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ORIGINAL ARTICLE

Abnormal Effective Connectivity in the Brain is Involved in Auditory Verbal Hallucinations in Schizophrenia

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Abstract Information flow among auditory and language processing-related regions implicated in the pathophysiology of auditory verbal hallucinations (AVHs) in schizophrenia (SZ) remains unclear. In this study, we used stochastic dynamic causal modeling (sDCM) to quantify connections among the left dorsolateral prefrontal cortex (inner speech monitoring), auditory cortex (auditory processing), hippocampus (memory retrieval), thalamus (information filtering), and Broca's area (language production) in 17 first-episode drug-naïve SZ patients with AVHs, 15 without AVHs, and 19 healthy controls using resting-state functional magnetic resonance imaging. Finally, we performed receiver operating characteristic (ROC) analysis and correlation analysis between image measures and symptoms. sDCM revealed an increased sensitivity of auditory cortex to its thalamic afferents and a decrease in hippocampal sensitivity to auditory inputs in SZ patients with AVHs. The area under the ROC curve showed the diagnostic value of these two connections to distinguish SZ patients with AVHs from those without AVHs. Furthermore, we found a positive correlation between the strength of the connectivity from Broca's area to the auditory cortex and the severity of AVHs. These findings demonstrate, for the first time, augmented AVH-specific excitatory afferents from the thalamus to the auditory cortex in SZ patients, resulting in auditory perception without external auditory stimuli. Our results provide insights into the neural mechanisms underlying AVHs in SZ. This thalamic-auditory cortical-hippocampal dysconnectivity may also serve as a diagnostic biomarker of AVHs in SZ and a therapeutic target based on direct *in vivo* evidence.

Keywords Effective connectivity · Stochastic dynamic causal modeling · Auditory verbal hallucinations · Schizophrenia

Baojuan Li, Long-Biao Cui, and Yi-Bin Xi have contributed equally to this work.

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Introduction

The neurocognitive and neurobiological mechanisms behind auditory verbal hallucinations (AVHs) in schizophrenia (SZ) remain poorly understood. Most recently, the International Consortium on Hallucination Research highlighted the great clinical potential of studying state and trait markers of AVHs using resting methods [1]. Our previous resting-state functional magnetic resonance imaging (fMRI) studies have provided provisional insights into the brain regions and networks involved in AVHs that have been challenging [2–4].

Convergent findings based on functional imaging suggest that the altered regional activation of auditory and language processing-related areas is implicated in the pathophysiology of AVHs in SZ. A coordinate-based meta-analysis by Jardri *et al.* identified increased cortical activations during AVHs in SZ, including Broca's area, precentral gyrus, hippocampus/parahippocampal gyrus, superior and middle temporal gyri, supramarginal gyrus, right frontal operculum, and bilateral anterior insula, demonstrating the association of AVHs with speech generation and perception, as well as verbal memory [5]. They further detected increased activity of Broca's area in adolescents with brief psychiatric disorders and experiencing AVHs [6]. Arterial spin labeling has also been successfully used to measure the decreased cerebral blood flow (CBF) in the frontal and temporal regions involving the left auditory cortex and Broca's area in SZ patients with AVHs who had an excellent clinical response to transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation [7, 8].

More importantly, AVHs in SZ involve aberrant interactions among the regions noted above. Lawrie *et al.* found that the functional connectivity (FC) between the left dorsolateral prefrontal cortex (DLPFC) and the temporal cortex is negatively correlated with AVH severity in SZ [9]. SZ patients with AVHs exhibit a higher FC between the hippocampal complex and thalamus than SZ patients with audio-visual hallucinations [10]. It has been reported that SZ patients show decreased FC of the left auditory cortex with the right hippocampal formation and the mediodorsal thalamus, and increased connectivity with the left frontoparietal regions relative to those without AVHs [11]. The SZ patients also have significantly reduced interhemispheric FC in both primary and secondary auditory cortices [12]. Wernicke's area-seeded FC with the left inferior frontal cortex, including the DLPFC, is significantly greater in SZ patients with AVHs than in those without AVHs [13]. Recently, Rolland *et al.* found that SZ patients with AVHs exhibit significantly enhanced FC between the nucleus accumbens and regions of the mesolimbic pathway [14], and Mondino *et al.* demonstrated that a reduction of AVHs by tDCS in SZ patients is associated with regulation of the FC within areas involved in inner speech production and monitoring (left DLPFC) [15]. Meanwhile, evidence from structural connectivity analysis supports the neuronal interaction deficits in SZ. It has been proposed that impaired structural connectivity between language process-related frontal and temporal cortices may result in AVHs [16]. SZ patients with AVHs show decreased fractional anisotropy in the left arcuate fasciculus (AF) [17–24] and left superior longitudinal fasciculus [18, 21, 25, 26], and similar findings—disruptions of white matter integrity in the left AF—have been reported in a recent meta-analysis [27]. The AF is a key anatomical connection between the frontal and temporal-parietal speech areas, involving Broca's area. The superior longitudinal fasciculus terminates in the DLPFC, which is one of the most important cortical regions in the pathogenesis of SZ, and the right DLPFC-left hippocampal formation dysconnectivity has been linked with the risk of developing SZ [28]. In addition, increased mean diffusivity in the left superior temporal gyrus white matter is correlated with AVHs in SZ patients [29], and the fractional anisotropy of interhemispheric auditory fibers connecting the bilateral auditory cortices is increased in these patients [30]. These findings suggest aberrant FC among distinct brain regions involved in auditory and language processing. Evidence from structural connectivity analysis also provides support for these neuronal interaction deficits.

Recent theoretical treatments of the disconnection hypothesis for SZ [31] have emphasized abnormal gain control, particularly in the context of encoding precision in predictive coding models of aberrant or false inference during hallucinations [32–34]. Recent dynamic causal modeling (DCM) of evoked electromagnetic responses in SZ suggests: "a failure to modulate the sensitivity of neurons responsible for passing sensory information of prediction errors up the visual cortical hierarchy" [35]. These proposals are particularly relevant to AVHs, given the potentially important role of predictive coding in language processing. In brief, a failure to attenuate sensory precision or gain—and compensatory changes at higher levels of cortical processing hierarchies—may underlie many of the symptoms and signs in SZ (e.g., hallucinations and attenuated mismatch negativity responses). As discussed by Adams *et al.* [32], AVHs in SZ may be better understood more precisely as a failure to attenuate the auditory consequences (corollary discharge) of sub-vocal [36] or inner speech [37] (self-made acts).

Although previous studies based on FC and structural connectivity analysis have discovered part of the brain networks associated with AVHs in SZ, information flow within these networks remains unclear. In contrast, effective connectivity (EC) is defined as the causal (directed) influence of one neural system over another. DCM is a technique for measuring the EC among brain regions [38], based on functional neuroimaging. DCM not only enables quantification of the connectivity among different regions, but also allows the investigation of directed information flow from one region to another. Conventional deterministic DCM has been used to clarify changes in EC within the speech network (focused on Broca's area and Wernicke's area and their homologs in the right hemisphere) in SZ patients with AVHs [39]. Compared with conventional deterministic DCM, stochastic DCM (sDCM) can be used to infer EC from resting-state fMRI data [40], and provide

more accurate parameter estimates [41]. Recent *in vivo* studies using sDCM have started to disclose the pathophysiology of several neuropsychological disorders [42–45]. In a recent study, sDCM revealed reduced EC from the posterior cingulate to the anterior frontal node of the default mode network (DMN) in first-episode SZ patients, reflecting reduced postsynaptic efficacy of prefrontal afferents [42]. More importantly, using DCM in SZ patients, we found altered EC related to a part of the DMN, the medial prefrontal cortex, indicating hippocampal-dorsolateral prefrontal-medial prefrontal hypoconnectivity [43].

In the current study, we used sDCM to elucidate the EC among previously reported auditory and language processing regions associated with AVHs based on fMRI data from five representative regions: DLPFC (inner speech monitoring), auditory cortex (auditory processing), hippocampus (memory retrieval), thalamus (signal filtering), and Broca's area (language production), in order to provide a better understanding of the pathophysiological correlates of AVHs in SZ. It has been well established that language function (Broca's area) is highly asymmetrical [46], and the lateralization, on the left side in particular, is known to be related to AVHs in SZ involving the DLPFC, hippocampus, thalamus, and auditory cortex on the basis of the studies described above. We hypothesized that directed connectivity to the auditory cortex may be augmented in SZ patients with AVHs, predisposing to false perceptual inference in the absence of external auditory stimuli.

Methods

Participants

This study was approved by the local Research Ethics Committee. All participants gave written informed consent after a full description of the aims and design of the study between May 2011 and Dec 2013. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision was used, and consensus diagnoses of SZ were made using all the available information. Seventeen first-episode, drug-naïve SZ patients who had suffered from AVHs at least once a day for the past four weeks were allocated to the AVH group. Fifteen patients who never or had not experienced AVHs within two years were assigned to the non-AVH group. All the patients were assessed by two senior clinical psychiatrists using the Positive and Negative Syndrome Scale developed by Kay *et al.* [47]. The Auditory Hallucination Rating Scale (AHRS) was used to evaluate the severity of AVHs. In addition, healthy controls (HCs) were recruited from the local community by advertisement. A full description of the demographic and clinical characteristics of the sample (Table S1) is available in the study by Cui *et al.* [4].

Image Acquisition

Information on the image acquisition was described in detail in our previous study [4]. None of the patients reported the presence of AVHs during MRI scanning.

Data Preprocessing

Resting-state fMRI images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). For each participant, fMRI scans were first realigned to correct for head motion. Exclusion criteria for excessive head motion were >2.5 mm translation and/or >3.0° rotation. Realigned images were then normalized to the Montreal Neurological Institute space and resampled to $2 \times 2 \times 2$ mm^3 voxels. Finally, the images were smoothed with an 8-mm FWHM (full width at half maximum) Gaussian kernel.

General Linear Model

At the first (within-subject) level, a general linear model was constructed for each participant as described in detail in our previous study [43]. The six motion parameters (describing the translation and the rotation) calculated from the realignment procedure, one constant regressor modeling the baseline, and cosine basis functions were included in this model. The resulting contrast images were then used to constrain the step of the extraction of regions of interest (ROIs) in the sDCM.

Regions of Interest

As stated above, most structural and functional alterations occur in the left hemisphere. In each participant, we selected five ROIs: left auditory cortex, DLPFC (consisting of Frontal_Sup_L and Frontal_Sup_Medial_L), hippocampus, thalamus, and Broca's area (consisting of Frontal_Inf_Tri_L and Frontal_Inf_Oper_L). Notably, considering the size of an ROI (i.e., avoiding too large area), we also selected the superior frontal gyrus and medial superior frontal gyrus, as in our previous study [48], to include regions containing as much of the DLPFC as possible. For each region, a mask was created using the WFU PickAtlas Tool and the automated anatomical labeling atlas template (Version 3.0.4, http://www.nitrc.org/projects/wfu_pickatlas/) [49]. For each ROI, participant-specific time series were extracted from a region defined by a thresholded SPM testing for the baseline and masked using the corresponding ROI from the WFU

PickAtlas Tool. The locations of the masks and ROI time series are shown in Fig. 1A.

Stochastic Dynamic Causal Modeling

As described in detail in our previous study [48], the EC among the left Broca's area, DLPFC, hippocampus, thalamus, and auditory cortex was investigated using sDCM. A fully connected model was constructed for each participant. This model was then inverted using generalized filtering [50]. The resulting (maximum *a posteriori*) estimates of connectivity were then treated as summary statistics for classical random effect inference at the second (between-subject) level using *t*-tests. Because our hypothesis directly concerned connections among the selected ROIs, we report (uncorrected) *P* values between the group levels for all other connections to demonstrate the specificity of differences.

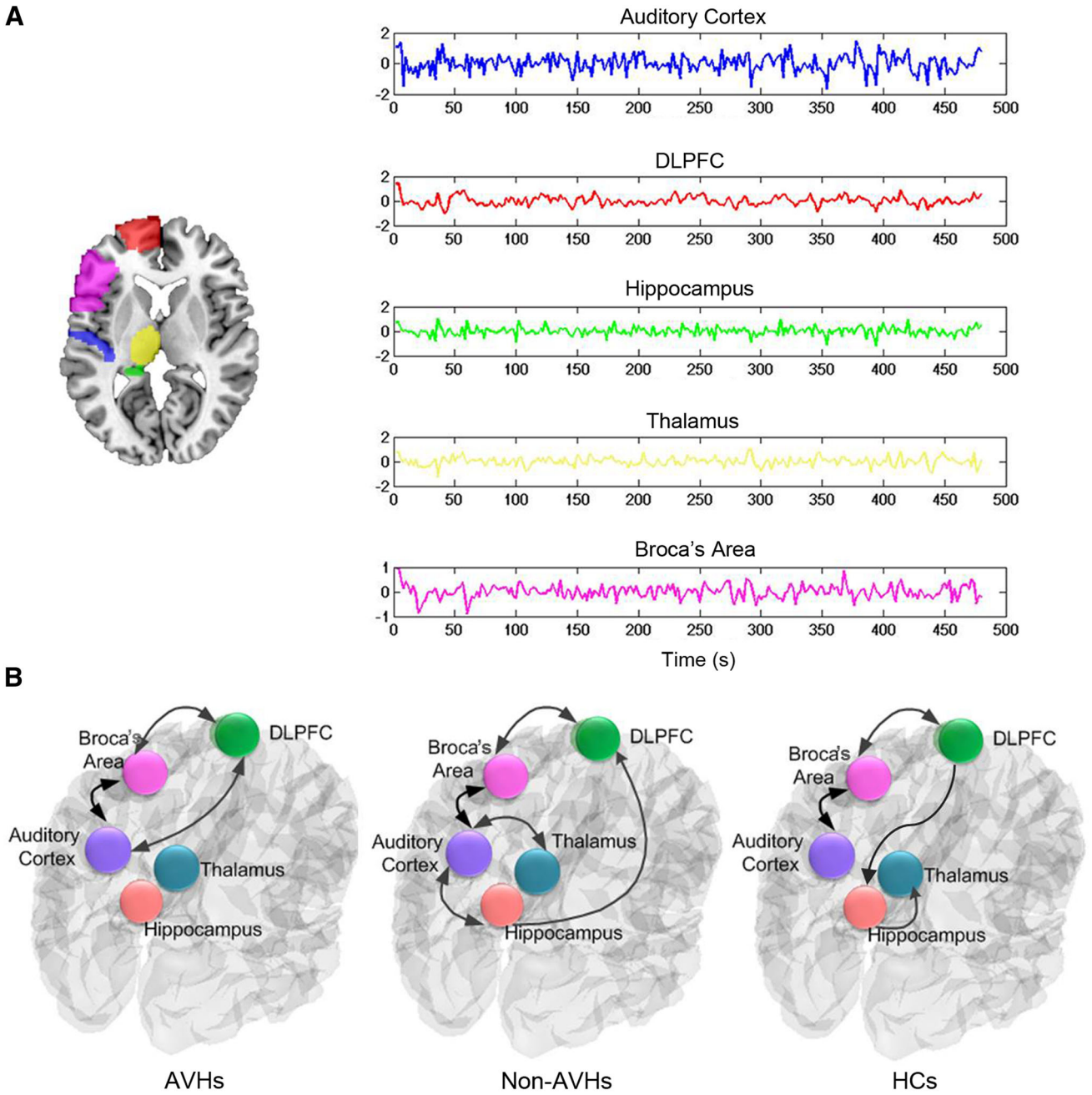

Fig. 1 Locations of the masks, time series of extracted ROIs, and significant effective connectivity (at the group level). **A** Locations and representative traces of ROIs selected for analysis (*blue*, auditory cortex; *red*, DLPFC; *green*, hippocampus; *yellow*, thalamus; *violet*, Broca's area). Vertical axes indicate regional activity at the locations. **B** Significant connections among ROIs in the AVH and non-AVH groups, and HCs. DLPFC, dorsolateral prefrontal cortex.

Statistical Analysis

Connection strength among groups was analyzed with one-way analysis of variance (ANOVA). Receiver operating characteristic (ROC) analysis was used to assess the diagnostic value of these image measures to distinguish SZ patients with AVHs from those without. In addition, Allen *et al.* recommended correlating individual differences in image measures with the severity of hallucinations [16]. To determine the correlations between EC and the severity of AVHs, Pearson correlation coefficients were computed between connection strength and AHRS score in patients with AHVs. We did not apply age, gender, or education as covariates in correlation analysis. A P value <0.05 was accepted as statistically significant, adjusted for multiple comparisons using Bonferroni correction.

Results

Effective Connectivity

Significant connections at the group level (one-sample t-test at a P value of 0.05, Bonferroni-corrected for multiple comparisons) are shown in Fig. 1B and Table 1 (in terms of simple main effects within groups). In patients with AVHs, the auditory cortex, DLPFC, and Broca's area formed a bi-directionally connected network (Fig. 1B). In contrast, a more distributed network was detected in patients without AVHs (Fig. 1B). In addition to the bi-directional connections between DLPFC and Broca's area and between the auditory cortex and Broca's area, reciprocal connectivity was also found between the auditory cortex and the hippocampus, and between the auditory cortex and the thalamus, together with unilateral connectivity from the hippocampus to the DLPFC. HCs also exhibited reciprocal connectivity between the auditory cortex and Broca's area, and between the DLPFC and Broca's area (Fig. 1B).

A two-sample t-test (at a P value of 0.05, uncorrected for multiple comparisons) revealed significantly higher EC from the thalamus to auditory cortex in SZ patients with AVHs than those without (Fig. 2A). Specifically, the connectivity strength from the thalamus to the auditory cortex was lower in patients without AVHs than in HCs, but higher in patients with AVHs than in those without. Notably, ANOVA revealed $P = 0.02$ for this thalamic-auditory cortical connection. Furthermore, the connection from the auditory cortex to the hippocampus was significantly decreased in patients with AVHs. EC from the thalamus to auditory cortex was significantly lower in the non-AVH group than in HCs (Fig. 2B).

ROC Analyses

We used ROC analysis to evaluate the diagnostic value of EC strength (Fig. 2C). The area under the ROC for thalamic-auditory cortical connectivity (0.79; 95% confidence interval, 0.64–0.95) and that for auditory cortical-hippocampal connectivity (0.70; 0.51–0.88) suggest that these connections have diagnostic value for distinguishing SZ patients with AVHs from those without.

Correlation Analyses

Finally, we calculated the correlation between the severity of AVHs and the strength of all the connections in the AVH group. There was no significant correlation of AHRS

Table 1 Strength (Hz) of connections in schizophrenia patients and healthy controls (HCs)

Connections	AVH patients	Non-AVH patients	HCs
Auditory cortex-DLPFC[a]	−0.1161 ± 0.1664	−0.0946 ± 0.3213	−0.0634 ± 0.2899
Auditory cortex-hippocampus[b]	0.0449 ± 0.2537[*]	0.2516 ± 0.2954	0.0664 ± 0.2879
Auditory cortex-thalamus[b]	0.0658 ± 0.3911	−0.2112 ± 0.3785	−0.0203 ± 0.3058
Auditory cortex-Broca's area[a,b,c]	0.1334 ± 0.2291	0.2413 ± 0.3168	0.1628 ± 0.2234
DLPFC-auditory cortex[a]	−0.2732 ± 0.5018	−0.0016 ± 0.4890	−0.1180 ± 0.5040
DLPFC-hippocampus[c]	0.1552 ± 0.5185	0.1698 ± 0.5039	0.2111 ± 0.4300
DLPFC-Broca's area[a,b]	0.3538 ± 0.4478	0.4347 ± 0.4076	0.3999 ± 0.3136
Hippocampus-auditory cortex[b]	0.1378 ± 0.4513	0.3213 ± 0.5378	0.1288 ± 0.4800
Hippocampus-DLPFC[b,c]	0.0967 ± 0.3150	0.2849 ± 0.3910	0.1583 ± 0.3462
Hippocampus-thalamus[c]	0.0130 ± 0.5061	0.1362 ± 0.6156	0.3128 ± 0.4269
Thalamus-auditory cortex[b]	0.0446 ± 0.2969[*]	−0.2738 ± 0.2916[#]	−0.0322 ± 0.3427
Broca's area-auditory cortex[a,b,c]	0.3543 ± 0.4509	0.3224 ± 0.3373	0.4199 ± 0.4566
Broca's area-DLPFC[a,b,c]	0.2910 ± 0.3452	0.3505 ± 0.2800	0.4051 ± 0.3354

Significant effective connectivity at the group level for [a] AVH patients, [b] non-AVH patients, and [c] HCs ($P < 0.05$, Bonferroni corrected). * $P < 0.05$ *versus* non-AVHs (uncorrected); [#] $P < 0.05$ *versus* HCs (uncorrected).

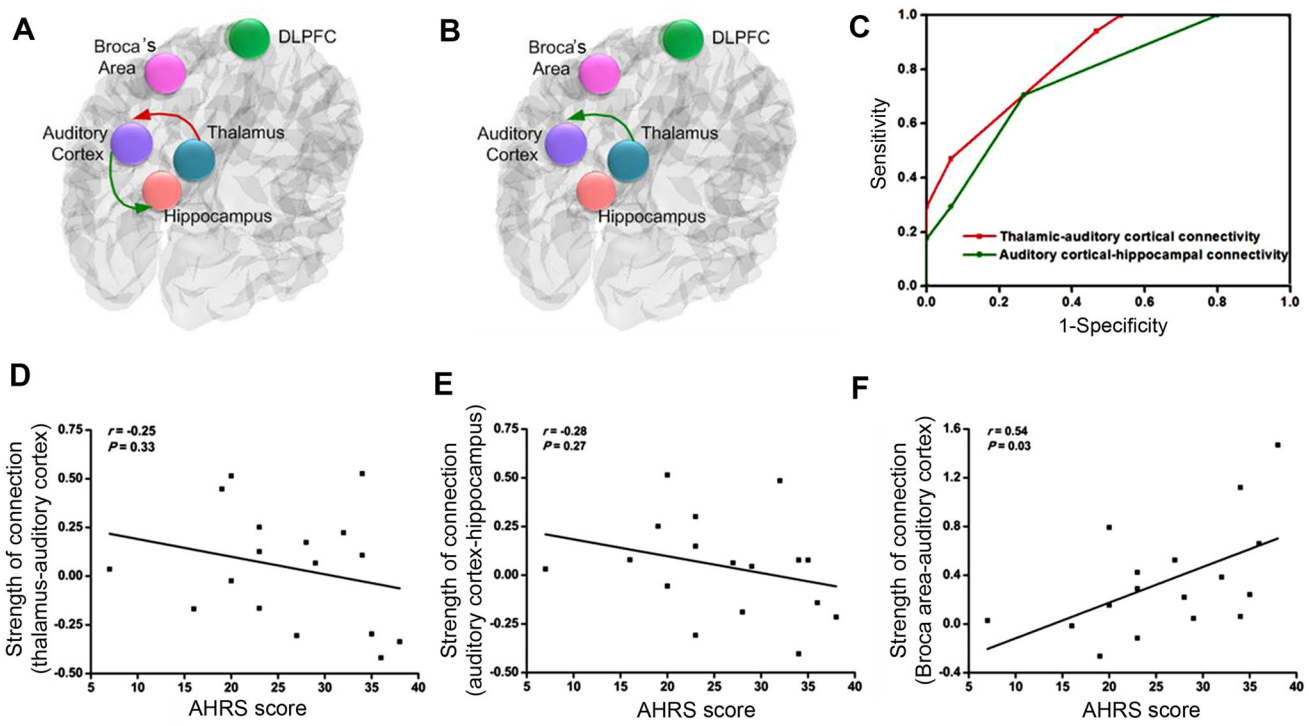

Fig. 2 Significant EC (at the between-group level) among ROIs between the SZ patients with and without AVHs, ROC analysis, and correlation analysis. **A** Increased (*red*) and decreased (*green*) EC in the AVH group compared with the non-AVH group. **B** Decreased (*green*) EC in the non-AVH group compared with HCs. **C** ROC analysis for distinguishing patients with AVHs from those without. **D–F** Correlations between the AHRS score and the strength of connection from thalamus to auditory cortex, from auditory cortex to hippocampus, and from Broca's area to auditory cortex.

score with the connection from thalamus to auditory cortex or from auditory cortex to hippocampus (Fig. 2D and E), but a positive correlation with the strength of connectivity from Broca's area to auditory cortex (Fig. 2F). No other significant correlation was found in SZ patients with AVHs (data not shown). These results provide a symptom-based validation of the EC estimates.

Discussion

In this study, the fMRI and sDCM results revealed thalamic-auditory cortical hyperconnectivity and auditory cortical-hippocampal hypoconnectivity in SZ patients with AVHs compared with those without AVHs. Intriguingly, there was no significant difference between SZ patients with AVHs and HCs in the strength of any connection, which seems counter-intuitive. The strengths of thalamic-auditory cortical-hippocampal connections in HCs were intermediate between those of the AVH and non-AVH groups, which implies disturbed brain functions in AVH patients in such a psychopathological setting, resulting in a connection strength in AVH patients comparable to that in HCs. Moreover, none of the patients in our study reported experiencing AVHs during scans. We therefore defined the current research as a trait-study, as described by Jardri *et al.* [5], that investigated the neural substrates of the susceptibility to AVHs in SZ patients.

AVH-Specific Findings in SZ: Thalamic-Auditory Cortical Hyperconnectivity

Our results suggest that SZ patients with AVHs show abnormal neurophysiological activity that can be explained by dysconnections, primarily involving the auditory cortex. Specifically, the thalamic-auditory cortical EC was elevated in SZ patients with AVHs, indicating a relative failure to attenuate excitatory afferents from the thalamus to the auditory cortex. This finding is understandable from the neuroanatomical point of view: the presynaptic terminals of neurons projecting from the medial geniculate nucleus of the thalamus to the auditory cortex release the excitatory neurotransmitter glutamate in the target regions. Thalamocortical dysconnectivity has been implicated in SZ [51]. At the molecular level, SZ has been modeled as a neurodevelopmental disorder with aberrant glutamate and dopamine neurotransmission. A neuroimaging study has found aberrant FC within the dopaminergic network in SZ patients suffering from AVHs [14]. In addition, using electrophysiological methods, Chun *et al.* demonstrated a

deficiency in the thalamic-auditory cortical synaptic transmission associated with AVHs in mouse models of SZ, therefore the D2 dopamine receptor-dependent thalamocortical disruption may represent a pathophysiological event underlying AVHs in SZ [52]. This is consistent with our fMRI findings of aberrant connectivity from the thalamus to the auditory cortex in SZ patients with AVHs. Specifically, SZ patients without AVHs showed significant thalamic-auditory cortical inhibition, suggesting effective gain control over thalamic afferents to the auditory cortex and an absence of the AVH symptom. On the contrary, SZ patients with AVHs failed to attenuate excitatory afferents from the thalamus to the auditory cortex. This suggests a failure to modulate ascending thalamic inputs to the auditory cortex, resulting in a predisposition to AVHs. Taken together, the thalamic-auditory cortical dysconnectivity may be a key factor in the pathophysiology of AVHs in SZ.

Predictive Coding, SZ, and False Inference

The failure to attenuate ascending sensory information in the auditory system—through aberrant neuromodulation—reproduces the findings of Fogelson *et al.* [35] using DCM of visual-evoked responses as measured with electroencephalography. More generally, our results are consistent with a failure to attenuate sensory (auditory) precision and the associated cortical gain control. Physiologically, this failure has been invoked as an explanation for the characteristic attenuation of oddball responses (e.g., mismatch negativity) to unpredicted stimuli (see Baldeweg *et al.* [34] for review). Functionally, this aberrant gain control has been interpreted within predictive coding as a failure to properly encode the precision or salience of ascending sensory information. As discussed elsewhere, the consequences of misattributing precision or salience to sensory cues (or their absence) can have profound effects on perceptual inference, possibly leading to hallucinations and secondary delusional collaborations (see Adams and Fletcher [32, 53] for a fuller discussion).

The thalamus may mediate the responses in auditory cortex *via* different pathways. Thalamic-auditory cortical projections are from many nuclei of the thalamus, including the medial and dorsal divisions, in addition to the ventral medial geniculate nucleus. The hyperconnectivity from the thalamus to the auditory cortex in AVH patients that we found reflects an overall effect of the thalamus on the auditory cortex (because in sDCM we summarized thalamic activity as a single brain region comprising all the nuclei). The comprehensive influence of diverse neurotransmitters/neuromodulators (dopamine, glutamate/glutamine, acetylcholine, noradrenalin, serotonin, and histamine) on the thalamus-related networks might subserve the emergence of hallucinations in SZ [54]. Moreover, the thalamus highlights certain inputs and inhibits others in SZ on the basis of impaired modulation of thalamocortical gamma activity by external sensory afferents [55, 56]. Some have suggested that AVHs are a result of dysfunctional thalamic filtering of external from internal speech [57, 58]. Our results contrast with more resolved studies focusing on glutamatergic neurons in thalamic-auditory cortical projections in animal models. In an SZ mouse model, Chun *et al.* found that an abnormal increase of D2 dopamine receptors in the thalamic nuclei caused a thalamocortical synaptic deficit owing to reduced glutamate release, and the defect was associated with the loss of a component of the microRNA-processing machinery encoded by the *dgcr8* (diGeorge syndrome critical region 8) gene [52]. Clearly, it is important to understand how abnormalities in modulatory neurotransmission lead to abnormal EC of the sort assessed with fMRI, particularly in the context of dense reciprocal thalamocortical and corticothalamic interactions.

Increased Activity of the Auditory Cortex in AVHs

Increased sensitivity of the auditory cortex to thalamic inputs may explain the elevated activity in the auditory cortex in patients with AVHs—as reported by arterial spin labeling studies which showed increased CBF in the auditory cortex [7, 8]. High levels of CBF may reflect increased excitability of the auditory cortex of SZ patients with AVHs, pointing to a role of hyperconnectivity from the thalamus in predisposing to AVHs. After treatment with tDCS or transcranial magnetic stimulation, CBF in the auditory cortex decreases significantly in SZ patients with AVHs who respond to the treatment and reduces the severity of the AVHs [7, 8]. In addition, a meta-analysis of 12 functional neuroimaging studies show increased activation in the left auditory cortex of SZ patients with AVHs in the absence of an external auditory stimulus [59]. Taking these results and our findings together, we postulate that auditory processing in SZ might originate from thalamocortical dysconnectivity [51], which has been previously proposed as the basis of cognitive dysmetria [60].

Auditory Cortical-Hippocampal Hypoconnectivity in SZ patients with AVHs

As for dysconnectivity between the auditory cortex and the hippocampus, we found weaker excitatory connectivity in SZ patients with AVHs than in those without. Amad *et al.* reported links between the hippocampus and AVHs in SZ patients using multimodal analyses that showed distinct patterns of FC between the hippocampus and thalamus, white matter connectivity (fasciculus), and hippocampal volume in SZ patients with only AVHs or with audio-

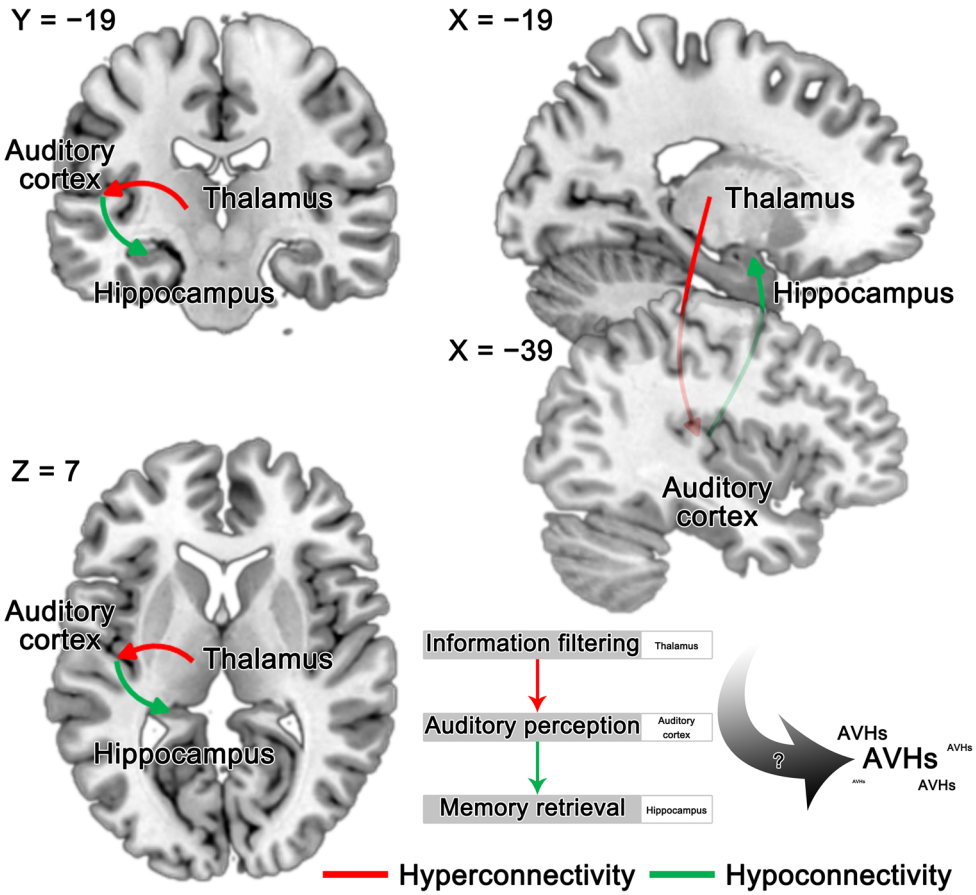

Fig. 3 A proposed mechanism for AVHs in SZ. Disrupted interactivation among sensory information filtering (thalamus), auditory perception (auditory cortex), and memory retrieval (hippocampus) might be involved in AVHs in SZ. The thalamic-auditory cortical-hippocampal dysconnectivity may lead to increased activation of the auditory cortex and false perceptual inference in the absence of auditory stimuli.

visual hallucinations [10]. Although no monosynaptic projections from the auditory cortex to the hippocampus have been detected anatomically, our results suggest the existence of functional interaction between them in SZ. Specifically, SZ patients with AVHs showed decreased auditory cortex-hippocampus connectivity. Given that the long fibers of the inferior longitudinal bundle connect visual areas and the hippocampus [61], we hypothesize that homologous auditory cortex-hippocampus projections are engaged in auditory information processing. It is possible that the weak auditory cortex-hippocampus connectivity contributes to AVHs in SZ, which might be another expression of abnormal gain control. Hierarchical modulatory gain control tends to show reciprocal changes at different levels of the cortical hierarchy. From the perspective of predictive coding, a failure to attenuate auditory precision in the auditory cortex is entirely consistent with a relative decrease in precision at a higher (hippocampal) level. Put simply, this would mean that the (sensory) levels of the auditory hierarchy would be more sensitive to ascending and descending afferents, while higher (e.g. hippocampal) levels would be less sensitive.

We postulated a relative hypersensitivity of auditory cortex to both ascending (thalamic) and descending (prefrontal) afferents. Combining the data from SZ patients with and without AVHs showed no significant difference in connectivity between the DLPFC or Broca's area and the auditory cortex in the three groups. However, we did find a significant positive correlation between the AHRS score and the strength of the EC from Broca's area to the auditory cortex, indicating that the severity of AVHs in SZ patients is associated with increasing sensitivity of the auditory cortex to afferents from Broca's area, leading to a plausible explanation for the increased Broca's area-auditory connectivity as a compensatory change resulting from the reduced Wernicke's area-Broca's area connectivity [39] for AVHs.

To our knowledge, this is the first study to use EC—as assessed with sDCM—to investigate AVHs in first-episode, drug-naïve SZ patients and to examine the symptom-

based EC patterns. Notably, Ćurčić-Blake *et al.* pointed toward a negative connection from Wernicke's area to Broca's area using DCM [39], and Dauvermann *et al.* found decreased thalamocortical connectivity in first- or second-degree relatives of SZ patients using nonlinear deterministic DCM during verbal fluency processing [62]. Using sDCM, we characterized EC in a system that has direct relevance to AVHs, and found dysconnectivity within three regions (thalamus, auditory cortex, and hippocampus) in drug-naïve SZ patients with AVHs, involving increased thalamic-auditory cortical and reduced auditory cortical-hippocampal EC, compared to SZ patients without AVHs. In addition, in a recent volumetric study, we found decreased bilateral thalamic gray matter volume in first-episode SZ patients with AVHs [3]. In other words, SZ patients with AVHs have a compensated augmented excitatory response to afferents from the thalamus in the auditory cortex due to reduced thalamic volume, and this may be the mechanism responsible for AVHs in SZ (Fig. 3).

Several limitations need to be pointed out. The sample size was limited due to the strict recruitment criteria for medication-naïve, first-episode patients. fMRI scans usually require a high degree of patient compliance, which is, however, lacking in many drug-naïve SZ patients. In addition to EC analysis, gray matter and white matter-based analyses and topological properties in the brain, as applied in previous studies [63, 64], should also be introduced in future AVH research to provide a full view of the potential neural underpinnings and neuroimaging features of this debilitating symptom of SZ.

In summary, we found hyperconnectivity from the thalamus to auditory cortex and hypoconnectivity from the auditory cortex to the hippocampus in AVH patients. In such patients, there is a failure to attenuate the sensitivity of auditory cortex to thalamic inputs with a complementary down-regulation of hippocampal responses to ascending auditory input. These findings demonstrate the thinking about dysconnection syndromes in SZ, particularly the aberrant modulation of neural modulatory gain control and its role of assigning aberrant precision or salience to sensory evidence in conditions like SZ. Our findings provide support for the dysconnectivity hypothesis of AVHs associated with auditory/language-processing regions, default mode regions, and other networks (insula and striatum), as reviewed recently [65]. Based on our direct evidence *in vivo*, the thalamic-auditory cortical-hippocampal circuit seems to be crucial for AVHs in SZ (Fig. 3).

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