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Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond

Paul Allen[1,*], Gemma Modinos[1], Daniela Hubl[2], Gregory Shields[3], Arnaud Cachia[4], Renaud Jardri[5], Pierre Thomas[5], Todd Woodward[6], Paul Shotbolt[3], Marion Plaze[7], and Ralph Hoffman[8]

[1]Department of Psychosis Studies, Institute of Psychiatry, King's College, DeCrespigny Park, London SE5 8AF, UK; [2]University Hospital of Psychiatry, Bern, Switzerland; [3]Department of Psychological Medicine, Institute of Psychiatry, King's College, London, UK; [4]UMR INSERM 894, Centre de Psychiatrie & Neurosciences, Centre Hospitalier Sainte-Anne & UMR CNRS 6232, Groupe d'imagerie neurofonctionnelle du développement, Sorbonne Université Paris Descartes, France; [5]Psychiatry Department, University Medical Centre of Lille, Lille North of France University, Lille, France; [6]Department of Psychiatry, University of British Columbia BC Mental Health and Addiction Research Institute, Vancouver, Canada; [7]Service Hospitalo-Universitaire & UMR INSERM 894, Centre de Psychiatrie & Neurosciences, Centre Hospitalier Sainte-Anne; Université Paris Descartes, France; [8]Department of Psychiatry, Yale University School of Medicine, New Haven, CT

*To whom correspondence should be addressed; tel: 0044-02078480958, fax: +44 (0)207 848 0976, e-mail: p.allen@kcl.ac.uk

Despite more than 2 decades of neuroimaging investigations, there is currently insufficient evidence to fully understand the neurobiological substrate of auditory hallucinations (AH). However, some progress has been made with imaging studies in patients with AH consistently reporting altered structure and function in speech and language, sensory, and nonsensory regions. This report provides an update of neuroimaging studies of AH with a particular emphasis on more recent anatomical, physiological, and neurochemical imaging studies. Specifically, we provide (1) a review of findings in schizophrenia and nonschizophrenia voice hearers, (2) a discussion regarding key issues that have interfered with progress, and (3) practical recommendations for future studies.

Key words: hallucinations/neuroimaging/MRI/PET/DTI/MRS

Introduction

The past 2 decades have seen an exponential increase in the use of neuroimaging techniques to examine the neural underpinning of the common symptoms seen in schizophrenia and other psychiatric illnesses. Neuroimaging studies of auditory hallucinations (AH), particularly in patients with schizophrenia, have allowed researchers to acquire a rudimentary understanding of the brain regions and networks involved in this fascinating but potentially debilitating symptom. Early studies established that AH are associated with changes in the anatomy and function in cortical areas responsible for auditory perception (ie, the primary auditory cortex (PAC) and secondary auditory cortex) and speech output (ie, pars opercularis and anterior insular).[1] In addition to changes in these speech and language areas, changes to a range of other cortical and subcortical regions are widely reported; these findings are detailed in previous reviews.[1,2] In the current review, we largely focus on more recent studies and include neurochemical and gyrification studies for the first time. We then attempt to synthesize these findings, highlight issues that have interfered with progress, and make recommendations for future research.

Neuroimaging Techniques Used to Study AH and Principle Findings

Structural Imaging Studies

Structural imaging studies using region of interest (ROI) and voxel-based morphometry (VBM) techniques have shown that AH are associated with gray matter volume (GMV) reductions in the superior temporal gyrus (STG), sometimes including left PAC, the middle temporal gyrus (MTG), and to a lesser extent in nontemporal lobe regions.[1] Volumetric reductions in temporal regions are confirmed by a recent meta-analysis of 9 VBM studies specifically examining gray matter abnormalities in patients with schizophrenia and AH.[3] The meta-analysis shows that the "severity" of AH is associated with gray matter reductions in the bilateral STG, including the PAC. Left superior temporal areas are known to be involved in speech perception, particularly the comprehension of the phonological and semantic characteristics of speech. A subthreshold effect was also reported in the right STG, thought to be involved in auditory and language processing, particularly of the emotional and prosodic aspect of speech stimuli.[4] These findings suggest that aberrations within neural systems involved at different levels of language processing are critical to AH in patients with schizophrenia. Single VBM

studies have also documented significant effects of AH in nonsensory regions, including the insula, anterior cingulate, posterior cingulate, and inferior frontal gyrus (IFG), thalamus, cerebellum, and precuneus.[1] In the largest VBM study to date (99 schizophrenia patients with AH), Nenadic and colleagues[5] report an association between AH severity and reduced GMV in the left postcentral gyrus and posterior cingulate, a region thought to facilitate the integration of self-referential stimuli.[6] Two VBM studies also report volumetric reduction in parahippocampal gyrus[7] and amygdala[8] supporting the idea that alterations in limbic regions that are important for emotional regulation and processing are associated with AH.[1] These studies demonstrate that volumetric changes in networks and regions beyond those involved in speech and language processing are clearly associated with AH. This has clear implications for neurocognitive models seeking to explain AH. Despite some divergence between studies, abnormalities in the auditory cortex and language-related brain regions seem to be the most replicated finding, consistent with evidence from functional neuroimaging studies in AH.[2] However, it should be noted that these areas are also widely implicated in patients regardless of symptoms[9] and functional associations and can only be inferred from structural imaging data. Finally, there have been no studies that investigate structural abnormalities associated with AH in patients with other psychiatric disorders such as affective psychoses.

Functional Imaging

Metabolic and functional abnormalities, particularly in speech and language areas, have been widely reported by positron emission tomography (PET) fluorodexyglucose (FDG-PET) imaging studies of schizophrenia patients with AH.[1] Increased cerebral blood flow (rCBF) in the left STG and right temporoparietal cortex in patients with relative to patients without AH has also been reported using magnetic resonance perfusion imaging.[10] The recruitment of the secondary auditory cortex during AH (reported by "state" or "capture" studies) is a widely replicated finding[1] and has been recently confirmed by a coordinate-based meta-analysis of the hallucinatory state.[2] This meta-analysis included 10 functional imaging studies investigating state activation during AH and evidenced that hallucinators showed increased activation likelihoods in a distributed bilateral frontotemporal network including Broca's area, anterior insula, precentral gyrus, frontal operculum, middle and STGs, inferior parietal lobule, hippocampus, and parahippocampal region. These findings emphasize the involvement of a disrupted network of frontal production and temporoparietal language perception areas in AH occurrence.[1,11] Interestingly, when such a pattern of activation in inferior frontal and temporoparietal language areas during AH is compared with that of normal language production, the lack of lateralization of AH-related activity becomes apparent.[12] Of note, an imaging study in a group of nonpatients with AH suggests that altered lateralization may be specific to schizophrenia rather than AH per se.[13] Another interesting finding of this meta-analysis is the activation seen in hippocampus/parahippocampal regions. Previous studies investigating cortical activations prior to the onset of AH reported deactivation of the parahippocampal cortex before symptom emergence as opposed to activation during hallucinations,[14] leading some authors to consider such oscillations to be an aberrant trigger of activations in language-related areas responsible for AH.[2] The parahippocampus is thought to play a central role in memory recollection, sending information from the hippocampus to the association areas. Dysfunction of this region could trigger inadequate activation of language areas during AH.[2] Results from the meta-analysis thus support 2 hypotheses: (1) aberrant activations within frontal-temporal language areas during AH and (2) a dysfunction of the verbal memory systems which could lead to the occurrence of AH. Moreover, these results invite new theoretical reflections about the involvement of primary and secondary auditory regions in AH experiences. While some brain-imaging studies failed to identify PAC activations during AH,[12,15] others do report activation in this region (eg, van de Ven et al[16]), questioning the exact role of this structure in AH. A meta-analysis of structural imaging studies also shows volume reduction in the PAC.[3] The fact that activations of the PAC found in some reports did not survive the quantitative functional meta-analysis suggest that this structure is not necessary for AH emergence and could be more related to specific clinical or phenomenological features, such as the vividness of hallucinatory experiences.

Two recent "state" studies have also investigated AH in cohorts of nonpatient hallucinators.[17,18] The study by Diederen and colleagues[17] revealed multiple common areas of AH-related activation in nonpatients and psychosis patients, consisting of the bilateral IFGs, insula, STGs, supramarginal gyri and postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole, and right cerebellum. Moreover, there were no significant differences in AH-related activation between the patient and nonpatient hallucinators. Using a similar experimental design in nonpatients, Linden and colleagues[18] report activation in human voice areas in the superior temporal sulcus as well as frontotemporal language areas and the supplementary motor area (SMA) during both AH and an auditory imagery task. Interestingly, AH were critically distinguished from imagery by lack of voluntary control reflected in the relative activation timing of prefrontal and sensory areas. Activity of the SMA preceded that of auditory areas during imagery, whereas during AH, the 2 processes occurred instantaneously.

However, a major issue with state studies is that the roles of many cortical regions in the generation of AH can only be inferred. For example, while activation in

language areas during AH is intuitive and fits well with inner speech models of AH, the role of areas such as the cerebellum, hippocampus, parahippocampal, SMA, and parietal regions is more speculative. Cognitive or ''trait'' studies may be a more suitable approach to address these questions. Early cognitive studies investigating AH were usually based upon verbal self-monitoring, verbal imagery, and source memory paradigms, designed to engage specific cognitive processes that purportedly overlap with those impaired in schizophrenia patients with AH. These studies have shown that patients with AH demonstrate attenuated activation in temporal, cingulate, premotor, cerebellar, and subcortical regions thought to subserve the monitoring of inner speech and/or verbal imagery.[1] A study utilizing a reality discrimination task, in which participants were asked to remember whether or not they had earlier generated a target word, showed reduced medial prefrontal cortex (mPFC) activity in schizophrenia patients.[19] The mPFC is thought to be involved in the evaluation of self-referential stimuli and is selectively engaged in the self-related task conditions.[6] However, this study did not directly compare patients with and without AH and impaired function in these regions may be the basis for the self-other confusion characteristic of schizophrenia in general.

A small number of functional imaging studies have begun to examine the neural correlates of the phenomenological and emotional characteristics associated with the AH. Vercammen and colleagues[20] examined the subjective physical characteristics (loudness and reality) of AH using a metrical stress evaluation task, which has been shown to activate both inner speech production and perception regions. Loudness of voices correlated with reduced task-related activity in bilateral angular gyri, anterior cinculate cortex (ACC), left IFG and insula, and the left temporal cortex while reality of AH was found to be associated with reduced language lateralization.[20] In a study by Raij and colleagues,[21] the subjective reality of patients' voices correlated with hallucination-related activation in the left IFG and coupling between the IFG and other cortical and subcortical regions including the ACC. Two studies have investigated emotional dysfunction in patients with AH. During the presentation of emotional auditory stimuli, relative to control subjects and patients without AH, patients with AH showed increased activity in the parahippocampal gyrus and the amygdala.[22] Conversely, in a similar study, during a task in which patients listened to emotional sounds, patients with AH showed reduced activation in the amygdala and bilateral hippocampus, relative to patients without AH.[23]

Connectivity—White Matter Studies. Given the involvement of frontal and temporal language regions as well as structures in the limbic system and other nonsensory/language regions, the question of how this network is connected and how these regions interact warranted further investigation. White matter (WM) fiber tracts connecting these regions have been the focus of a number of studies using a magnetic resonance technique called Diffusion Tensor Imaging (DTI). DTI assesses the directionality of water diffusion (anisotropy), which is restricted by boundaries such as WM fibers. Reduced fractional anisotropy (FA) implies a loss of WM integrity. An early DTI study reports that patients with AH show higher directionality between auditory and language regions compared with patients without AH and healthy controls.[24] Subsequent studies report compatible findings in that FA in the superior longitudinal fasciculus is positively correlated with the severity of AH (eg, Shergill et al[25]). These fibers, connecting frontal and temporal language areas, expressed higher FA indicating higher structural integrity. A study in a relatively large sample of patients with schizophrenia ($n = 88$) reports a positive correlation between WM volumes in temporal, occipital, and cingulate regions and positive symptoms, in particular AH.[26] Furthermore, there is some evidence that WM alterations may occur early in the illness. A study of patients in the early course of the illness (duration < 4 y) reports that FA in left inferior fronto-occipital regions was positively correlated with severity of AH.[27] However, a recent study of 44 patients with AH reports ''decreased'' rather than ''increased'' FA, in frontotemporal WM tracts.[28] This conflicting result may be due to small sample sizes used in previous studies as well as differences in the methods arising from the former studies using voxel-based methods compared with an ROI-based tracking approach. The study also reports that patients with chronic treatment resistant hallucinations show decreased FA in the arcuate fasciculus associated with an increase in positive symptoms and coupled with an increase in magnetic transfer ratio (MTR) values indicating an increase in free water concentrations caused by degraded integrity of axons or glia cells.[28] Increased MTR in the arcuate fasciculus is also seen in nonpsychotic individuals who experience voices indicating a specific association with AH rather than other positive and negative symptoms or medication.[29] A study that directly compared patients with and without AH reports that patients with AH show reduced FA in bilateral arcuate fasciculi that is specific to connections between posterior temporal and anterior regions in the inferior frontal and parietal lobe.[30] This study offers a more refined account of the neuroanatomy of WM alterations in patients with AH and shows that there may be selective vulnerability of specific anatomical connections to posterior temporal regions in schizophrenia. Nonfrontotemporal WM has also been implicated in AH. In the first study to compare patients with and without AH higher FA in the corpus callosum was reported in patients with AH exactly where the auditory fibers cross.[24] Makris and colleagues[26] also reports changes

in occipital and cingulate WM associated with positive symptoms.

Connectivity—Functional Studies. Functional connectivity (FC) computed from functional magnetic resonance imaging (fMRI) data is being increasingly utilized for ascertaining neurocircuitry abnormalities contributing to AH in schizophrenia. FC reflects correlations between BOLD activity time-course determined for 2 or more regions. An initial study assessed FC during a sentence completion task and reported reduced FC between left dorsolateral PFC and temporal regions in patients with schizophrenia compared with controls, with the magnitude of these correlations negatively correlating with AH severity.[31] Mechelli and colleagues[32] studied schizophrenia patients with and without AH using fMRI while subjects made judgments about the source of prerecorded speech (self vs other speech). Using an effective connectivity approach, the functional impact of one region on another was assessed relative to the stimuli conditions. For healthy controls and patients without AH, the impact of left superior temporal on anterior cingulate activity was greater for "other-person" spoken words compared with self-spoken words; this finding was reversed for hallucinators. These data provide relatively clear evidence of patient subgroup differences in response to speaker source. A later study using a source judgments task of externally presented self/other speech reported similar findings showing that connectivity between the mPFC (a cortical midline region involved in self referential processing) and the left STG was altered in patients with schizophrenia relative to healthy controls.[33] However, this study did not directly compare patients with and without hallucinations.

A small number of studies have used a "no-task" or "resting-state" FC approach. This offers the possibility of detecting spontaneous network interactions leading to AH because no specific task is utilized during data collection. Vercammen and colleagues[34] calculated no-task FC relative to a seed region located at the left and right temporoparietal junction to compare patients with active AH and healthy controls. Their patient group demonstrated altered left temporoparietal FC linking with the right homotope of Broca's area. Within the patient group, more severe AH were associated with reduced FC linking the left temporoparietal seed region and the bilateral anterior cingulate and bilateral amygdala. Gavrilescu and colleagues[35] examined cross-hemisphere resting FC linking the PACs and secondary auditory cortices in patients with schizophrenia and AH, similarly diagnosed patients without AH, and healthy controls. FC was estimated from resting state fMRI data using ROI defined for each participant based on functional activation maps in response to listening to words. Hallucinators were found to demonstrate significant reductions in interhemispheric FC compared with the other 2 groups. Hoffman and colleagues[36] compared patients with schizophrenia-spectrum disorder and AH, with similarly diagnosed patients without AH and healthy controls. FC was seeded from a bilateral Wernicke's region. FC summed along a loop linking the Wernicke's and IFG seed regions and the putamen was robustly greater for hallucinating patients compared with nonhallucinating patients and healthy controls. FC was reduced between the bilateral Wernicke's seed region and the anterior cingulate in patients compared with controls; however, this finding was not specific to hallucinators.

Gyrification Studies

"Postmortem" brain photographs of patients with "Dementia Praecox" proposed a relation between "auditory hallucinosis" and cortical folding in the temporal lobe. The advent of magnetic resonance imaging (MRI)-based computational tools for visualization and measurement in vivo of brain structure has confirmed abnormalities in cortical surface morphology (or gyrification) in schizophrenia patients and subtle gyrification deviations associated to AH.[37] The cortical folding process begins from the 10th week of fetal life, and during the third trimester of pregnancy, the cerebral cortex changes from a relatively smooth lissencephalic surface, to a complex folded structure.[38] Several factors contribute to developmental processes that influence the shape of the folded cerebral cortex, including structural connectivity through axonal tension forces leading to a compact layout that optimizes the transit of neuronal signals between brain regions.[39]

Early gyrification studies of AH were based on the assessment of hand-traced regions of interest derived from 2-dimensional MRI slices. Analysis of the insular cortex surface of drug-naïve first-episode schizophrenia patients revealed a specific correlation with delusions and hallucinations.[40] A recent study using exactly the same methodology, but in a large and heterogeneous sample of 225 schizophrenia-spectrum patients, indicated that AH were the most correlated clinical dimensions to insular surface area.[41] Functional abnormalities in language system, including frontal motor-speech and temporal semantic areas, have repeatedly been associated to AH pathophysiology.[1] Involvement of the PAC remains, however, controversial. The comparison of the folding pattern of Heschl's gyrus (HG), the cortical region hosting the PAC, revealed that schizophrenia patients with a history of AH show a trend toward a higher number of duplicated HG in comparison with both patients without history of AH and healthy controls.[42] This finding suggests specific early morphogenesis PAC deviations in schizophrenia patients with history of AH. The development of computer-based methods now allows the automated extraction of the cortical folds across the whole cortex, reliably measuring their complexity, variability, and 3-dimensional shape.[37] Based on this approach, a significant sulcal area decrease was detected in 30 schizophrenia patients with resistant AH in comparison with 28

healthy controls[43] in language-related cortex. No correlation was detected between the sulcal areas and AH severity, patients' age or drug dose. Taken together, these findings suggest that the detected sulcal deviations could be better viewed as a "trait" feature of AH vulnerability rather than a state feature of AH severity. The same morphometrical approach was recently used to investigate a phenomenological aspect of AH, the neural substate of spatial location.[44] In comparison with healthy subjects, opposite sulcus displacements were detected in patients with inner space AH and patients with outer space AH in the right Temporoparietal junction (rTPJ), a key region of the "where" auditory pathway. The detected tilt in the junction of the superior temporal sulcus and its anterior terminal branch (or angular sulcus) suggests deviations during early brain maturation.[44] As sulcus morphology in an adult subject can be seen as the integration of both normative and pathological influences exerted on brain development, such "sulcal dysjunction" might reflect an illness-associated developmental variation. These findings lead to the speculation that the preference for attaching either an "external" or "internal" location to AVH could be associated with particularities of early rTPJ neurodevelopmental trajectory.

Neurochemistry

N-acetyl-aspartate (NAA) concentration is a marker of neuronal volume loss and/or viability, and the ^{1}H Magnetic Resonance Spectroscopy (MRS) choline (Cho) signal is a marker of cell membrane turnover[45] and both can be measured using MRS. Glutamate and glutamine can also be measured by ^{1}H MRS and are implicated in the *N*-Methyl-D-aspartate receptor hypothesis of schizophrenia. Theberge and colleagues[46] found increased glutamine in the left thalamus and a negative correlation between thalamic NAA and the duration of positive symptoms in a study of 21 patients with chronic schizophrenia and matched controls. They also found decreased glutamate and glutamine in the left ACC, which may be due to disease chronicity and neurodegeneration or the effects of medication.[46] In a subsequent study, they found decreased NAA/Cho ratios in the thalamus of patients with schizophrenia and in the right thalamus of patients with AH relative to patients without AH and normal controls.[47] A decrease in NAA concentration in the hippocampus of schizophrenia patients during the occurrence of AH has also been reported.[48]

The first study to directly examine dopaminergic function in relation to AH used a sample of nonpatient voice hearers, allowing findings to be interpreted in the absence of other symptoms and medication confounds.[49] Using [18F]-DOPA PET, the study reports no significant difference in dopamine synthesis capacity in the striatum, or its functional subdivisions, between groups, and no relationship between subclinical psychotic symptom severity and dopamine synthesis capacity in the nonpatient AH group. This finding suggests altered dopamine synthesis capacity is unlikely to underlie subclinical AH. However, the relationship between dopaminergic function and AH in schizophrenia patients is still unknown. Investigating this relationship is likely to be more difficult due to antipsychotic medication confounds.

Summary of Findings

There is currently insufficient neuroimaging evidence to fully understand the neurobiological substrate of AH. However, modern imaging techniques have allowed us to begin to understand what is happening in the brain of those who experience AH at anatomical, physiological, and neurochemical levels. Volumetric and functional studies consistently report altered structure and function in sensory regions, mainly in the STG and MTG and these findings have been confirmed by 2 meta-analyses.[2,3] Volumetric and functional changes in nonsensory regions (prefrontal, premotor, cingulate, cerebellar, temporal, and subcortical regions), thought to be involved in language and speech monitoring processes, are also reported. However, the role of these regions in AH is often inferred, and more sophisticated cognitive approaches are needed to fully understand their contribution to the experience. Studies have also begun to shed light on the neural correlates of AH phenomenology reporting that the loudness, subjective reality, and spatial location of voices are related to functional and anatomical changes in discrete regions and networks. However, these studies are few in number, and replication is needed before a richer understanding of the relationship between phenomenology and neurobiology is understood. The neural substrate of AH in nonpatients who experience the phenomenon has also been investigated. These studies report ostensibly similar AH-related activation, in a network of cortical and subcortical regions, to that seen in patients with schizophrenia, suggesting a neural substrate specific to AH rather than schizophrenia. Voxel-based DTI studies examining WM connectivity in patients with AH report an increase in FA associated with AH severity. It has been proposed that altered structural connectivity between frontal and temporal regions, involved in language processes, may result in conduction delays in the "efference copy" or "forward-signal" initiated by willed actions.[50] This failure to suppress the sensory consequences of willed actions could result in ambiguity as to the origins of those actions leading to passivity experiences and AH. It is tempting to speculate that the findings of Linden and colleagues,[18] in which AH-related activity in the SMA and auditory areas occurred instantaneously, as opposed to asynchronously during imagery, are broadly consistent with this idea. However, 2 DTI studies using a tractography-based approach found a decrease in frontotemporal and parietal WM associated with AH.[28] It is possible that AH are associated with both decreased and increased FA

at different and specific loci in frontotemporal WM tracts. Connectivity studies using functional imaging and no-task/resting data have also highlighted disconnection as a factor in AH, showing alterations in cross-hemispheric linkages[35] and frontotemporal connectivity.[34] One FC study that directly compared patients with and without AH reports greater connectivity between Wernicke's and IFG seed regions and the putamen in hallucinators.[36]

Gyrification studies indicate that AH are associated with insular surface area deviations and alterations in the morphology of PAC/HG, findings that are consistent with volumetric studies. The few neurochemical studies conducted to date report decreased neuronal integrity (reduced NAA/Cho) in the right thalamus and hippocampus of patients with AH but, at present, only one study has examined the role of dopaminergic function in AH, reporting no significant difference in dopamine synthesis capacity in the striatum between nonpatient hallucinators and a control group. More investigation of the neurochemical basis of AH is warranted given the clear hallucinogenic effects of lysergic acid diethylamide, cannabis, and stimulants. The picture thus remains a complex one in which multiple factors across anatomical, physiological, and neurochemical domains are likely to contribute to the hallucinatory phenomenon. Future imaging studies of AH should incorporate multiple methodologies to rigorously compare and contrast competing explanatory models of AH in the same subjects.

Key Issues That Have Interfered With Progress

Sample Size

The vast majority of studies have small sample sizes making it difficult to generalize their findings. This confound is particularly evident in studies which make a categorical distinction between patients with and without AH.

State vs Trait

Interpretation of findings is made difficult by state and trait factors. The different ways hallucinating and nonhallucinating patients are defined could potentially lead to the same patient meeting the criteria for a hallucinator in one study and a nonhallucinator in another. This is why it may be important to study patients with severe hallucinations as a separate group.

Temporal Course

In terms of hallucination events, it is often hard to differentiate between activation triggering hallucinations, vs activation involved in the genesis of these experiences, vs activation reflecting downstream consequences (such as secondary shifts in auditory attention). Determination of the fMRI time course of activation could provide informative clues regarding the sequencing of these activations. However, the temporal resolution of fMRI is rather coarse for hallucination events, which may only last a few seconds. A useful parallel approach would be to use electroencephalography or magnetoencephalography for such studies, where temporal resolution is much greater.

Cognition

Cognitive studies generally address processes that share overlapping cognitive operations. The role of secondary auditory cortex is fairly clear (although the majority of studies report secondary involvement only); however, the role of the PAC is less clear and its involvement could be more related to specific clinical or phenomenological features. The role of nonsensory regions in AH is also largely speculative giving rise to issues with construct validity. While these studies may help us to understand anatomical and functional underpinnings that overlap, deficits in these processes are not the basis of AH. Deficits in several processes are likely to contribute to the AH (ie, self-monitoring, source monitoring, episodic memory, etc). Furthermore, the neural substrates that underpin these processes in healthy subjects are not well understood.

Specificity

The specificity of these cognitive operations (and their neural correlates) to AH is not clear. For example, dysfunction in language networks is seen generally across schizophrenia and is particularly associated with thought disorder.

Medication Confounds

Many studies negate this problem by either using a nonhallucinating patient group matched for medication or by studying the same patients when they are actively hallucinating and then again when their symptoms have remitted. However, a substantial number of studies do not control for the effects of medication (usually antipsychotics) upon neural activation measured by either fMRI or PET making these studies more difficult to interpret. Antipsychotic medication makes investigating the role of dopamine in AH particularly difficult. Plasmatic nicotine levels can also interfere with BOLD signal, and patients suffering from schizophrenia smoke a larger amount of cigarettes than healthy controls.

Connectivity Studies

The challenge of selecting optimal seed regions is paramount; many candidate regions can be proposed based on the literature, including Wernicke's area, primary or secondary auditory association cortex, superior and middle temporal regions activated during hallucination events themselves, and the thalamus. Moreover, it is entirely plausible that a hyperconnected neurocircuitry involving some brain regions will secondarily induce hypoconnected neurocircuitry in other overlapping brain regions—and

vice versa. Therefore, the question of what is cause and what is effect again becomes critical.

The Need for Integrative Neurobiological Model(s)

Explanatory models need to account for (1) phenomenological aspects of AH (such as internal vs external, loudness, multiple overlapping voices, etc—most neuroimaging research has neglected phenomenological features of AH in favor of holistic accounts), (2) sustained vulnerability factors and factors that explain why AH are intermittent (ie, cognitive vulnerability vs state factors such as dopamine elevation); in essence, there needs to be 2 or perhaps 3 sets of findings for AH that account for vulnerability lasting months to years, active psychotic state lasting days to weeks, and event state lasting seconds to minutes, and (3) mechanisms to improve treatment.

Practical Recommendations for Future Research

Based on the issues outlined above the following practical recommendations for future research are proposed:

1. Clear characterization of the current and past history of AH and the comparison of hallucinating and nonhallucinating groups within a diagnostic category, and/or correlate individual differences in imaging measures with severity of hallucinations.
2. Clear characterization of phenomenology so that these features can be applied to neuroimaging data.
3. Examination of the effects of cognitive (IQ) and clinical (chronicity, medication) confounds.
4. Careful consideration of the cognitive and perceptual tasks and ensuring construct validity.
5. Differentiation of vulnerability, macrostate, and microstate variables.
6. Given the large number of areas implicated in AH pathology, consideration of functional neuroimaging data in terms of networks instead of individual regions has considerable advantages over and above univariate methodology/theorizing.
7. Future research should examine hallucinations occurring in other sensory modalities (in neurological patients), allowing a comparison between hallucinations in schizophrenia and other disorders.

To conclude, the present review provides a comprehensive up-to-date summary of findings from studies examining the brain basis of AH across different modalities (brain structure, function, and neurochemistry) and populations (schizophrenia patients, nonclinical individuals with AH). The main contributions with relative consistency across studies refer to decreases in GMV and FC, while increases in brain activation during AH and in WM connectivity are commonly reported. Our review also highlights, for the first time, investigations on neurochemistry and gyrification and recent evidence of aberrant neurochemical integrity and gyrification abnormalities. Despite a number of methodological challenges to this body of work, we provide recommendations for future research that may help unravel the seemingly complex neural underpinnings of the hallucinatory experience.

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References

1. Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev*. 2008;32:175–191.
2. 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;168:73–81.
3. Modinos G, Costafreda SG, van Tol MJ, McGuire PK, Aleman A, Allen P. Neuroanatomy of auditory verbal hallucinations in schizophrenia: a quantitative meta-analysis of voxel-based morphometry studies [published online ahead of print February 01, 2012]. *Cortex*.
4. Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. *Nat Neurosci*. 2000;3:277–283.
5. Nenadic I, Smesny S, Schlosser RG, Sauer H, Gaser C. Auditory hallucinations and brain structure in schizophrenia: voxel-based morphometric study. *Br J Psychiatry*. 2010;196:412–413.
6. Northoff G, Bermpohl F. Cortical midline structures and the self. *Trends Cogn Sci*. 2004;8:102–107.
7. Marti-Bonmati L, Lull JJ, Garcia-Marti G, et al. Chronic auditory hallucinations in schizophrenic patients: MR analysis of the coincidence between functional and morphologic abnormalities. *Radiology*. 2007;244:549–556.
8. Garcia-Marti G, Aguilar EJ, Lull JJ, et al. Schizophrenia with auditory hallucinations: a voxel-based morphometry study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:72–80.
9. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005;162:2233–2245.
10. Wolf ND, Gron G, Sambataro F, et al. Magnetic resonance perfusion imaging of auditory verbal hallucinations in patients with schizophrenia. *Schizophr Res*. 2012;134:285–287.

11. Shergill SS, Bullmore E, Simmons A, Murray R, McGuire P. Functional anatomy of auditory verbal imagery in schizophrenic patients with auditory hallucinations. *Am J Psychiatry*. 2000;157:1691–1693.
12. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain*. 2008;131(pt 12):3169–3177.
13. Diederen KM, De Weijer AD, Daalman K, et al. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. *Brain*. 2010;133(pt 12):3734–3744.
14. Diederen KM, Neggers SF, Daalman K, et al. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry*. 2010;167:427–435.
15. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2000;57:1033–1038.
16. van de Ven VG, Formisano E, Roder CH, et al. The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage*. 2005;27:644–655.
17. Diederen KM, Daalman K, de Weijer AD, et al. Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals [published online ahead of print April 28, 2011]. *Schizophr Bull*.
18. Linden DE, Thornton K, Kuswanto CN, Johnston SJ, van de Ven V, Jackson MC. The brain's voices: comparing nonclinical auditory hallucinations and imagery. *Cereb Cortex*. 2011;21:330–337.
19. Vinogradov S, Luks TL, Schulman BJ, Simpson GV. Deficit in a neural correlate of reality monitoring in schizophrenia patients. *Cereb Cortex*. 2008;18:2532–2539.
20. Vercammen A, Knegtering H, Bruggeman R, Aleman A. Subjective loudness and reality of auditory verbal hallucinations and activation of the inner speech processing network. *Schizophr Bull*. 2011;37(5):1009–1016.
21. Raij TT, Valkonen-Korhonen M, Holi M, Therman S, Lehtonen J, Hari R. Reality of auditory verbal hallucinations. *Brain*. 2009;132(pt 11):2994–3001.
22. Escarti MJ, de la Iglesia-Vaya M, Marti-Bonmati L, et al. Increased amygdala and parahippocampal gyrus activation in schizophrenic patients with auditory hallucinations: an fMRI study using independent component analysis. *Schizophr Res*. 2010;117:31–41.
23. Kang JI, Kim JJ, Seok JH, Chun JW, Lee SK, Park HJ. Abnormal brain response during the auditory emotional processing in schizophrenic patients with chronic auditory hallucinations. *Schizophr Res*. 2009;107:83–91.
24. Hubl D, Koenig T, Strik W, et al. Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry*. 2004;61:658–668.
25. Shergill SS, Kanaan RA, Chitnis XA, et al. A diffusion tensor imaging study of fasciculi in schizophrenia. *Am J Psychiatry*. 2007;164:467–473.
26. Makris N, Seidman LJ, Ahern T, et al. White matter volume abnormalities and associations with symptomatology in schizophrenia. *Psychiatry Res*. 2010;183:21–29.
27. Szeszko PR, Robinson DG, Ashtari M, et al. Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. *Neuropsychopharmacology*. 2008;33:976–984.
28. de Weijer AD, Mandl RC, Diederen KM, et al. Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. *Schizophr Res*. 2011;130:68–77.
29. de Weijer AD, Neggers SF, Diederen KM, et al. Aberrations in the arcuate fasciculus are associated with auditory verbal hallucinations in psychotic and in non-psychotic individuals [published online ahead of print November 23, 2011]. *Hum Brain Mapp*.
30. Catani M, Craig MC, Forkel SJ, et al. Altered integrity of perisylvian language pathways in schizophrenia: relationship to auditory hallucinations. *Biol Psychiatry*. 2011;70:1143–1150.
31. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biol Psychiatry*. 2002;51:1008–1011.
32. Mechelli A, Allen P, Amaro E, et al. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Hum Brain Mapp*. 2007;28:1213–1222.
33. Wang L, Metzak PD, Woodward TS. Aberrant connectivity during self-other source monitoring in schizophrenia. *Schizophr Res*. 2011;125:136–142.
34. Vercammen A, Knegtering H, den Boer JA, Liemburg EJ, Aleman A. Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporoparietal area. *Biol Psychiatry*. 2011;67:912–918.
35. Gavrilescu M, Rossell S, Stuart GW, et al. Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. *Psychol Med*. 2009;40(7):1–10.
36. Hoffman RE, Fernandez T, Pittman B, Hampson M. Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia. *Biol Psychiatry*. 2011;69:407–414.
37. Mangin JF, Jouvent E, Cachia A. In-vivo measurement of cortical morphology: means and meanings. *Curr Opin Neurol*. 2010;23:359–367.
38. White T, Su S, Schmidt M, Kao CY, Sapiro G. The development of gyrification in childhood and adolescence. *Brain Cogn*. 2010;72:36–45.
39. White T, Hilgetag CC. Gyrification and neural connectivity in schizophrenia. *Dev Psychopathol*. 2011;23:339–352.
40. Crespo-Facorro B, Kim J, Andreasen NC, O'Leary DS, Bockholt HJ, Magnotta V. Insular cortex abnormalities in schizophrenia: a structural magnetic resonance imaging study of first-episode patients. *Schizophr Res*. 2000;46:35–43.
41. Crespo-Facorro B, Roiz-Santianez R, Quintero C, et al. Insular cortex morphometry in first-episode schizophrenia-spectrum patients: diagnostic specificity and clinical correlations. *J Psychiatr Res*. 2010;44:314–320.
42. Hubl D, Dougoud-Chauvin V, Zeller M, et al. Structural analysis of Heschl's gyrus in schizophrenia patients with auditory hallucinations. *Neuropsychobiology*. 2010;61:1–9.
43. Cachia A, Paillere-Martinot ML, Galinowski A, et al. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. *Neuroimage*. 2008;39:927–935.
44. Plaze M, Paillere-Martinot ML, Penttila J, et al. "Where do auditory hallucinations come from?"—a brain morphometry study of schizophrenia patients with inner or outer space hallucinations. *Schizophr Bull*. 2011;37:212–221.
45. Ross AJ, Sachdev PS. Magnetic resonance spectroscopy in cognitive research. *Brain Res Brain Res Rev*. 2004;44:83–102.
46. Theberge J, Al-Semaan Y, Williamson PC, et al. Glutamate and glutamine in the anterior cingulate and thalamus of

medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS. *Am J Psychiatry*. 2003;160:2231–2233.

47. Martinez-Granados B, Brotons O, Martinez-Bisbal MC, et al. Spectroscopic metabolomic abnormalities in the thalamus related to auditory hallucinations in patients with schizophrenia. *Schizophr Res*. 2008;104:13–22.
48. Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus*. 2001;11:520–528.
49. Howes OD, Shotbolt P, Bloomfield M, et al. Dopaminergic function in the psychosis spectrum: an [18F]-DOPA imaging study in healthy individuals with auditory hallucinations [published online ahead of print January 26, 2012]. *Schizophr Bull*.
50. Whitford TJ, Ford JM, Mathalon DH, Kubicki M, Shenton ME. Schizophrenia, myelination, and delayed corollary discharges: a hypothesis [published online ahead of print September 20, 2010]. *Schizophr Bull*.