

Cortical Activations During Auditory Verbal Hallucinations in Schizophrenia: A Coordinate-Based Meta-Analysis

Renaud Jardri, M.D., Ph.D.

Alexandre Pouchet, M.D.

Delphine Pins, Ph.D.

Pierre Thomas, M.D., Ph.D.

Objective: Auditory verbal hallucinations (AVHs) constitute severe, incapacitating symptoms of schizophrenia. Despite increasing interest in the functional exploration of AVHs, the available findings remain difficult to integrate because of their considerable variability. The authors' aim was to perform a robust quantitative review of existing functional data in order to elucidate consistent patterns observed during the emergence of AVHs and to orient new pathophysiological models of hallucinations.

Method: Ten positron emission tomography or functional magnetic resonance imaging studies were selected for the meta-analysis after systematic review. A total of 68 patients with schizophrenia spectrum disorders experiencing AVHs during scanning were included. According to a random-effects activation likelihood estimation algorithm, stereotaxic coordinates of 129 foci, reported as significant in the source studies, were extracted and computed to estimate the brain locations most consistently associated with AVHs

across studies (cluster-extent threshold: 200 mm³).

Results: Patients experiencing AVHs demonstrated significantly increased activation likelihoods in a bilateral neural network, including the Broca's area (activation likelihood estimation=1.84×10⁻³), anterior insula (1.78×10⁻³), precentral gyrus (1.46×10⁻³), frontal operculum (1.29×10⁻³), middle and superior temporal gyri (1.59×10⁻³), inferior parietal lobule (1.33×10⁻³), and hippocampus/parahippocampal region (1.90×10⁻³).

Conclusions: This meta-analysis demonstrated that experiencing AVHs is associated with increased activity in fronto-temporal areas involved in speech generation and speech perception, but also within the medial temporal lobe, a structure notably involved in verbal memory. Such findings support a model for AVHs in which aberrant cortical activations emerge within a distributed network involved at different levels of complexity in the brain architecture. Critical future directions are considered.

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Hallucinations can be defined as perceptions without corresponding sources in the external world. This feature represents one of the main positive symptoms of schizophrenia spectrum disorders, and 60%–70% of patients meeting the diagnostic criteria for this pathology experience hallucinations (1). Even though they may involve any of the senses, auditory verbal hallucinations (AVHs) are most prevalent in such a psychiatric context. Patients experiencing AVHs usually describe hearing words, sentences, and conversations that are often intrusive or comment on their thoughts. In about 25% of patients, this symptom can be drug-resistant and become chronic (2), causing an impaired quality of life. The pathophysiology of AVHs is still poorly understood, even though neuroimaging exploration has expanded in the recent decades to address various morphometric, functional, and connectivity issues in patients with schizophrenia. Many underlying mechanisms for AVHs have been proposed (3), most of which are not mutually exclusive. Three main mechanisms are briefly presented in the present meta-analysis. First, some authors have postulated that AVHs could result from aberrant perceptions generated in auditory regions.

Primary support for this theory came from the generation of involuntary auditory or verbal material during per-operative electrical stimulations of the temporal cortex in nonschizophrenia subjects (4). Another influential hypothesis concerning the origin of AVHs is external misattribution of self-inner speech. According to this model, patients with schizophrenia are unable to identify their own thoughts as self-generated and, furthermore, interpret them as intrusive alien voices within their heads (5). Finally, possible dysfunctions in the neural substrates of episodic verbal memory have been proposed to account for the involuntary emergence of AVHs (6).

An initial reappraisal of the functional imaging procedures developed to test these pathophysiological hypotheses allowed us to conceptually distinguish between two main study categories. First are the cognitive studies comparing hallucinators and nonhallucinators. These studies, called trait-studies, investigate the neural bases of the susceptibility to hallucinate, independent of the subjects' experience during scanning. Second are state-studies conducted during the occurrence of an AVH, which are of particular significance for our purpose, since they directly

measure brain activations associated with symptom emergence. However, the problem of disentangling the previously evoked hypotheses regarding the origin of AVHs is actually exacerbated by the fact that only a few studies have directly explored the AVH state, resulting in inconsistencies between findings. Some authors have identified restrictive activations in the Heschl's gyrus (7, 8) or in Broca's area (9, 10) in support of a strict sensory or motor origin for AVHs. Meanwhile, other studies have identified more distributed fronto-temporal networks coupled with subcortical structures (11–13). Notable reasons for this difference include the fact that an AVH constitutes an unpredictable subjective event, for which various detection designs have been proposed. In a first subset of studies, symptom occurrence was signaled by pressing a response button when experiencing an AVH during scanning (7, 10, 13, 14). Other authors have employed a discontinuous acquisition method: the random sampling approach, in which a large number of functional magnetic resonance imaging (fMRI) volumes were acquired at random intervals during AVHs (11, 15). Patients reported their sensory experiences immediately after each acquisition. Besides these hypothesis-driven methods, some studies have used more data-driven methods, such as spatial Independent Component Analysis. This method does not rely on a pre-defined model of brain activity (16). In these studies, AVH occurrences were sometimes signaled by button presses (8, 17) or on the basis of a posteriori standardized interviews (12, 18) to help select the components of interest.

Another plausible explanation for disparities across studies could be considerable interindividual variability of the brain areas involved in AVHs, supporting several possible underlying mechanisms. However, since the available reports often included small samples or did not perform group analyses, it remains difficult to draw definitive conclusions and generalize to the whole population of patients based on the findings. Quantitative meta-analytic techniques have been precisely developed to provide objective measures of functional data and resolve such conflicting views. In the present review, we employed a revised version of the activation likelihood estimation algorithm (19) to describe the brain locations most consistently active during the activation likelihood estimation state across studies. Activation likelihood estimation was recently judged to be the best coordinate-based meta-analysis method when compared with the gold standard of image-based procedures (20). This method allowed us to perform a random-effects meta-analysis and to control for one of the major drawbacks of the previous fixed-effects procedures (i.e., their strong tendency to be dominated by one or a few individual studies) (21). In the present meta-analysis, we postulated that AVHs in patients suffering from schizophrenia spectrum disorders could rely on the interaction between several brain areas involved in a widespread cortical network rather than on restricted sensory or motor activations.

Method

Literature Selection, Data Collection, and Preparation

We first conducted systematic MEDLINE searches to identify all neuroimaging studies about the hallucinatory phenomenon that were published between 1990 and May 2009 (Figure 1). The following key words were employed: "hallucination," "activation," "blood flow," "metabolism," "fMRI," "PET" (positron emission tomography), and "SPECT." We also used the related articles function of the PubMed database and the reference list of retained studies to identify additional articles. A total of 59 studies were collected using this process. We then specifically selected state studies of the AVH phenomenon in people suffering from schizophrenia spectrum disorders. Each article under consideration was independently assessed on this main judgment criterion by two raters (Drs. Jardri and Pouchet) prior to reaching a consensus according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (<http://www.prisma-statement.org/statement.htm>). After reviewing all abstracts, articles that did not meet this criterion were excluded. This was the case for systematic reviews (22, 23), activation studies exploring AVHs in people outside of the schizophrenia spectrum (24–34), trait studies comparing patients with hallucinations with nonhallucinators (35–58), studies of isolated extraauditory hallucinations (59), and studies measuring brain activation prior to the onset of AVHs (60–62). After full-text review, secondary exclusions were made of resting state perfusion studies that did not address AVH occurrence (63–65) and studies in which stereotaxic results were not reported (9, 66–68). E-mail contact was made directly with the authors of the latter articles in an attempt to establish these stereotaxic coordinates, but this attempt was unsuccessful. Finally, since two studies reported partially overlapping samples (7, 8), only data resulting from brain-wide analysis methods were retained (7) to minimize the possibility of nonindependent observations. Importantly, it was not necessary to exclude single-case reports from the meta-analysis, since a weighting factor for the sample size of the retained studies was implemented in the activation likelihood estimation algorithm (19). In summary, 10 whole-brain activation studies using PET or fMRI were selected. Five studies used a button-press method to signal AVH occurrences (6, 7, 10, 13, 14), two employed the random sampling method (11, 15), and three used either data-driven analyses combined with a response box (17) or a posteriori interviews (12, 18). For each of the 10 remaining articles listed in Table 1, we extracted the coordinates (x, y, z) for the 129 foci of interest and the corresponding number of subjects. Only overactivation foci reported as significant at a p value <0.05 in the source studies were included. Nevertheless, when different sensory modalities were involved during hallucinations (15, 17), only foci related to AVHs were selected for further analysis. When necessary, a transformation from the Montreal Neurological Institute to the Talairach space (69) was performed using the *icbm2tal* algorithm (70), implemented in the *GingerALE* software (www.brainmap.org/ale/).

Meta-Analysis Procedure

A widely used technique for coordinate-based meta-analyses of neuroimaging data is activation likelihood estimation, which treats reported foci not as points but as spatial probability distributions centered at the given coordinates (71). In the present research, we used a revised version of the activation likelihood estimation algorithm implemented in the *GingerALE* Version 2.0 software (Research Imaging Center, University of Texas at San Antonio, San Antonio, Tex.) (72). This revised activation likelihood estimation implementation has been shown to be more specific than previous algorithms, while retaining comparable sensitivity (19). The activation likelihood estimation meta-analysis followed three steps.

TABLE 1. Characteristics of Included Studies Measuring Functional Brain Activity Associated With Auditory Verbal Hallucinations in Schizophrenia Spectrum Disorders

Study	Imaging Modality	Patients	Diagnostic Criteria	Design	Number of Foci	Original Stereotaxic Space
Copolov et al. (6)	PET	Schizophrenia (N=7); schizoaffective disorder (N=1)	DSM-IV	Online button press during auditory verbal hallucinations	6	Talairach and Tournoux standardized
Dierks et al. (7)	fMRI	Schizophrenia (N=3)	DSM-III-R	Online button press during auditory verbal hallucinations	23	Talairach and Tournoux standardized
Jardri et al. (18)	fMRI	Childhood-onset schizophrenia (N=1)	DSM-IV-TR	Independent component analysis + a posteriori interview	4	Talairach and Tournoux standardized
Jardri et al. (17)	fMRI	Schizophrenia (N=1)	DSM-IV-TR	Independent component analysis + online button press during auditory verbal hallucinations	10	Talairach and Tournoux standardized
Jardri (12)	fMRI	First-episode schizophrenia (N=15)	DSM-IV-TR	Independent component analysis + a posteriori interview	14	Talairach and Tournoux standardized
Lennox et al. (14)	fMRI	Schizophrenia (N=4)	ICD-10	Online button press during auditory verbal hallucinations	19	Talairach and Tournoux standardized
Shergill et al. (11)	fMRI	Schizophrenia (N=6)	DSM-IV	Random sampling	20	Talairach and Tournoux standardized
Shergill et al. (15)	fMRI	Schizophrenia (N=1)	DSM-IV	Random sampling	3	Talairach and Tournoux standardized
Silbersweig et al. (13)	PET	Schizophrenia (N=5)	DSM-IV	Online button press during auditory verbal hallucinations	9	Talairach and Tournoux standardized
Sommer et al. (10)	fMRI	Schizophrenia (N=18); schizoaffective disorder (N=3); psychosis not otherwise specified (N=3)	DSM-IV	Online button press during auditory verbal hallucinations	21	Montreal Neurological Institute

The first step was to compute modeled activation maps for each included study. All of the foci reported for a given study were modeled as Gaussian distributions and then merged into a single three-dimensional volume. Rather than using a prespecified full-width half maximum for the Gaussian distribution, an uncertainty modeling algorithm implemented in GingerALE Version 2.0 was employed to empirically estimate the between-subjects and between-templates variability of the included studies. The second step was to compute the activation likelihood estimation values on a voxel-to-voxel basis by taking the union of these individual modeled activation maps. This analysis was constrained to a gray matter mask that defined the outer limit of the Talairach space. Finally, to assess above-chance clustering between experiments, an empirical null distribution of random spatial association was established to distinguish between noise and true convergences. To do so, an iterative permutation procedure (10^{11}) was used by sampling each activation likelihood estimation result at an independently chosen random location. This test was corrected for multiple comparison bias using the false discovery rate (73) method, with standard values recommended by the authors of the software, so that the *q* value (the number of expected false positives) was set at 0.05 and a cluster-extent threshold of 200 mm³ was chosen. Final activation likelihood estimation results were exported as a NIfTI file into the Mango software (<http://ric.uthscsa.edu/mango/>) and were overlaid onto an anatomical template generated by spatially normalizing the International Consortium for Brain Mapping template to Talairach space (74).

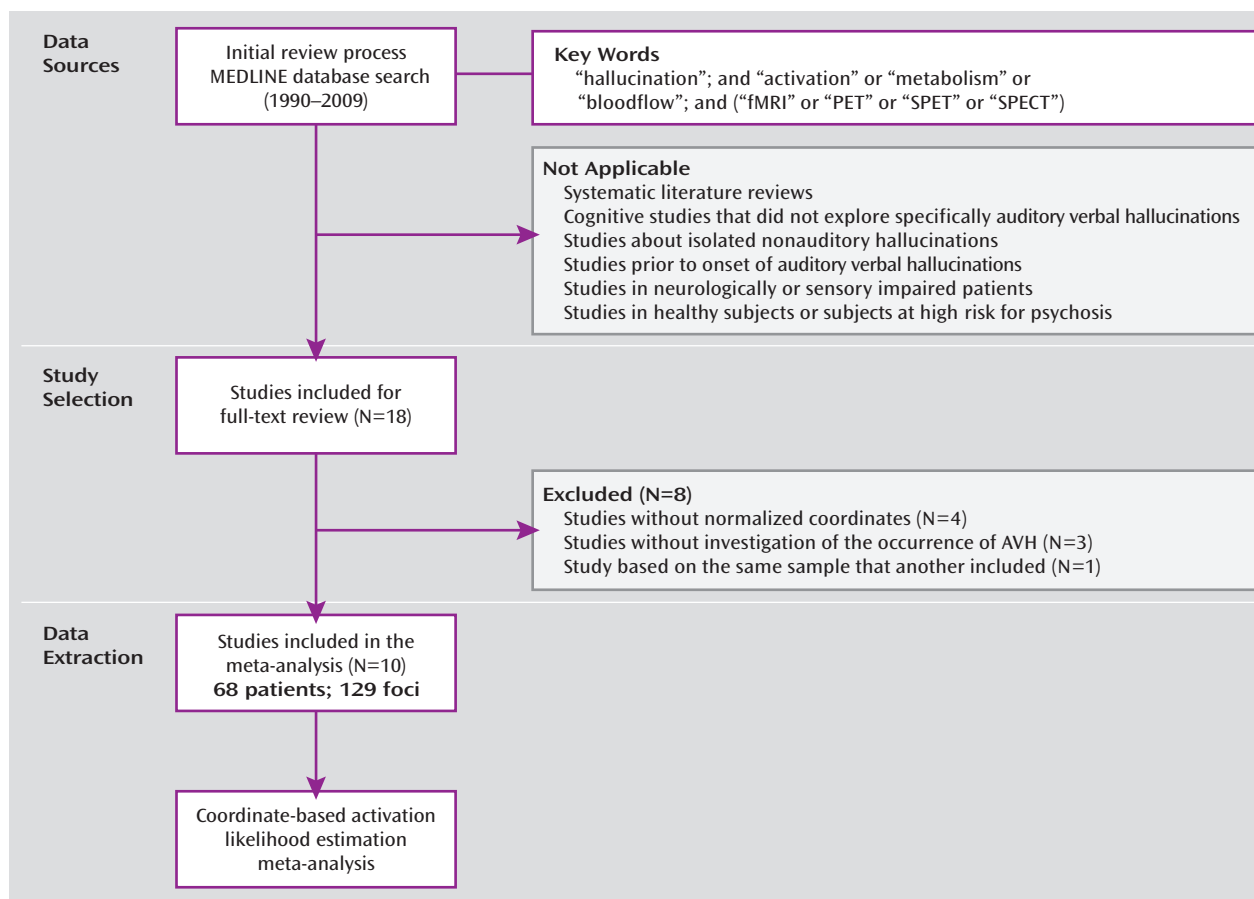
Results

When experiencing AVHs, patients with schizophrenia spectrum disorders demonstrated significantly increased

activation likelihoods in five clusters distributed in temporal, parietal, frontal, and subcortical sites. The meta-analysis results of these 10 studies are synthesized in Table 2 and Figure 2. The largest clusters were located in the left inferior frontal gyrus at the level of the pars opercularis (Brodmann's area 44), the left precentral gyrus (Brodmann's area 6), the bilateral anterior insula (Brodmann's area 13), and the frontal operculum (Brodmann's area 47). Increased values were also measured in the left middle temporal (Brodmann's area 21) and superior temporal gyri (Brodmann's area 22). This was in addition to the left hippocampus/parahippocampal region (Brodmann's area 27). Additional elevated activation likelihood was measured in the inferior parietal lobule at the level of the left supramarginalis gyrus (Brodmann's area 40). Finally, increased likelihoods were measured in the right-sided internal globus pallidus.

Discussion

In the present review, we used coordinate-based meta-analysis to determine the brain areas predominantly recruited during AVHs in people suffering from schizophrenia spectrum disorders. Critically, the random-effects activation likelihood estimation method used allowed generalization of the results to the entire population of studies from which the analyzed experiments were drawn.

FIGURE 1. Flow Diagram of Article Selection Process^a

^a Data include the numbers of studies initially selected and reasons for exclusion; 10 studies were finally selected, with a total of 68 patients and 129 foci of interest.

TABLE 2. Brain Regions With Significantly Elevated Likelihoods of Activation During Auditory Verbal Hallucinations in Subjects With Schizophrenia Spectrum Disorders

Identified Clusters	Brodmann's Area	Brain Laterality	Talairach and Tournoux Coordinates (x,y,z) ^a	Cluster Size (mm ³)	Activation Likelihood Estimates (×10 ⁻³) ^b
Cluster A					
Broca's convolution	44	Left	-48, 10, 7	1,312	1.84
Anterior insula	13	Left	-42, 0, 6	1,240	1.78
Precentral gyrus	6	Left	-54, 0, 14	488	1.46
Cluster B					
Hippocampus/parahippocampal gyrus	27	Left	-24, -32, -4	1,664	1.90
Cluster C					
Anterior insula	13	Right	44, 6, -4	964	1.66
Frontal operculum	47	Right	42, 12, -10	265	1.29
Cluster D					
Superior and middle temporal gyri	21–22	Left	-54, -44, 16	800	1.59
Cluster E					
Supramarginalis gyrus	40	Left	-52, -20, 15	304	1.33

^a Data indicate coordinates in the stereotaxic space of the weighted center for each cluster showing greater probability of activation during auditory verbal hallucinations.

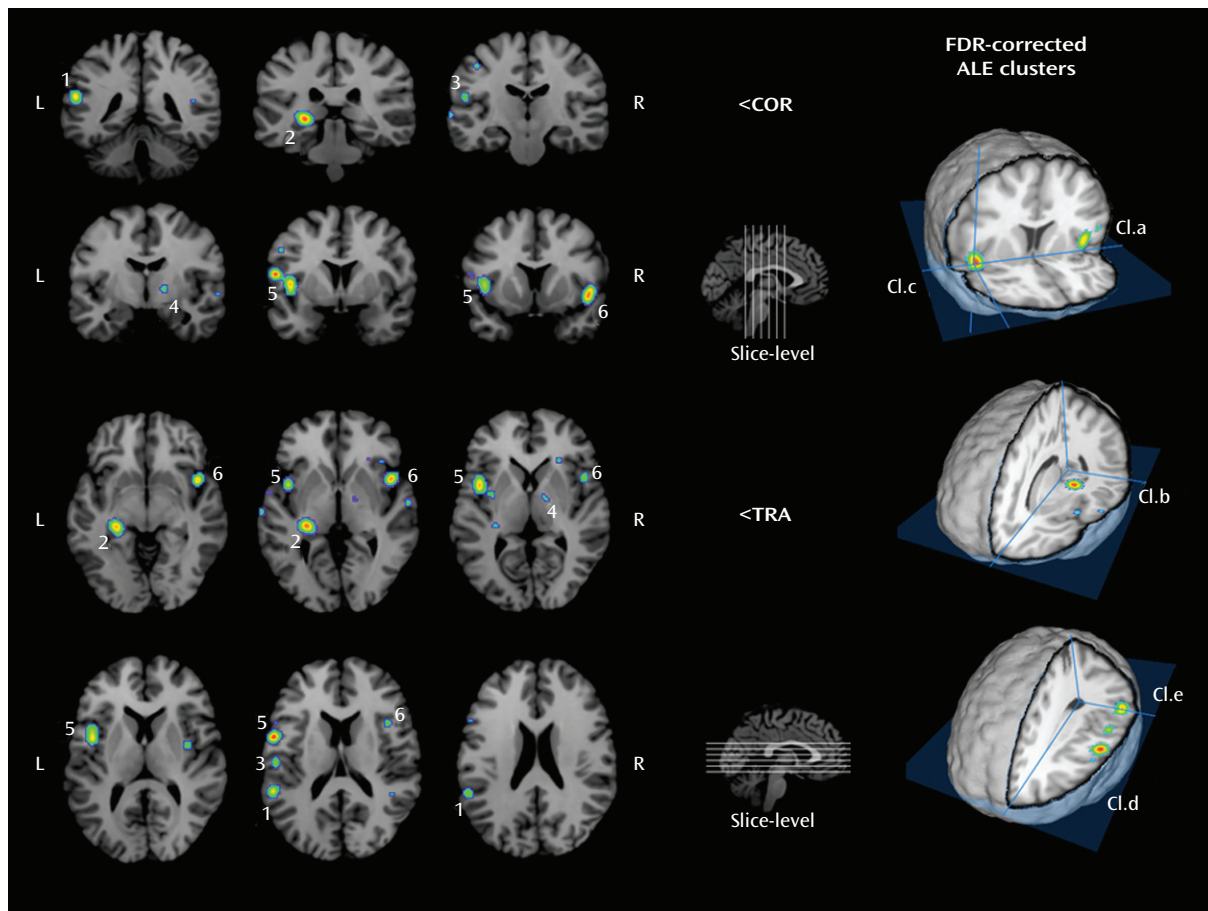
^b Estimates are reported for each cluster with a significance of a corrected value ($p < 0.05$).

Its robustness was reinforced by a weighting procedure of the localizing power in favor of the studies with larger sample sizes.

This meta-analysis first identified a widespread set of dysfunctional language-related areas that present increased

activity when patients experience AVHs. The largest clusters were identified in cortical areas involved in speech generation. The left pars opercularis (Brodmann's area 44), located in the inferior frontal gyrus, is part of Broca's area. This region is bounded by the premotor precentral gyrus

FIGURE 2. Results of Included Studies Measuring Functional Brain Activity Associated With Auditory Verbal Hallucinations in Subjects With Schizophrenia Spectrum Disorders^a



^a The first three columns depict the activation likelihood estimation (ALE) results on coronal (COR) views (upper panel) as well as on transverse (TRA) views (lower panel) of the brain anatomy. The fourth column depicts slice levels shown on sagittal views. The fifth column shows clusters (Cl.a to Cl.e) of consistent activity among patients with schizophrenia spectrum disorders experiencing auditory verbal hallucinations, projected over a standardized template (see Table 2 for peak coordinates; all clusters were >200 mm³, with false discovery rate [FDR]-corrected p values <0.05). Greater likelihoods were measured within the left inferior parietal lobule, left hippocampus/parahippocampal region, left superior temporal gyrus, Globus pallidum, Broca's convolution, right anterior insula, and frontal operculum. Abbreviations: L=Left; R=Right.

(Brodmann's area 6) to its posterior and in depth by the anterior insula (Brodmann's area 13). Overall, the insula constitutes one element of the homologous region of Broca's area on the right side of the brain. Lesion and functional imaging studies have revealed the critical involvement of this extended Broca's convolution in syntactic processing (75–77) and also during verbal imagery (78). In up to 90% of healthy right-handed subjects, this region shows strong functional left lateralization (79). Some authors have suggested that reduced language lateralization in the frontal lobes of schizophrenia patients could account for the emergence of AVHs (80–82). Our meta-analytic data, which show significant activations during AVHs within the left Brodmann's area 44 and the right Brodmann's area 13, fully support this theory.

The present meta-analysis also showed increased likelihoods within the left middle (Brodmann's area 21) and superior temporal gyri (Brodmann's area 22), which compose the associative auditory cortices. The inferior parietal

lobule (Brodmann's area 40), part of Wernicke's convolution on the left side of the brain, was also identified as a region of increased activity and is notably involved in speech processing (83). Interestingly, structural imaging studies report a correlation between the severity of hallucinations and gray matter volume reductions within the left superior (84, 85) and middle temporal gyri (86). The potential involvement of these language-related perceptual and motor areas in AVHs is reinforced by research using gyrification and diffusion measures. First, abnormalities in cortical gyrification of the bilateral superior temporal sulci, the left middle frontal sulcus, and the left sylvian fissure (Broca's area) have been seen in chronic hallucinators suffering from schizophrenia, which suggests a neurodevelopmental susceptibility to AVHs in schizophrenia populations (87). Second, the measured fractional anisotropy within the arcuate fasciculus, a white matter bundle connecting Broca's and Wernicke's regions (88), was significantly increased in a subgroup of patients

experiencing frequent AVHs relative to nonhallucinators (89, 90), which speaks in favor of a fronto-temporal disconnectivity.

Aside from the language network, other regions of significance were identified by our meta-analytic procedure. Activation of the left hippocampus/parahippocampal region (Brodmann's area 27) was apparent. This region is known to be involved in the formation of new memories about autobiographical events and conscious recollection (91), and it connects widely distributed association cortices, including the language areas. Moreover, severe damage to this structure usually results in retrograde amnesia, whereas its ictal stimulation may cause experiential hallucinations, such as those experienced during the dreamy state phenomenon (92). Although abnormalities of this region have been frequently reported in schizophrenia independently of AVHs (93), some authors have proposed that hippocampal dysfunction might alter dopamine release in the basal ganglia, potentially causing positive psychotic symptoms (94). Interestingly, other studies investigating cortical activations prior to the onset of AVHs have reported deactivation of the parahippocampal region before symptom onset as opposed to activation during hallucinations (60, 95). Such parahippocampal deactivation has been shown to be associated with the memory recollection process (96) and could be involved in the inadequate trigger of activations in language-related areas responsible for the hallucinatory experience. Taken together, these data support models of abnormal remembered episodic memories of speech and suggest the plausible involvement of memory retrieval during AVHs (6).

The right basal ganglia focus deserves further attention. Strangely, this activation is rarely discussed in the source studies. First, it seems unlikely that this cluster could be related to motor control because more than 80% of the patients involved in studies using a button press paradigm signaled the occurrence of AVHs with their right hand and no complementary activation was measured within the precentral gyrus or the cerebellar cortex. Second, a dysregulation of dopamine systems within thalamo-cortico-striatal circuitry is regularly proposed to account for delusions and hallucinations. However, the medial globus pallidus, which has been shown to be active during AVHs, is devoid of dopaminergic afferents (97). Finally, the main contributors to this cluster are PET studies (6, 13). We argue that fMRI might be less sensitive than PET studies for detecting activation within this area. A loss in the blood-oxygen-level-dependent signal could be a consequence of the particular vascular system of the globus pallidus compared with the rest of the capillary bed, or it could be a consequence of an elevated tissue iron level (97). These data need to be considered in the design of future studies, since explorations of the subcortical structures involved in AVHs move beyond a strict dopamine hypothesis.

Altogether, the findings of the present meta-analysis allow us to discuss the three main pathophysiological

theories of AVHs that were previously mentioned. Our results fully support the following two hypotheses: 1) aberrant activations within sensorimotor cortices and 2) a dysfunction of the verbal memory system during the emergence of AVHs. Therefore, we postulate that abnormal memory retrieval involving the hippocampal/parahippocampal region could trigger dispersed neocortical storage sites, notably those within the language areas, which are responsible for the involuntary emergence of AVHs. Interestingly, in psychotic patients experiencing AVHs, reduced connectivity has been found in neural substrates of episodic verbal memory (hippocampus) and central auditory processing (98), in accordance with the present meta-analytic findings. A third model suggests that a potential underlying mechanism for AVHs could be a reduced ability to attribute the source of speech (5, 43, 44, 51, 99, 100). The present review did not find evidence for activations of the cortical midline structures commonly involved in source attribution during AVHs. However, in our view, this does not rule out the mechanism of misperceptions of unbidden thoughts as external speech in hallucinators. Such cognitive dysfunctions in patients with AVHs could be present independent of the hallucinatory state. We believe that further insight in the validation of the misattribution model could be provided by another quantitative review of brain imaging trait studies that compare patients with and without hallucinations during verbal monitoring tasks.

We are aware that this study has some limitations. First, a minimum of 20 to 100 coordinates are usually needed to produce a robust meta-analysis map, depending on the complexity of the underlying cognitive processing. Even though the number of foci included in the present research was substantial (129 foci of interest), we were only able to integrate a modest number of articles and few high-quality studies that did not report stereotaxic coordinates were excluded (9, 66–68), limiting the power of our analysis to detect more subtle activations. Furthermore, we were not able to control for medication status or patient age across studies as covariates of interest. Incorporation of additional weighting factors for the acquisition methods (magnetic resonance field strengths, etc.) and the intensity scores of activation for all clusters will be incorporated into an upcoming version of the activation likelihood estimation algorithm (72) and should be considered in future meta-analytic studies of AVHs. Nevertheless, the goal of the present research was to clearly define the spatial localizations of the most frequently replicated activations during AVHs rather than to estimate their magnitudes. Despite the cited shortcomings inherent to the activation likelihood estimation method, our data provide strong evidence for concomitant activations in brain areas involved at different levels of complexity in patients' brain architectures. Thus, they allow us to propose an original view of the pathophysiology of AVHs, integrating previous hypotheses that focus on aberrant activations resulting from disturbed interactions within language and verbal-memory networks. Thus, in

our view, the experience of voices can be understood as the combination of distinct mechanisms. First, unbidden auditory memories activate verbal areas of the auditory cortex, making the experience sensory. Then, because the self-tag is missing from these sensory experiences, the phenomenon is experienced as voices. These results also invite new theoretical perspectives because although hyperactivation of the primary sensory cortex (Heschl's gyrus) was identified in some reports (7, 8, 14), results for this area were not significant after quantitative meta-analysis, and thus the area does not seem necessary for the emergence of AVHs. Even if the present data do not permit drawing conclusions about causality, such a hypothesis is consistent with previous reports about the generation of inner speech or auditory verbal imagery, in which Heschl's gyrus is not activated (39). We postulate that activation of the primary auditory cortex, sometimes measured during AVHs, might result from the backpropagation of activity in associative cortices. It is possible that increased severity, vividness, or external spatial voice localizations may be related to propagation of such activation to the brain areas directly receiving sensory inputs. Further research will be needed to confirm this last proposal.

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