DOI: 10.14744/DAJPNS.2019.00002
Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2019;32:4-13

RESEARCH ARTICLE

Intrinsic oscillations of auditory networks in schizophrenia and bipolar disorder

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ABSTRACT

Objective: Several types of evidence have shown that auditory networks are dysfunctional in schizophrenia (Sch) and bipolar disorders (BD). Auditory cortices show abnormalities in hallucinations or during remission. This study aimed to assess resting-state connectivity of auditory cortices in Sch and BD.

Method: Patients with BD-1 (n=28), BD-2 (n=21), Sch (n=30), and healthy controls (HC, n=30) were enrolled into the study. A 3 Tesla whole-body magnetic resonance imaging (MRI) system with a 32-channel phase-array head coil was used to acquire the MRI data. T1-weighted anatomical and gradient-echo based Echoplanar Imaging sequences were used. MATLAB and Freesurfer software packages were used for data analyses. Connectivity alterations within the auditory network guided our further seed-based connectivity analysis.

Results: The left angular gyrus volume was decreased in Sch and BD-2 groups. The supramarginal gyrus had hyperconnectivity with the medial prefrontal cortices and decreased connectivity with the medial superior temporal gyrus (STG) in the BD-1 and BD-2 groups. The left superior temporal sulcus (STS) had increased connectivity with the bilateral posterior cingulate cortex in BD-1 and BD-2 and increased connectivity with the dorsal prefrontal cortices in the Sch group. The STS had increased connectivity with the medial STG in the BD-1 and Sch groups, whereas connectivity decreased in the BD-2 group.

Conclusion: These findings suggest that functional connectivity of resting-state networks are altered in BD and Sch. Auditory network alterations may predispose to dysfunctional auditory information processing. Further studies are needed to determine the relationship between symptoms and auditory network dysfunction.

Keywords: Auditory cortex, bipolar disorder, network, schizophrenia.

How to cite this article: Atagun MI, Akin B, Algin O, Sikoglu EM, Can SS, Ulusoy-Kaymak S, Caykoylu A, Moore C, Philips M, Ongur D. Intrinsic Oscillations of Auditory Networks in Schizophrenia and Bipolar Disorder. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2019;32:4-13.

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Received: July 04, 2018; **Revised:** October 23, 2018; **Accepted:** December 13, 2018

INTRODUCTION

The developmental trajectory of the auditory cortices extends until late adolescence and is vulnerable to disruption (1,2). Several lines of evidence have demonstrated that auditory cortices are among the most volatile brain regions in patients with schizophrenia and bipolar disorder. Pressured speech, flight of ideas, auditory hallucinations, and verbal memory deficits are the symptom domains related with the auditory cortices in schizophrenia and bipolar disorder (2). Several histopathological examinations (3-5) and neuroimaging studies (6-17) have consistently reported abnormalities in auditory cortices in schizophrenia and bipolar disorder.

The primary auditory cortex (PAC), Wernicke's Area (WA), the inferior parietal lobe (IPL), and Broca's Area (BA) and their anatomical connections constitute the auditory networks, notably including two central heteromodal association areas (i.e. Wernicke's and Broca's Areas) (18). Different units within the auditory cortices participate in processing different features of auditory input (19). Hence, the integration between the components of the auditory cortices by hardly-wired networks at diverse scales is crucial for such distributed and collaborative procedures of auditory perception. Two main pathways, the ventral and dorsal streams, are associated with semantic and spatial processing, respectively (20).

Resting-state functional connectivity is based on the correlations of spontaneous brain activity while the brain is not engaged in any task. Correlations of low-frequency fluctuations are interpreted as evidence of intrinsic, functional connections between brain regions. As auditory hallucinations typically emerge at rest, it has been shown that the correlation of the brain activity shows that resting-state functional connectivity abnormalities of the auditory cortices are significantly higher in hallucinating patients, in comparison to non-hallucinating patients with schizophrenia (21,22). Shinn et al. (23) have observed differences between schizophrenia patients with and without auditory hallucinations in resting-state functional connectivity of the left superior temporal gyrus. The authors reported that left superior temporal gyrus (STG) had hyperconnectivity with cortical regions of the forebrain that are involved in speech, memory formation, executive functions, and self-referential thoughts. On the other hand, abnormalities of the auditory cortices are not limited to auditory hallucinations in schizophrenia and bipolar disorder. Auditory emotional (24,25) and cognitive (10-12) processing deficits are observed in schizophrenia and bipolar disorder. These findings may indicate a dysfunction in auditory networks even when the patients are in remission (10).

Independent component analysis (ICA)-based resting-state functional Magnetic Resonance Imaging (fMRI) studies have reported abnormal connectivity between auditory cortices and other brain regions in schizophrenia and bipolar disorder (26,27). Voxel-wise functional connectivity analyses are the sum of ICA-derived within- and between-network analyses (28). Preprocessing steps and statistical analyses differ between the methods. Voxel-wise correlation analysis is able to show correlation between time series of brain regions and the voxel of interest. Therefore, this study aimed to assess seed-based resting-state functional connectivity between auditory cortices and other brain regions in schizophrenia and bipolar disorder.

METHOD

This study was approved by the local Ethics Committee. All participants provided written informed consent before enrollment. Consecutive outpatients were invited to participate in the study and accepting patients were enrolled, including 30 (12 women) patients with schizophrenia, 28 (15 women) with bipolar I disorder (BD-1), 21 (12 women) with bipolar II disorder (BD-2) and 30 (17 women) healthy controls (HC). Diagnoses were checked by Structured Clinical Interview According to DSM-IV (SCID-1) (29). Young Mania Rating Scale (YMRS) (30,31), Hamilton Depression Rating Scale (HDRS) (32,33), Brief Psychiatric Rating Scale (BPRS) (34), Scale for the Assessment of Negative Symptoms (SANS) (35,36), Scale for the Assessment of Positive Symptoms (SAPS) (37,38), and Edinburgh Handedness Inventory (39) were the clinical evaluation tools (administered by MIA). MRI scans were performed immediately after the clinical assessments. All patients included in this study were clinically stable. Exclusion criteria were any history of brain surgery or major physical trauma, diabetes mellitus, hypertension, metallic implants that are not compatible with MRI sessions, hearing disabilities, and any psychiatric comorbidity or lifetime history of substance abuse. We enrolled patients regardless of psychotropic medications; only patients on benzodiazepines were excluded.

Data Acquisition

A 3 Tesla whole-body magnetic resonance imaging (MRI) system (Magnetom Tim Trio, Siemens AG, Erlangen Germany) with a 32-channel phase-array head coil was used to acquire the MR data at the

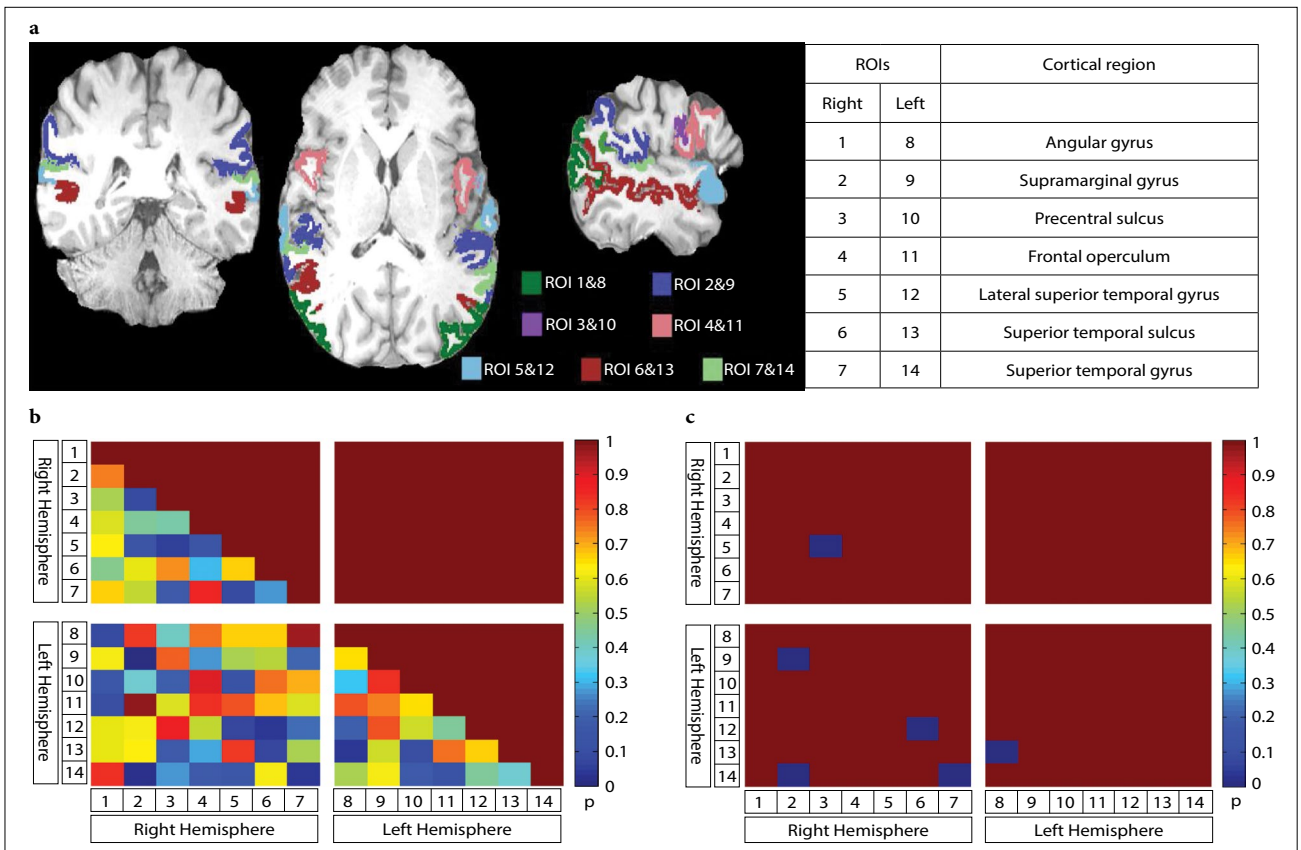
UMRAM (National Magnetic Resonance Research Center, Ankara, Turkey). T1-weighted anatomical MRIs (MPRAGE sequence, 256x256 voxels, TR: 2000 msec, TE: 3.02 msec, FOV read: 215, FOV phase: 100, slice thickness: 0.84, 192 slices) were acquired for diagnostic and localization purposes. A gradient echo-based EPI sequence was used to acquire functional MRI data (TR: 2000 msec, TE:40 msec, Flip Angle: 71° and 3 mm isometric-voxel resolution, 64x64x32 matrix size with 90 volumes). Patients were instructed to close their eyes but not to sleep during the scan.

Data Analysis

Brain extraction (FSL 5.0 BET) was performed on T1-weighted anatomical images and linear transformation matrices for their individual functional spaces were calculated. Automatic cortical parcellation was performed using Freesurfer v5.3.0 (40) and 14 auditory regions of interest (ROIs) defined previously were labeled for each subject (Figure 1a). The first two volumes of functional data were discarded and slice-scan time correction was performed. Motion correction was done by using rigid body linear registration (FSL 5.0 MCFLIRT). A band-pass filter was applied to restrict signal variations in between 0.01 and 0.1 Hz (41). Auditory regions in anatomical space registered to individual functional spaces. Mean time courses were extracted for each of the 14 previously labeled ROIs. Pairwise functional connectivity changes of 14 ROIs were investigated. Within-auditory network analysis revealed connectivity changes in SMG and primary auditory cortices (Table 3). The ROIs with significant pairwise connectivity changes were used as seeds (Figure 1a) and a whole-brain connectivity map with these seed ROIs was further investigated. The connectivity of the seeds (ROI 9, 13 and 14) that had significant whole-brain connectivity differences between the groups is presented in Figure 2.

Statistical Analysis

All processing routines were performed using MATLAB R2016b. One-way ANOVA was conducted on pairwise correlation values to assess functional group differences. Functional data was smoothed with Gaussian kernel (FWHM=7mm); then whole-brain connectivity maps



ROIs		Cortical region
Right	Left	
1	8	Angular gyrus
2	9	Supramarginal gyrus
3	10	Precentral sulcus
4	11	Frontal operculum
5	12	Lateral superior temporal gyrus
6	13	Superior temporal sulcus
7	14	Superior temporal gyrus

Figure 1: Brain regions of interest demonstrated in one subject (a), One-way ANOVA results of pairwise correlations (b). p<0.05 thresholded table (c). Four separate subplots show inter-hemispheric pairwise correlations (between left and right hemispheres) and intra-hemispheric (between left and left, right and right) correlations. Color bars represent p values.

were calculated using those regions as a seed (42). T-test with FDR (q≤0.05) correction was used to get seed-based connectivity maps. Statistical analyses of the volumes were performed separately. Other statistical analyses were performed with SPSS 22 (IBM Corp., Armonk, NY). Distribution characteristics of the data were checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables with Gaussian distribution were compared with t test and one-way ANOVA. Categorical variables were compared with chi-square test. Homogeneity of variances was checked with Levene's homogeneity of variance test for post-hoc tests. Tukey test was performed for variables with homogeneous variances, whereas Tamhane test was performed for non-homogeneous variances. The level of statistical significance for p values was 0.05.

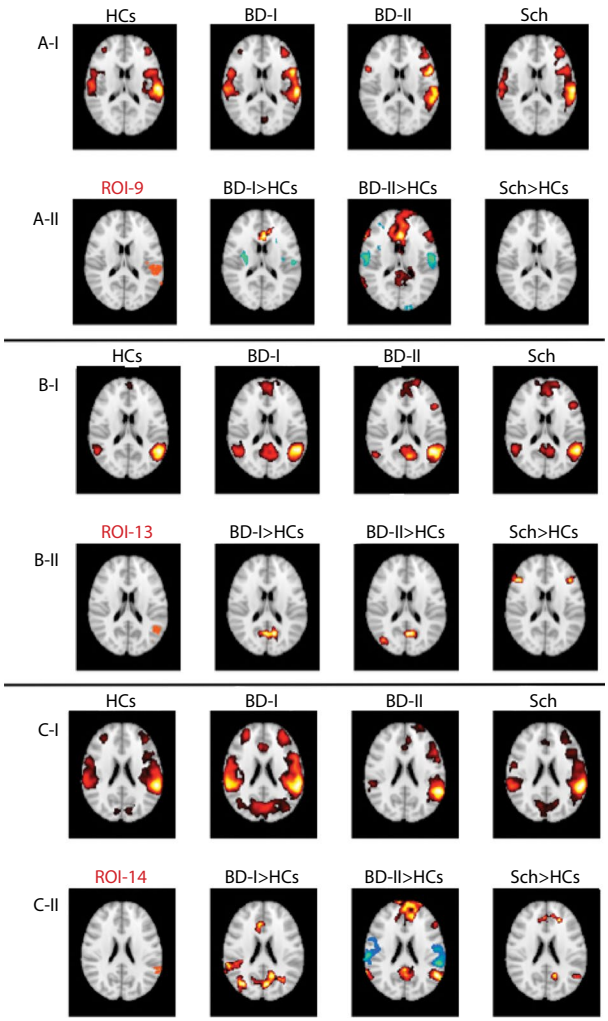


Figure 2: Group-level connectivity maps by using (A) left supramarginal gyrus (ROI-9; Brodmann 40), (B) medial left superior temporal sulcus (ROI-13; Brodmann 41, 42) and (C) lateral left superior temporal gyrus (ROI-14; Brodmann 21, 22) as seeds. Color bars represent Pearson Correlation values (r>0.5). Connectivity maps of each group are presented in A-I, B-I, and C-I. Significant connectivity differences between groups are presented in A-II, B-II and C-II. Changes of connectivity values are presented as increase (red-yellow) and decrease (blue-green) with t scores [|t|>2] in comparison to the HC group. HCs: Healthy Controls, BD-I: Bipolar I Disorder, BD-II: Bipolar II Disorder, Sch: Schizophrenia. There were significant connectivity differences between the groups at ROI-9 (A-II: BD-I vs. HC, BD-II vs. HC), ROI-13 (B-II: BD-I vs. HC, BD-II vs. HCs, Sch vs. HCs) and ROI-14 (C-II: BD-I vs. HCs, BD-II vs. HCs, Sch vs. HCs).

RESULTS

Sociodemographic and clinical characteristics of the patient groups are presented in Table 1. There were no significant age and sex differences between patient groups and healthy subjects. BPRS scores differed between the groups: The schizophrenia group had a significantly higher score than the bipolar I disorder (BD-1) ($p<0.001$) and bipolar II disorder (BD-2) ($p<0.001$) groups.

ANOVA showed that there were volume differences between groups at the following locations: right hemisphere lateral STG (ROI-5), left angular gyrus (ROI-8), and left STG (ROI-14) (Table 2). Post-hoc comparison showed that the mean volume of the left angular gyrus in the schizophrenia and bipolar II disorder groups was significantly smaller than in healthy controls. The left STG in the schizophrenia group was significantly smaller than in the healthy control group. The difference between the groups in the lateral part of the STG in the right hemisphere (ROI-5) was at trend level in post-hoc comparison (schizophrenia<healthy controls, $p=0.0578$; schizophrenia<bipolar 1 disorder, $p=0.061$).

Pairwise correlations between seed regions showed that the most significant functional connectivity changes are at SMG (ROI-2 and ROI-9) and STG (ROI-7 and ROI-14) (Table 3). In addition, whole brain connectivity maps revealed that hyperconnectivity was found between left SMG and medial-prefrontal cortices (mPFC) in patients with bipolar disorder (Figure 2a). On the other hand, the SMG had decreased connectivity with the left medial STG in bipolar I disorder and bipolar II disorder. The left STS (ROI-13) had increased connectivity with the bilateral posterior cingulate cortex (PCC) in bipolar I disorder and bipolar II disorder and increased connectivity with the dorsal prefrontal cortices in the schizophrenia group (Figure 2b). The left lateral superior temporal gyrus had increased connectivity with the medial STG in the bipolar I disorder and schizophrenia groups and decreased connectivity in the bipolar II disorder group (Figure 2c).

Table 1: Demographic and clinical variables of the participants

	BD-1		BD-2		Sch		HCs		χ^2/t/F	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age**	35.32	9.12	38.38	13.84	38.67	12.46	32.77	10.65	1.66	0.181
	n		n		n		n			
Sex (women)	15		12		12		17		2.23	0.527
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Education**	10.89	4.86	12.10	4.10	9.30	3.24	10.20	3.36	2.26	0.085
Age at onset**	23.57	8.66	24.71	9.63	22.45	6.35			0.47	0.625
Duration of the disease*	92.21	107.69	153.43	126.48	147.52	132.13			2.02	0.140
Number of hospitalizations	1.36	1.77	0.43	0.68	2.37	5.13			2.09	0.130
Number of Episodes										
Total	7.82	5.46	8.50	6.87					0.145	0.705
Mania***	2.77	2.18	3.50	3.52					0.751	0.391
Depression	4.22	3.42	4.90	4.15					0.376	0.543
BPRS	2.43	2.86	2.24	1.72	7.67	4.29			24.56	<0.001
HDRS	3.46	3.51	3.38	3.20					0.007	0.932
YMRS	1.07	1.61	1.48	1.50					0.803	0.375
SANS					11.00	6.66				
SAPS					14.13	8.56				

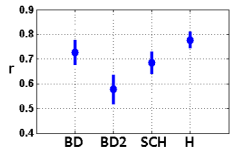
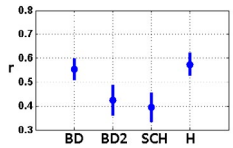
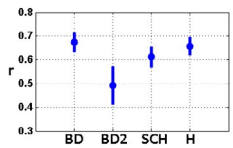
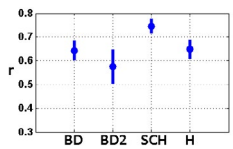
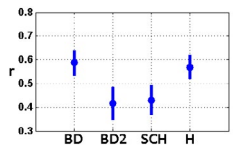
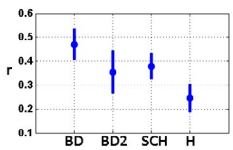
One-way ANOVA, SD, Chi-square and t tests. BD-1: Bipolar 1 Disorder, BD-2: Bipolar 2 Disorder, Sch: Schizophrenia, HCs: Healthy Controls. BPRS: Brief Psychiatric Rating Scale, HDRS: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, *Months, **Years, ***Hypomania for BD-2

Table 2: Regions with significant volume changes across groups. Significant ROIs are shown highlighted in yellow and marginally significant ones in orange

ROIs	HS	Regions	p-Value	Post-hoc Comparisons
1	Right	Angular Gyrus (AG)	0.3960	-
2	Right	Supramarginal Gyrus (SMG)	0.5104	-
3	Right	Precentral sulcus (PCS)	0.2896	-
4	Right	Frontal operculum (FO)	0.1814	-
5	Right	Lateral superior temporal gyrus (L-STG)	0.0578	HC>Sch (p=0.0117) HC>BD-1 (p=0.0610)
6	Right	Superior temporal sulcus (STS)	0.1388	-
7	Right	Superior temporal gyrus (STG)	0.5903	-
8	Left	Angular Gyrus	0.0223	HC>Sch (p=0.0246) HC>BD-2 (p=0.0082)
9	Left	Supramarginal Gyrus	0.3976	-
10	Left	Frontal operculum	0.0557	-
11	Left	Frontal operculum	0.0822	-
12	Left	Lateral superior temporal gyrus	0.0920	-
13	Left	Superior temporal sulcus	0.0680	-
14	Left	Superior temporal gyrus	0.0185	HC>Sch (p=0.0027)

HC: Healthy Controls, Sch: Schizophrenia, BD-1: Bipolar 1 Disorder, BD-2: Bipolar 2 Disorder

Table 3: Pairwise connectivity differences across groups are shown as mean and standard error plots in the "Groups" column, post-hoc tests shown where pairwise group comparisons have significant differences

ROIs	Groups	p	Post-Hoc
ROI-2 – ROI-9		0.0091	BD-1>BD-2 (p=0.060) HCs>BD-2 (p=0.0052)
ROI-2 – ROI-14		0.0170	HCs>Sch (p=0.035) BD-1>Sch (p=0.080)
ROI-6 – ROI-12		0.0369	BD-1>BD-2 (p=0.0395) HCs>BD-2 (p=0.055)
ROI-8 – ROI-13		0.0372	Sch>BD-2 (p=0.0244)
ROI-7 – ROI-14		0.0427	~
ROI-3 – ROI-5		0.0491	BD-2>HCs (p=0.0359)

BD: Bipolar 1 Disorder, BD2: Bipolar 2 Disorder, Sch: Schizophrenia, H: Healthy Controls

DISCUSSION

In this study, the most significant volume difference between the groups was in the superior temporal cortices. The gray matter volume was smaller in the left hemisphere AG, lateral and medial STG in patients with schizophrenia. Interestingly, there was a difference between the bipolar disorder subgroups: the effect on the angular gyrus was only significant in bipolar I disorder, and similarly the lateral STG (Wernicke's Area) was only affected significantly in bipolar I disorder. Connectivity differences were similar between bipolar I disorder and bipolar II disorder groups. There was increased connectivity between the left SMG – mPFC and the left STS – PCC in the bipolar disorder subgroups. These groups had decreased connectivity between the left lateral STG and the bilateral medial STG. Decreased functional connectivity observed bilaterally in precentral gyrus and inferior parietal lobes was only seen in the bipolar II disorder group (Table 3, Figure 2). The schizophrenia group had increased

connectivity between left superior temporal sulcus and bilateral dorsal prefrontal cortices.

A connectivity change between lateral and medial STG in bipolar disorder might indicate a deficit in the integration of processed auditory information from specialized tonotopic fields of the primary auditory cortices, which may lead to impaired auditory information processing. Ambiguity of auditory information may lead to deficits in cognitive or emotional auditory information processing. Abnormal activation and connectivity changes in components of the auditory networks may be related with several cognitive mechanisms. Deficient cortical auditory processing, emotional motivation, beliefs, cognitive bias, intentional alteration of attention to auditory inputs and insight might be related with auditory cortex abnormalities (43,44). In addition, the mPFCs were associated with selective attentional and executive networks (45), and hyper-connectivity between the left STG and mPFC may reflect increased coupling in higher cognitive networks for auditory processing. The mPFC and PCC are components of the default mode network, and dysconnectivity in this network may reflect self-referential thought disorders (46). These findings are in line with a hypothesis postulating that dysfunction of association areas might play an important role in cognitive decline in schizophrenia and bipolar disorder (47). Since the auditory system is related to various symptoms and cognitive dysfunction in schizophrenia and bipolar disorder (2), dysconnectivity between the auditory cortices might be related with the symptoms and deficits involved. This study was performed in resting state; task-based studies may investigate the association more reliably. On the other hand, the symptoms are perpetual and are observed even at rest. Therefore, resting-state activity may also reflect disturbances in spontaneous activity.

A substantial body of evidence has demonstrated volumetric decay in gray matter (14), cortical folding abnormalities (48-50) and deteriorated laminar structure (3) in the superior temporal cortices in schizophrenia. Moreover, structural alterations (51,52), volumetric loss (15), metabolic abnormalities (53,54) and functional alterations (13,23,47,55,56) of the auditory cortices were related to auditory hallucinations in patients with schizophrenia. Enhanced resting-state activity of the primary auditory cortices and auditory hallucinations were predisposed by aberrant connectivity between the default-mode network and auditory cortices. While the schizophrenia patients were not categorized according to hallucinations, the whole group had abnormal connectivity in both schizophrenia and bipolar disorder groups.

Volumetric loss in bipolar I disorder was observed in the STG, and this finding is in line with a meta-analysis in bipolar disorder (57). Moreover, auditory processing abnormalities (6,7,11,12,16) are more severe in psychotic patients with bipolar disorder than in non-psychotic patients (11). The bipolar II disorder group had a significant volumetric decrease in the AG. The AG region has been evaluated as a physiologic trait marker of depression, mania and euthymia in bipolar II disorder (58). The bipolar II disorder group had decreased connectivity between Wernicke's Area and the primary auditory cortices, while this finding was not observed in bipolar I disorder.

Limitations of this study are its small sample size; some of our results showed trend level significance and thus should be tested further in larger samples. The cross-sectional nature of our study did not allow us to perform analyses for clinical factors and medications. In addition, longer functional scan times are preferable to understand the attentional alterations better. Clinical variables such as medications of psychosis (for bipolar disorder) could not be controlled.

Overall, the schizophrenia group was more prone to displaying volumetric changes in the auditory cortices. On the other hand, functional alterations were observed in the bipolar disorder groups. These findings suggest that differences in the functional connectivity of resting-state networks in bipolar disorder and schizophrenia are related with functional auditory connections. Development of the auditory cortices continues until late adolescence, and neurobiological effects of schizophrenia and bipolar disorder may disrupt the development of the auditory networks (1). Impairment of the auditory networks may predispose for either symptoms or cognitive dysfunction. The accumulation of further evidence may help to determine abnormalities in networks for specific disorders. Further studies considering symptoms and cognitive background of these disorders may contribute to our understanding of the neurobiology of psychiatric conditions.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.I.A., D.O., M.P., C.M.
	Data acquisition	M.I.A., S.S.C., S.U.K., A.C.
	Data analysis/Interpretation	M.I.A., B.A., O.A., E.M.S.
Category 2	Drafting manuscript	M.I.A., B.A., E.M.S.
	Critical revision of manuscript	C.M., M.P., E.M.S
Category 3	Final approval and accountability	M.I.A., B.A., O.A., E.M.S., S.S.C., S.U.K., A.C., C.M., M.P., D.O.
Other	Technical or material support	B.A., O.A., E.M.S.
	Supervision	M.P., C.M., D.O.
	Securing funding (if applicable)	N/A

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Dr. Kaymak participated in a relevant Otsuka Pharmaceutical clinical trial. Dr. Can participated in a relevant Janssen Pharmaceutica clinical trial. The other authors declare that they have no conflicts of interest.

Financial Disclosure: The study was funded by the Scientific Research Commission of Ankara Yildirim Beyazit University (Project No. 803).

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