Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta Morphologica et Anthropologica, 33 (1-2)
Sofia ● 2026

MORPHOLOGY 33 (1)

Original Articles

Altered Hemispheric Lateralization of Heschl's Gyrus in Schizophrenia with Auditory Verbal Hallucinations: A Resting-State fMRI Study

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Hemispheric lateralization plays a crucial role in language and auditory processing, typically showing left-hemispheric dominance. Alterations in this organization have been implicated in schizophrenia, particularly in relation to auditory verbal hallucinations. This study examined hemispheric lateralization of resting-state functional activity in Heschl's gyrus in schizophrenia patients with auditory verbal hallucinations. The sample included 105 participants (42 patients and 63 healthy controls). Resting-state fMRI data were acquired on a 3T scanner and analyzed using the CONN toolbox and SPM12. Seed-based connectivity analyses were conducted for bilateral Heschl's gyrus. Compared with controls, patients showed increased resting-state functional connectivity between the right Heschl's gyrus and the right postcentral gyrus, and between the left Heschl's gyrus and the right lateral occipital gyrus. These results suggest altered intrinsic connectivity of auditory cortical regions in schizophrenia, potentially reflecting disrupted functional lateralization associated with hallucinatory experiences.

Key words: schizophrenia, auditory verbal hallucinations, resting-state, functional magnetic resonance imaging, Heschl's gyrus

Introduction

Hemispheric lateralization is a fundamental organizational principle of the human brain that enables specialized cognitive and perceptual functions to be preferentially processed within one cerebral hemisphere. In healthy individuals, language and auditory processing typically show left-hemispheric dominance, reflecting the asymmetric organization of cortical networks involved in speech perception and production. Disruptions in hemispheric specialization have been proposed as a neurobiological feature of psychiatric disorders and may contribute to disturbances in language and auditory processing [1]. Early theoretical models suggested that abnormal cerebral lateralization may contribute to core cognitive and perceptual disturbances observed in schizophrenia, particularly those involving language and auditory processing [5]. Subsequent neuroimaging studies have supported this view, demonstrating altered structural and functional asymmetries in several cortical regions associated with language and auditory perception [14, 17].

Heschl's gyrus (HG), located on the superior temporal plane of the temporal lobe, contains the primary auditory cortex and represents the first cortical stage of auditory processing. It plays a key role in the analysis of fundamental acoustic properties such as frequency, intensity, and temporal structure that are necessary for the perception of complex sounds, including speech. In healthy populations, HG often shows structural asymmetry with a tendency toward leftward dominance. The region also demonstrates considerable anatomical variability, particularly in gyrification and duplication patterns, which may influence auditory cortical organization. Neuroimaging evidence suggests that atypical gyrification and duplication of HG may be associated with altered auditory processing and may occur more frequently in neuropsychiatric conditions such as schizophrenia [8].

Schizophrenia has been linked to structural and functional abnormalities within temporal lobe regions involved in auditory and language processing. These alterations may contribute to the frequently observed deficits in auditory perception and speech processing. Auditory verbal hallucinations (AVH) are among the most common symptoms of schizophrenia, affecting approximately 60–80% of patients during the course of the illness. AVH involve the perception of voices or speech in the absence of external auditory stimuli and are often experienced as intrusive and distressing. Neuroimaging studies have demonstrated increased activation in auditory cortical regions, including HG and the superior temporal cortex, during hallucinatory episodes [9], supporting the hypothesis that hallucinations may arise from abnormal activity within auditory processing networks.

Resting-state functional magnetic resonance imaging (rs-fMRI) provides an important method for examining intrinsic brain activity and functional connectivity by measuring spontaneous low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. This approach is particularly useful in clinical populations because it minimizes confounding effects related to task performance. Studies using rs-fMRI have reported widespread connectivity disruptions in schizophrenia [20], particularly within networks involving frontal and temporal regions [22]. Altered resting-state connectivity between auditory cortex and language-related regions has been associated with the presence and severity of AVH [13]. Additional work has reported disturbances in large-scale brain networks related to hallucinatory states [11] as well as abnormal connectivity involving thalamocortical and auditory cortical pathways in schizophrenia [19]. Structural and functional alterations in temporal cortical regions have also been linked to variations in hallucination severity and phenomenology [4, 7].

Despite increasing interest in the neural mechanisms of AVH, relatively few studies have specifically examined hemispheric lateralization of intrinsic functional activity within HG using resting-state fMRI. Investigating the functional organization of HG in schizophrenia patients experiencing AVH may therefore provide further insight into the neural mechanisms underlying hallucinatory experiences.

The present study aimed to examine hemispheric lateralization of resting-state functional activity in HG in schizophrenia patients experiencing AVH compared with healthy controls (HC) by analyzing intrinsic BOLD signal patterns within bilateral HG.

Material and Methods

Participants

The study included 105 participants (42 schizophrenia patients with auditory verbal hallucinations (AVH) and 63 age- and sex-matched HC), aged 18–61, after excluding five individuals due to poor-quality MRI data. Patients met DSM-5 criteria for schizophrenia and had severe AVH (Positive and negative syndrome scale (PANSS) P3 item > 3). Controls were recruited from the local community and screened to exclude neurological, psychiatric, or cognitive impairments. Additional exclusion criteria for all participants included metallic implants or MRI contraindications. All procedures were approved by the Ethics Committee of Medical University of Plovdiv (Protocol №1/11.01.2024), and written informed consent was obtained in accordance with the Helsinki Declaration.

MRI Acquisition

Imaging was performed on a 3T GE Discovery 750w scanner. High-resolution structural images were acquired using a sagittal 3D T1-weighted sequence (1 mm isotropic voxels, TR = 7.2 ms, TE = 2.3 ms, flip angle = 12°). Resting-state functional images were collected using a 2D EPI sequence (TR = 2s, TE = 30ms, 36 slices, voxel size = 3.44 × 3.44 × 3.5mm^3, 160 volumes). Participants were instructed to keep their eyes closed, remain still, and avoid focused thoughts.

Image Processing and Statistical Analysis

Functional data were preprocessed and analyzed using CONN toolbox 21.a with SPM12 in MATLAB R2024a. Standard preprocessing included motion correction, slice-timing correction, normalization to MNI space, outlier detection, and 8-mm FWHM smoothing. Denoising included regression of white matter and cerebrospinal fluid signals. Seed-based connectivity analyses were conducted for the right and left

HG. Group-level analyses were thresholded at $p<0.05$, FWE-corrected. Demographic and clinical variables were analyzed using IBM SPSS Version 28.0 (NY: IBM Corp). Student's t-test and chi-square test were used for the statistical analysis. The level of statistical significance was set at $p<0.05$ for all tests.

Results

Socio-demographic and clinical characteristics

The study revealed that there were no statistically significant differences between the patients with schizophrenia and the healthy controls with regard to age or sex. Expectedly, due to the early clinical onset of the condition, statistically significant disparities were identified between the two groups with respect to education. As anticipated, the PANSS scores were found to be significantly higher for the patient group than for the control group (**Table 1**).

Table 1. Socio-demographic and clinical characteristics.

	P (n=42)	**HC (n=63)**	**p**
Age (mean, SD)	35.3 ± 12.4	36.0 ± 12.5	**0.770[a]**
Sex (M/F)	26/16	31/32	**0.234[b]**
**Education (primary/ secondary/higher)	8/26/6	1/33/29	***0.000[b]**
***PANSSP3 score (mean, SD)**	5.1 ± 0.6	1.0 ± 0.0	***0.000[a]**

P – patients, HC – Healthy controls, SD – Standard Deviation, [a]Student's t-test, [b]$\chi 2$ – test, *p<0.05, **Two of the patients were excluded from the analysis due to missing data on education, ***PANSSP3 score – AVH (Auditory Verbal Hallucinations)

Functional connectivity of the Heschl's gyrus

The comparison between the patients with schizophrenia and the HC revealed increased FC between the right HG and a cluster encompassing the right postcentral gyrus in the patient group as compared to the control group (**Table 2, Figure 1**).

Table 2. Between group differences of functional connectivity of the Right Heschl's Gyrus seed.

Between-group contrast	**MNI coordinates x, y, z**	**Cluster-size**	**Cluster-threshold (*p<0.05*, FWE)**	**Regions within the cluster**
P>HC	+34 -32 +48	211	0.001	Right Postcentral Gyrus

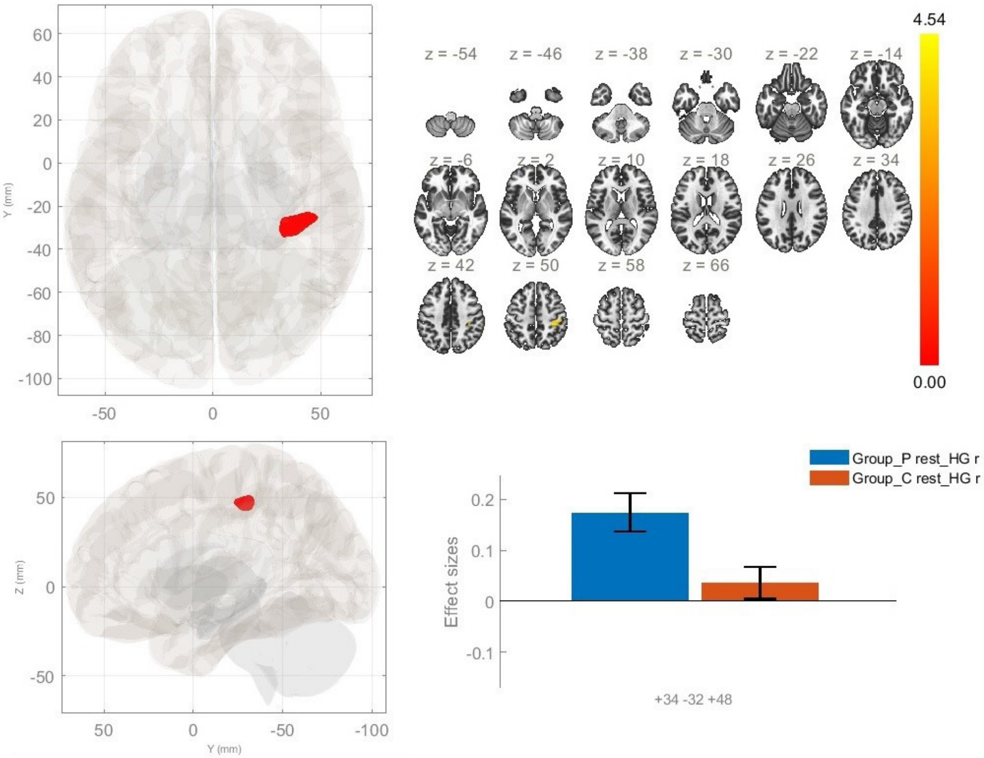

Fig. 1. Functional connectivity of the right Heschl's gyrus seed in schizophrenia compared to the HC group and effect sizes for each significant cluster with a cluster threshold p<0.05 cluster-level FWE correction. Increased rsFC between the right Heschl's gyrus and the right postcentral gyrus (cluster coordinates +34 -32 +48) in the patient group in comparison with HC was observed.

Hyperconnectivity was detected also between the left HG and the right lateral occipital gyrus, superior division in schizophrenia in contrast to the HC (**Table 3, Figure 2**).

Table 3. Between group differences of functional connectivity of the Left Heschl's Gyrus seed.

Between-group contrast	**MNI coordinates x, y, z**	**Cluster-size**	**Cluster-threshold (*p<0.05*, FWE)**	**Regions within the cluster**
P>HC	+36 -62 +38	177	0.002	Right Lateral Occipital Cortex, Superior Division

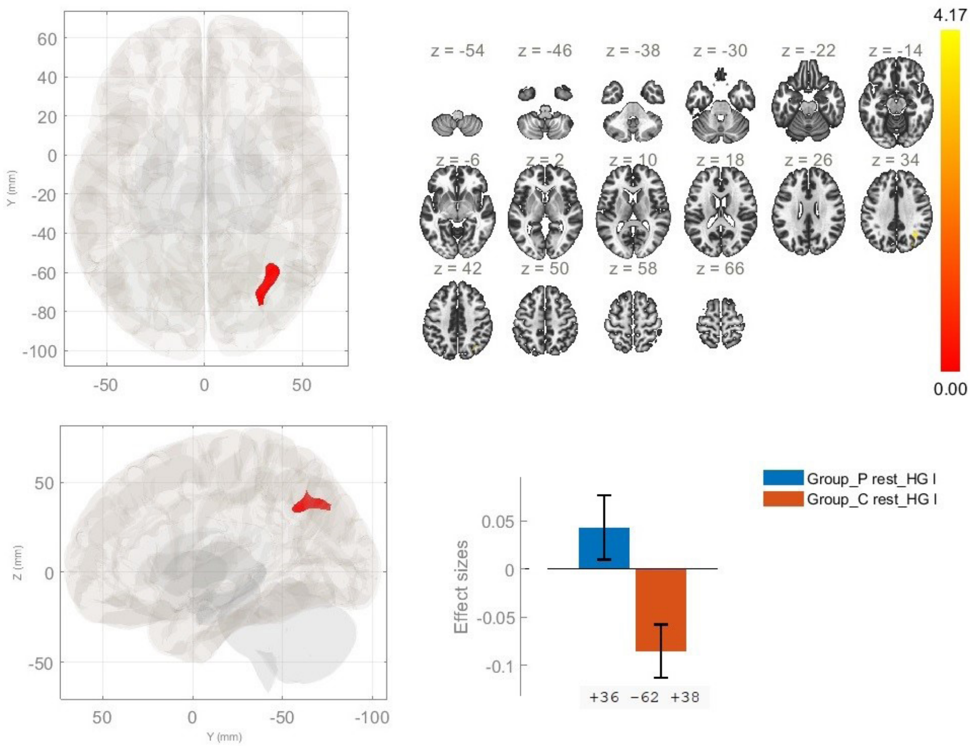

Fig. 2. Functional connectivity of the left Heschl's gyrus seed in schizophrenia compared to the HC group and effect sizes for each significant cluster with a cluster threshold $p<0.05$ cluster-level FWE correction. Increased rsFC between the left Heschl's gyrus and the right lateral occipital cortex, superior division (cluster coordinates +36 -62 +38) in the patient group in comparison with HC was observed.

Furthermore, we repeated the analyses, incorporating the level of education as a covariate of no interest. The results remained consistent in terms of the number of significant clusters, the regions within them, and the peak coordinates. A non-significant change in the size of the clusters was observed, with a reduction amounting to a couple of voxels.

Discussion

The current study identified several significant differences in the rsFC of the HG in patients with AVH as compared to HC. First, an enhanced rsFC was identified between the right HG and the right postcentral gyrus in the patient group in comparison to the control group. Next, we identified hyperconnectivity between the left HG and the superior division of the right lateral occipital cortex in schizophrenia, as opposed to the control group.

The present findings are consistent with the mounting evidence from neuroimaging studies that suggests altered FC in the temporal region. The current analysis revealed increased rsFC between the right HG and the postcentral gyrus in the AVH group. The primary somatosensory cortex is known to be located in the postcentral gyrus. This region has been implicated in the pivotal role of integrating information regarding mouth movements into the process of speech perception [15]. Multiple studies have reported abnormal rsFC between this region and the temporal cortex in schizophrenia [10, 16]. Defective monitoring of inner speech has been identified as a contributing factor to the onset of AVH, and has been linked to the disruption of integration of sensorimotor processing and the processing of auditory information. The elevated risk of experiencing AVH has been demonstrated to be positively correlated with such language-related disturbances [2, 6].

Our findings also identified increased rsFC between the left HG and the right lateral occipital cortex in the patient group. The occipital lobe is known to be involved in phonological and semantic modulation. It has been hypothesized that disturbances in such functions may be indicative of the pathophysiology of schizophrenia. In consideration of the potential relationship between abnormal semantic processing and the development of AVH, the existence of any anomalies in the FC between the occipital lobe and the primary auditory cortex might also serve as a contributing factor to the observed impairments in auditory perception [18]. As postulated by Xue et al., the underlying mechanisms of AVH occurrence in schizophrenia may be associated with aberrant dynamic FC between occipital and temporal regions [21]. The findings of the present study are consistent with those reported in the extant literature, suggesting that aberrant occipito-temporal connectivity may potentially contribute to the development of AVH.

One notable finding of the current study was that the pattern of dysconnectivity in HG was limited to regions of the right hemisphere, thereby indicating a predominant right-hemisphere involvement in AVH. As indicated by previous studies, diminished functional lateralization has been found to demonstrate a negative correlation with the severity of positive symptoms, as measured by the PANSS. Furthermore, reduced left>right language asymmetry has been shown to correlate negatively with the onset of AVH, thus indicating that the reduced lateralization is implicated in the development of AVH [3, 12].

Conclusion

The present study elucidated lateralized impairment in the FC of the right and left HG. Aberrant connections were identified between the explored temporal regions and right postcentral gyrus and right lateral occipital cortex. The observed dysconnectivity lends support to the hypothesis of reduced functional L > R asymmetry in AVH, indicating the reduced functional lateralization as an underlying pathophysiological mechanism in schizophrenia.

Acknowledgments: S.K. and D.S. have been funded by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0007-C03.

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