the STG and increased FC between the STG and the IFG and the inferior parietal cortex. Changes in network connectivity brought about by rtf-MRI-NF may have improved communication between speech motor and sensory regions. Intriguingly, enhanced FC between these regions was accompanied by a change in patients' beliefs about the origins of their voices (Orlov et al. in press).

CONCLUSIONS AND FUTURE DIRECTIONS

AVH are a complex phenomenon and researchers are still some way from understanding the neural substrate of these aberrant auditory perceptions. Whilst neurocognitive models and brain imaging findings can only go so far in explaining the complex phenomenology associated with AVH, some progress has been made and encouragement can be taken from empirical work that supports existing theoretical models of AVH. Whilst it is not always possible to reconcile neuroimaging findings with existing models of AVH, there is a substantial body of neuroimaging evidence that supports the basic notion that AVH arise through impaired signaling *within* sensory regions and *between* sensory, motor and monitoring regions. This raises the possibility that interventions enabling the modulation of activity and/or the reconfiguration of connectivity between these regions in patients with AVH could have 'theoretically-guided' therapeutic benefits. This is important because basing such intervention on theoretical models allows researchers to better understand mechanisms of action and to formulate clear prediction. The secondary auditory cortex and TPJ region, the IFG, and cortical midline structures encompassing the mPFC, ACC and PCS all appear to be suitable regions for therapeutic intervention using state-of-the-art techniques such as TMS, tDCS and rt-fMRI-NF. A handful of preliminary studies have demonstrated that regulating activity within these regions and altering connectivity between them can

reduce the severity of AVH in patients with treatment refractory symptoms. However, large randomized control trials are now needed to carefully test the efficacy of these interventions, particularly the longer-term effects. It is also likely that brain stimulation and neurofeedback interventions will not work for all patients with AVH. Thus, it is important that predictors of treatment response are established during preliminary studies.

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