pISSN 2384-1095
eISSN 2384-1109

iMRI
Investigative Magnetic Resonance Imaging

iMRI 2019;23:55-64 https://doi.org/10.13104/imri.2019.23.1.55

Original Article

# Changes in the Laterality of Functional Connectivity Associated with Tinnitus: Resting-State fMRI Study

**Yeji Shin[1], Chang-Woo Ryu[1], Geon-Ho Jahng[1], Moon Suh Park[2], Jae Yong Byun[2]**

[1]Department of Radiology, Kyung Hee University Hospital at Gangdong, School of Medicine, Kyung Hee University, Seoul, Korea
[2]Department of Otorhinolaryngology, Kyung Hee University Hospital at Gangdong, School of Medicine, Kyung Hee University, Seoul, Korea

Received: November 21, 2018
Revised: December 10, 2018
Accepted: December 11, 2018

**Correspondence to:**
Chang-Woo Ryu, M.D.
Department of Radiology, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.
**Tel.** +82-2-440-6186
**Fax.** +82-2-440-6932
**E-mail:** md.cwryu@gmail.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2019 Korean Society of Magnetic Resonance in Medicine (KSMRM)

**Purpose:** One of the suggested potential mechanisms of tinnitus is an alteration in perception in the neural auditory pathway. The aim of this study was to investigate the difference in laterality in functional connectivity between tinnitus patients and healthy controls using resting state functional MRI (rs-fMRI).
**Materials and Methods:** Thirty-eight chronic tinnitus subjects and 45 age-matched healthy controls were enrolled in this study. Connectivity was investigated using independent component analysis, and the laterality index map was calculated based on auditory (AN) and dorsal attention (DAN), default mode (DMN), sensorimotor, salience (SalN), and visual networks (VNs). The laterality index (LI) of tinnitus subjects was compared with that of normal controls using region-of-interest (ROI) and voxel-based methods and a two-sample unpaired t-test. Pearson correlation was conducted to assess the associations between the LI in each network and clinical variables.
**Results:** The AN and VN showed significant differences in LI between the two groups in ROI analysis ($P < 0.05$), and the tinnitus group had clusters with significantly decreased laterality of AN, SalN, and VN in voxel-based comparisons. The AN was positively correlated with tinnitus distress (tinnitus handicap inventory), and the SalN was negatively correlated with symptom duration ($P < 0.05$).
**Conclusion:** The results of this study suggest that various functional networks related to psychological distress can be modified by tinnitus, and that this interrelation can present differently on the right and left sides, according to the dominance of the network.

**Keywords:** Tinnitus; Functional connectivity; Laterality; Resting state functional MRI

## INTRODUCTION

The potential mechanism of subjective tinnitus is an alteration of perception in the neural auditory pathways. Therefore, tinnitus is often the focus of neuroscience research that involves functional connectivity, related to temporal synchrony or interregional cooperation between two or more spatially separate regions.

Hemispheric functional laterality is a fundamental characteristic of the brain's functional architecture. Although the left hemisphere is dominant for language processing, the right hemisphere has a limited lexicon, with no phonological abilities, but active involvement in the processing of context (1). In a prior study, stimuli involving language elicited brain activity lateralized to the left hemisphere, whereas visuospatial and attentional stimulations were represented more strongly in the right hemisphere (2). This inherent network laterality can be altered by influence of various genetic and environmental factors, and this change reflects interhemispheric variation in perception processing. In several previous studies, this alteration was associated with the deterioration of auditory and psychologic symptoms in various neuropsychiatric conditions, such as epilepsy, cognitive impairment, and mild traumatic brain injury (3, 4). Furthermore, some studies have reported that cognitive training effects the lateralization of intrinsic networks in healthy older adults and stroke patients (5, 6). Therefore, we hypothesize that there will be laterality changes in the auditory network (AN) and other networks associated with AN in tinnitus patients. Determining the laterality of functional connectivity in patients with tinnitus may be helpful in understanding a neurophysiological feature unique to symptomatology. In a few previous studies, functional lateralization in tinnitus was conducted with auditory task-based PET or fMRI, focusing on lateralization in task-related data (7-9). However, to our knowledge, it has not been investigated in terms of global networks, including non-auditory networks.

The objective of this study was to investigate the difference of laterality in functional connectivity between tinnitus subjects and healthy controls using rs-fMRI, and the association between laterality and clinical characteristics. Therefore, this investigation will increase understanding of the complex alteration of functional connectivity in tinnitus.

## MATERIALS AND METHODS

### Subjects

Written informed consent for participation and procedures in involved in the study was obtained from each subject. This study was conducted according to the guidelines of the Helsinki Declaration, and was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong.

This cross-sectional study included patients who were diagnosed with tinnitus at our tinnitus clinic and prospectively registered in the tinnitus database from 2011 to 2012. Inclusion criteria were as follows: 1) continuous and chronic tinnitus for more than six months, 2) unilateral tinnitus, 3) moderate tinnitus handicap inventory (THI) score higher than 38, and 4) right-handedness.

Exclusion criteria were as follows: 1) history of treatment for a neuropsychological disorder included in the DSM-IV-TR, 2) alcohol or drug addiction, 3) a gross cochlear or retrocochlear abnormality on MRI, and 4) presence of a cardiac pacemaker, claustrophobia, cochlear implant, or other contraindications of MRI. Forty-one tinnitus patients were initially enrolled, and three patients with left-sided tinnitus were excluded by random selection in order to include the same number of right- and left-sided tinnitus cases.

Healthy adults matched to the patient group with respect to age, sex, and right-handedness were recruited as the control group. Ultimately, a total of 83 subjects were enrolled in this study: 19 right-sided tinnitus (mean age 51.1 years, 9 males) patients, 19 left-sided tinnitus (mean age 51.5 years, 6 males) patients, and 45 healthy controls (mean age 51.6 years, 25 males).

### Assessment of Audiological Examination and Tinnitus Related Distress

We recorded audiometry testing and psychologic information from tinnitus patients. Audiometry tests assessed tinnitus pitch (Hz), which was defined as the frequency matching the tinnitus and loudness (dBSL). The severity of tinnitus and tinnitus-related distress were measured using the established THI by Newman (10). The subjects also were evaluated using the Korean version of the Beck Depression Inventory (BDI) test score, a self-assessment psychological test for depression, and duration of symptoms.

### Acquisition of MRI

All enrolled subjects underwent rs-fMRI using a 3.0 Tesla MRI system (Achieva, Philips Healthcare, Best, the Netherlands). A resting-state axial blood oxygen-level-dependent (BOLD) fMRI was also acquired, with a single-shot gradient-echo echo-planar imaging sequence, using an eight-channel head coil. The imaging parameters were as follows: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 240 × 240 mm, acquisition matrix size = 80 × 80, acquisition resolution = 3.0 mm × 3.0 mm × 4.5 mm, number of slices = 31, slice thickness = 4.5 mm with no gap between slices, number of scans = 176, SENSE factor = 2.0, and scan time = 6 minutes. In addition, sagittal structural threedimensional (3D) T1-weighted images (T1WI) were acquired to create templates for anatomical brain image registration. Acquisition parameters were as follows: TR = 8.1 ms, TE = 3.7 ms, flip angle = 8°, FOV = 236 × 236 $mm^2$, and voxel size = 1 × 1 × 1 $mm^3$. Furthermore, T2-weighted axial images were acquired to screen for gross structural abnormalities in the temporal bones or brain.

### Preprocessing

Preprocessing was performed using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). The first four scans of the BOLD rs-fMRI were discarded, and the remaining raw BOLD rs-fMRIs were realigned to the first image from each session in order to correct for interscan head motion. The mean realigned fMRI of each subject was co-registered with 3D T1WI to transform the fMRI data to a symmetric template space. For laterality comparisons, a bilateral symmetric template was created by averaging the native T1-weighted template and its flipped image in the left/right direction, according to a previously published method (11). The T1WIs in the standard Montreal Neurological Institute (MNI) space for each subject were spatially warped to the symmetric T1-weighted template. The rs-fMRI data were also spatially normalized to the created symmetric template space. Finally, spatial smoothing was applied by convolving each rs-fMRI volume with the Gaussian kernel of an 8 × 8 × 8 $mm^3$ full width at half maximum.

### Group-Independent Component Analysis of rs-fMRI

Using the normalized and smoothed rs-fMRI data, an independent component analysis (ICA) was performed using the fMRI toolbox (GIFT; icatb.sourceforge.net) (12). Analyses of rs-fMRI using GIFT were processed with the Informax algorithm and Icasso (13). Back-reconstructions of individual ICs and time-courses were performed with GICA3 (14). Thirty independent component maps were identified based on the similarity between localized spatial connectivity patterns and those identified in previous research (15); and AN, dorsal attention network (DAN), default mode network (DMN), salience network (SalN), sensorimotor network (SMN), and visual network (VN) maps were identified based on the similarity between localized spatial connectivity patterns (16) (Fig. 1). To limit the statistical significance of the laterality within each network defined by ICA, a binary symmetric region-of-interest (ROI) mask was created for each network using the following method. A one-sample t-test with native and flipped network maps of whole subjects was performed to determine the FC map for each network, thresholding with two standard deviations (SD, σ). Regions 8 mm medial from the edges of the brain were excluded to prevent compounding bias of the overlapping

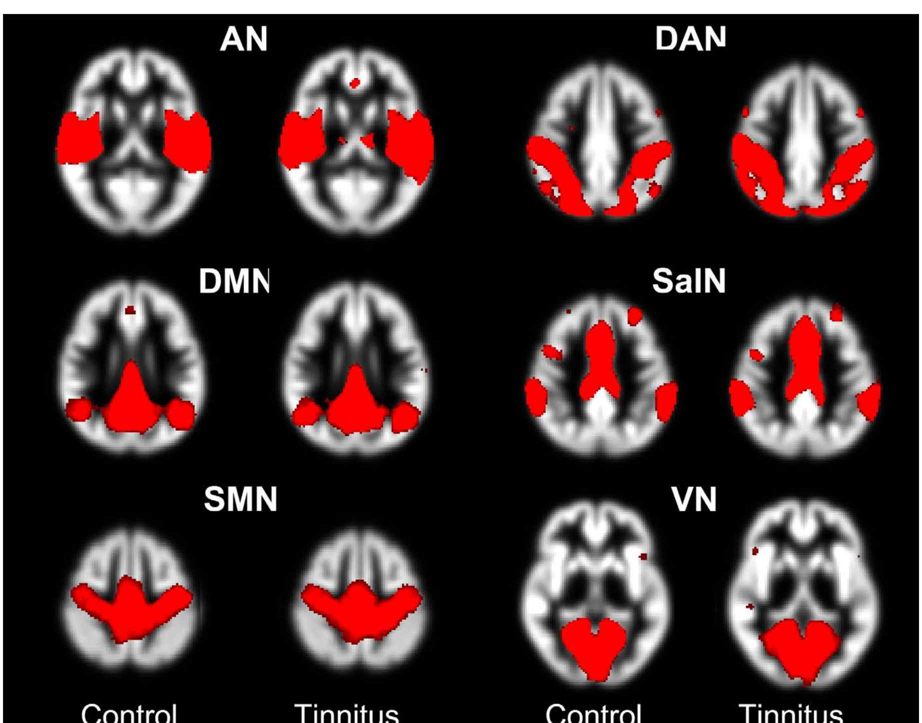



**Fig. 1.** Spatial maps of the six independent components of interest, grouped by network in tinnitus patients (right column) and controls (left column). Auditory (AN), dorsal attention network (DAN), default mode network (DMN), sensorimotor (SMN), salience network (SalN), and visual (VN) networks. Spatial maps are plotted as the t-statistics thresholded over two standard deviations. Background images are bilaterally symmetric gray-matter templates created from specific subjects.

images at the midline.

### Laterality Index Mapping

To evaluate the hemispheric asymmetries of each functional network, we computed LI maps based on each left hemisphere's functional network map and its homotopic (geometrically corresponding) voxel from the right hemisphere. We employed the modified version of the classic LI formula using the absolute values in the denominator (17, 18): $LI = (Lvh-Rvh)/(|Lvh|+|Rvh|)$, where R and L represent the z-scores of the right hemisphere and the left hemisphere for each homotopic voxel vh, respectively. LI maps were created for the left side only. LI values ranged between -1 and +1, and the lateralization of a network was determined according to the mean LI and 95% confidence interval (CI). Negative values were considered to represent right-sided lateralization, and positive values represented left-sided lateralization. Mean LI values of the ROIs derived from six networks were extracted from each subject. We also computed the volume of the left lateralized voxels ($LI_{Lt}$; over SD) and the right lateralized voxels ($LI_{Rt}$; under -SD) from the ROI of each network, and calculated the volumetric laterality ratio (LvR) of each subject: $LvR = LI_{Lt}/(LI_{Lt}+ LI_{Rt})$.

### Statistical Analysis

Age, sex, and other clinical information were compared between the study groups using the independent t-test and Pearson's Chi-square test. Mean LI values and LvR extracted from the ROI of each network were compared using unpaired t-test between the tinnitus and control groups. These values were also compared between the right- and left-sided tinnitus patients.

In addition to evaluating the laterality of the brain networks based on the average values across the subjects, we also assessed voxel-based group differences using an unpaired t-test, with age and sex as co-regressors. In order to count only the most functionally active part of the component, each network was localized using the left-side ROI that was calculated previously. The resulting statistical maps were corrected with Alphasim analysis (REST software [http://resting-fmri.sourceforge.net]) that employ Monte-Carlo simulation (thresholds were set at corrected $P < 0.01$, with a voxel-level of $P < 0.001$ and a minimum cluster size of 21 voxels using AlphaSim).

The value of LI and LvR extracted from the ROI that showed significant difference between groups in each network in the tinnitus group were tested for their correlations with clinical variables (THI, BDI, loudness, duration, and pitch of tinnitus) using the Pearson correlation coefficient. P-values less than 0.05 were considered significant.

## RESULTS

There were no significant differences in demographics between the control group and the tinnitus group. Fourteen of 45 controls (31.1%) and 63 of 67 subjects (94%) in the tinnitus group experienced hearing loss. Median THI score (interquartile range), BDI score, loudness, duration, and tinnitus pitch were 61 (52-70), 10 (5-23), 5 (2-7), 30 months (12-60), and 3000 Hz (1375-8000), respectively. Right- and left-sided tinnitus groups did not show any significant difference in clinical variables (Table 1).

### Group Comparison: Tinnitus versus Control

The AN showed leftward lateralization, while DAN, SalN, and VN exhibited rightward lateralization, and DMN and

**Table 1. Clinical Variables of Left- and Right-Sided Tinnitus**

| | Left-sided tinnitus (19) | | Right-sided tinnitus (19) | |
|---|---|---|---|---|
| | Median | IQR | Median | IQR |
| Age, years | 52 | 49.25 to 55.00 | 51 | 44.50 to 58.50 |
| Sex | 6 males | | 9 males | |
| Tinnitus handicap inventory | 66 | 56.00 to 75.75 | 58 | 46.00 to 67.25 |
| Beck depression inventory | 10 | 7.00 to 22.75 | 7 | 4.00 to 23.00 |
| Loudness (dBSL) | 5 | 2 to 7 | 5 | 4 to 9 |
| Duration, months | 48 | 16.5 to 73.5 | 24 | 12.0 to 57.0 |
| Tinnitus pitch, Hz | 4,000 | 375 to 8,000 | 3,000 | 1,500 to 8,000 |

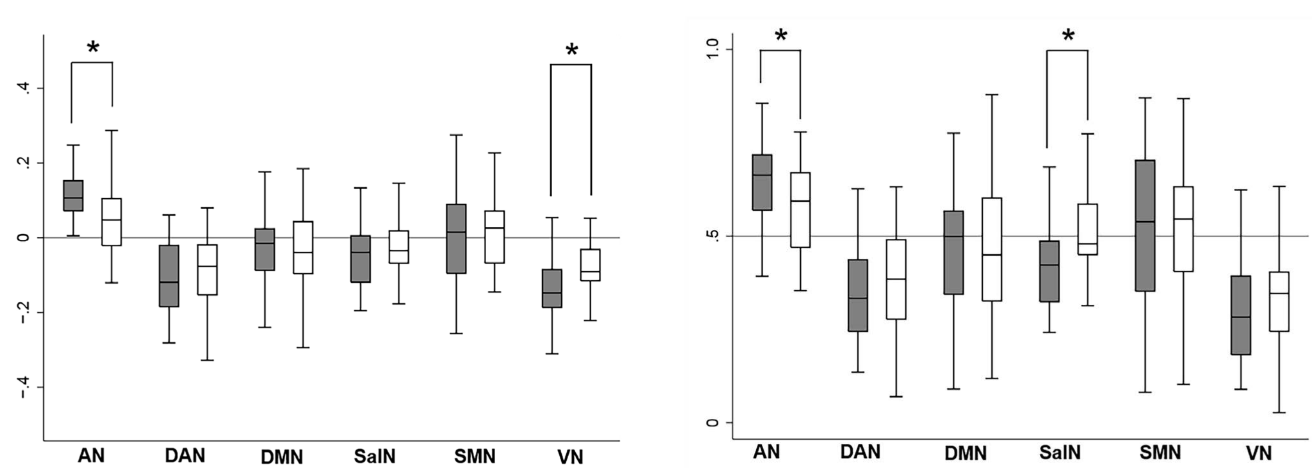
IQR = interquartile range

SMN were not lateralized in the control group. The LI of AN exhibited less left lateralization in the tinnitus group compared with the controls (0.0536 vs. 0.0979, P-value: 0.0181), and the VNs were less right lateralized in the tinnitus group (-0.0985 vs. -0.1441, P-value: 0.0314) (Table 2, Fig. 2a). A statistical comparison of LvR revealed that the left lateralized volume of the AN and the right lateralized volume of the SalN in the tinnitus group were smaller than those in controls (0.5735 vs. 0.6436, P-value: 0.0094; 0.4805 vs. 0.4296, P-value: 0.0383) (Table 2, Fig. 2b). The

**Table 2. ROI Comparison of Laterality Index and Lateralized Volume Ratio between Tinnitus and Control Groups**

| Network | | Tinnitus (38) | | | Controls (45) | | | Unpaired t-test | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | 95% CI | Dominance | Mean | 95% CI | Dominance | t | P-value |
| AN | LI | 0.0536 | 0.0247 to 0.0825 | Left | 0.0979 | 0.0741 to 0.1217 | Left | -2.414 | 0.0181* |
| | LvR | 0.5735 | 0.5343 to 0.6127 | | 0.6436 | 0.6076 to 0.6796 | | -2.661 | 0.0094* |
| DAN | LI | -0.0889 | -0.1207 to -0.0572 | Right | -0.1122 | -0.1410 to -0.0835 | Right | 1.101 | 0.2741 |
| | LvR | 0.3737 | 0.3282 to 0.4193 | | 0.3471 | 0.3089 to 0.3853 | | 0.439 | 0.3645 |
| DMN | LI | -0.0257 | -0.0659 to 0.0146 | Indeterminate | -0.0365 | -0.0672 to -0.00575 | Indeterminate | 6.499 | 0.6618 |
| | LvR | 0.4636 | 0.4025 to 0.5246 | | 0.4639 | 0.4168 to 0.5110 | | -0.009 | 0.9928 |
| SalN | LI | -0.0187 | -0.0437 to 0.0063 | Indeterminate | -0.0483 | -0.0724 to -0.0241 | Right | -1.711 | 0.0909 |
| | LvR | 0.4805 | 0.4460 to 0.5149 | | 0.4296 | 0.3955 to 0.4637 | | -2.106 | 0.0383* |
| SMN | LI | 0.0260 | -0.0150 to 0.0669 | Indeterminate | 0.0003 | -0.0406 to 0.0411 | Indeterminate | -0.892 | 0.3753 |
| | LvR | 0.5256 | 0.4601 to 0.5911 | | 0.5130 | 0.4473 to 0.5788 | | 0.272 | 0.7860 |
| VN | LI | -0.0985 | -0.1283 to -0.0687 | Right | -0.1441 | -0.1733 to -0.1148 | Right | -2.190 | 0.0314* |
| | LvR | 0.3427 | 0.2868 to 0.3986 | | 0.3087 | 0.2642 to 0.3533 | | -0.972 | 0.3338 |

* Statistically significant in two-sample unpaired t-test.
AN = auditory network; CI = confidence interval; DAN = dorsal attention network; DMN = default mode network; LI = laterality index; LvR = lateralized volume ratio; SalN = salience network; SMN = sensorymotor network; VN = visual network




a b

**Fig. 2.** Box and whisker plots showing the laterality index (a), and volumetric laterality ratio values (b) of the auditory (AN), dorsal attention network (DAN), default mode network (DMN), sensorimotor (SMN), salience network (SalN) and visual (VN) networks in the tinnitus and control groups. The grey bar represents the control group, and the white bar represents the tinnitus group. Positive value of Y-axis means left laterality.

comparison between right- and left-sided tinnitus groups did not show any significant difference in LI or LvR in any network.

In the voxel-based LI comparison in the AN, the cluster in the transverse gyrus intersecting precentral sulcus (tgPCS) and postcentral gyrus showed a lower LI in the tinnitus group than in controls. An area with a higher LI of SalN in the tinnitus group was also seen in the supplemental motor area and middle frontal gyrus. In the tinnitus group, an area with a higher LI of VN was observed in the lingual gyrus and precuneus (Table 3, Fig. 3). In terms of laterality, the functional connectivity of the AN, SalN, and VN in the tinnitus group was less lateralized than that in the control group.

## Correlation Analysis with Clinical Variables

In an ROI-based correlation analysis of the tinnitus group, the LI and LVR of the significant regions (tgPCS) in AN were

Table 3. **Voxel-Based Comparison of Laterality Index between Tinnitus Subjects and Healthy Controls**

| Network | Region (Nearest Brodmann's area) | Number of voxels | Peak intensity | MNI coordinate** | | |
|---|---|---|---|---|---|---|
| | | | | X* | Y | Z |
| AN | Postcentral gyrus (43) | 93 | -4.0807 | \|62\| | -6 | 18 |
| | tgPCS (6) | 22 | -3.6249 | \|50\| | -3 | 38 |
| SalN | Supplemental motor area (6) | 76 | 3.9689 | \|10\| | 2 | 56 |
| | Middle frontal gyrus (6) | 24 | 3.8871 | \|50\| | 2 | 44 |
| VN | Precuneus (19) | 89 | 4.4266 | \|10\| | -76 | 26 |
| | Lingual gyrus (18) | 208 | 4.2507 | \|18\| | -54 | -4 |
| | Lingual gyrus (18) | 66 | 3.6009 | \|8\| | -76 | -4 |

* Coordinate X is presented with absolute value.
** Coordinate for center of gravity of cluster.
AN = auditory network; MNI = Montreal Neurological Institute; SalN = salience network; tgPCS = transverse gyrus intersecting precentral sulcus; VN = visual network

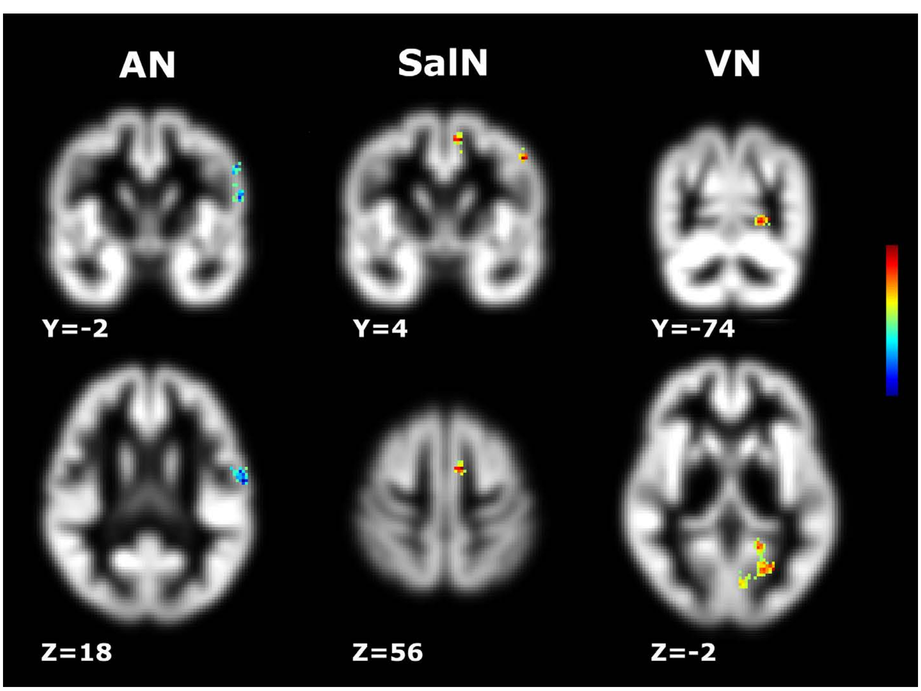



Fig. 3. Regions showing significant differences in laterality index (LI) between tinnitus patients and healthy controls. Thresholds were set at corrected P < 0.01, with a voxel-level of P < 0.001 and a minimum cluster size of 21 voxels using AlphaSim. The LI of the auditory network (AN) in the tgPCS and postcentral gyrus were lower in tinnitus subjects than in controls (left column; cluster with blue color). The LI of the salience network (SalN) in the supplemental motor cortex and middle frontal gyrus (middle column), and the LI of the visual network (VN) in the precuneus (right column) are higher in tinnitus subjects than in controls (cluster with yellow to red color). Note that significant clusters are shown only in the left cerebral hemisphere.

positively correlated with THI score (r = 0.4098, 95% CI, 0.1037 to 0.6450; r = 0.4114, 95% CI, 0.1056 to 0.6461) (Fig. 4a). Tinnitus duration was negatively correlated with LI and LvR of significant region within middle frontal gyrus of the SalN (r = -0.3539, 95% CI, -0.6051 to -0.03855; r = -0.3479, 95% CI, -0.6008 to -0.03179) (Fig. 4b).

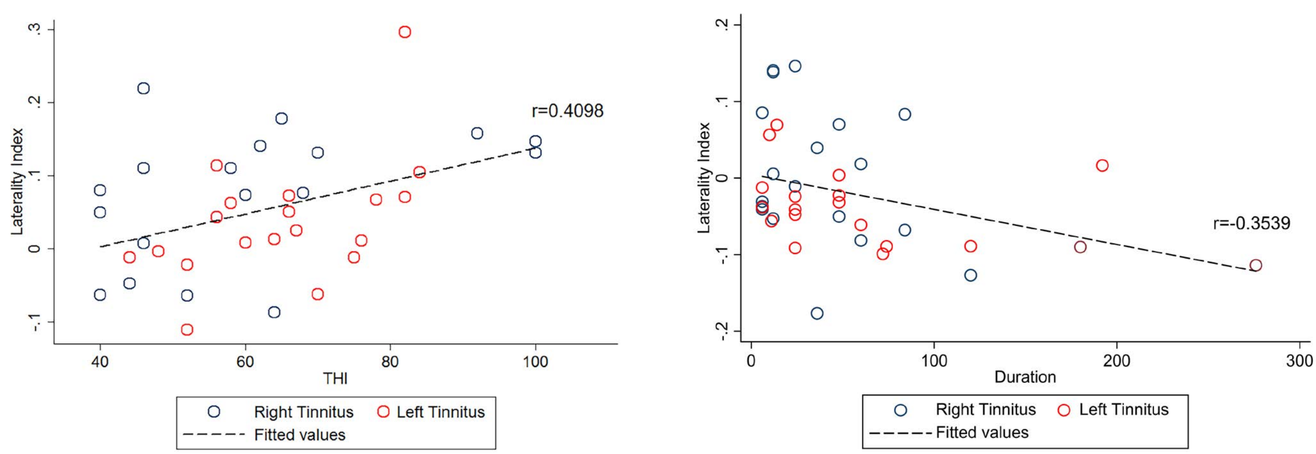
## DISCUSSION

### Alteration in Asymmetry of Functional Connectivity Related to Tinnitus

One of the main findings of this study was that the left laterality of AN was diminished in tinnitus patients. This was consistent with several previous studies using PET or fMRI; most have focused on lateralization in a task-related region. A few previous PET studies that tested the asymmetry of the auditory cortex in tinnitus patients reported left hyperactivity in the control group and right-dominant activity in tinnitus patients (7, 9). The abnormal lateralization of functional connectivity has been reported in other neuropsychological disorders (3, 19). It has been hypothesized that disease-induced damage of the dominant functional site of a brain region weakens the functional connectivity, and this disorganization is compensated for by the strengthening of contra-lateral functional connectivity. Consistent with this hypothesis, our research suggests that change of laterality in an auditory network implies that the stimulation of tinnitus and/or the tinnitus induced neuronal damage leads to diminished functional connectivity in the normally dominant side of the auditory circuit and/or to enrichment of the contra-lateral side of functional connectivity by a compensatory mechanism.

The abnormal lateralization of functional connectivity was also shown in SalN in tinnitus patients. Several rs-fMRI studies (20, 21) revealed that tinnitus was associated with alterations encompassing the sensory, attention, memory and emotional networks, and these results are in agreement with the hypothesized implication of non-auditory regions in tinnitus physiopathology (22). The function of SalN allows accurate initial predictions and effectively reduces prediction errors (23, 24). MDD patients with dysfunction of SalN disturbed efficient energy regulation of brain, consequently they suffer from negative affect, withdrawal, fatigue and poor sleep due to inefficient energy regulation (25).

Severity of anxiety has also been correlated with intrinsic functional connectivity of the salience network (26). Our




a    b

Fig. 4. Scatter plots of the correlations between clinical variables (THI, duration) and the laterality of networks (auditory and salience networks) in the tinnitus group. The navy and red circles represent right-sided and left-sided tinnitus, respectively. The regression line is also shown. (a) Scatter plots between tinnitus distress (THI) and the LI values of tgPCS of the auditory network. The X-axis is THI scores, and the Y-axis is LI values extracted from ROI (shown in Fig. 3, left column). The correlation coefficient was 0.4098 (95% CI, 0.1037 to 0.6450; P < 0.05). (b) Scatter plots between tinnitus duration (month) and the LI values for middle frontal gyrus of the salience network. The X-axis is symptom duration (months), and the Y-axis is LI values extracted from ROI (shown in Fig. 3, middle column). The correlation coefficient was -0.3539 (95% CI, -0.6051 to -0.03855; P < 0.05).

**Table 4.** Voxel-Based Analysis of Correlation between Laterality Index and Clinical Variables in Tinnitus Patients

| Network | Region (Nearest Brodmann's area) | Number of voxels | Peak intensity | MNI coordinate** | | |
|---|---|---|---|---|---|---|
| | | | | X* | Y | Z |
| AN-THI | Superior temporal gyrus (42) | 67 | 0.6038 | \|52\| | -32 | 10 |
| | Superior temporal gyrus (22) | 22 | 0.5627 | \|68\| | -8 | 2 |
| SalN-duration | Inferior parietal lobule (40) | 29 | -0.5078 | \|58\| | 36 | 50 |

* Coordinate X is presented with absolute value.
** Coordinate for center of gravity of cluster.
AN = auditory network; MNI = Montreal Neurological Institute; SalN = salience network; THI = tinnitus handicap inventory

results support the hypothesis that network alterations caused by tinnitus are expressed in the mood depressive symptoms of tinnitus patients.

The present study shows decrease of the laterality in VN of the dominant network with/without compensatory strengthening of a contralateral network. In a previous fMRI scan, tinnitus patients showed altered functional connectivity for auditory and visual networks, compared with age-matched controls, and connectivity for the right primary visual cortex negatively correlated with activity in the auditory cortex (21).

## Laterality of Functional Networks and Tinnitus Distress

In our study, the LI and LvR of the tgPCS of AN were positively correlated with THI score on ROI-based correlation analysis of the tinnitus group. This demonstrated that an increase in subjective tinnitus distress was related to left lateralization of the AN. Specifically, the laterality of the AN in patients with higher tinnitus distress was closer to normal left lateralization, while the laterality of the AN in patients with lower tinnitus distress was different than the fundamental characteristics of the AN. We interpret this finding to mean that the shift in laterality of the AN to the contralateral side is related to compensation for tinnitus distress. The tgPCS is known as a region of auditory attention and has a role in temporal processing of auditory stimulation (27). Our data supports the findings of a previous study showing a correlation between subjective tinnitus distress and change in interhemispheric coordination within the superior temporal gyrus (20), and a negative functional connectivity of the right thalamus and left STG with tinnitus duration (28).

Additionally, the LI and LvR of the middle frontal gyrus of SalN were negatively correlated with tinnitus duration on ROI-based correlation analysis of the tinnitus group. Long-term tinnitus might restore the neutralization of the connectivity to the original right laterality of the SalN, thereby explaining the negative correlation between symptom duration and the LI of the SalN. This result suggests that patients with recent onset tinnitus may have a distorted emotional response to the percept because they have not yet been habituated to it. Those with long periods of tinnitus may have time to restore this altered laterality of the salience network to fundamental status.

Several studies have reported alterations in functional connectivity associated with tinnitus distress and tinnitus duration (20, 28-30). In tinnitus patients, a positive correlation was found between tinnitus duration and the resting state of interhemispheric functional connectivity of the uncus (20), a part of the limbic system. The posterior cingulate and insula may be associated with an early emotional reaction to tinnitus. Over time, tinnitus patients may recruit more frontal regions to better control their emotional response (30). These studies hypothesized that the altered functional connectivity was linked with specific tinnitus characteristics. This notion is supported in the present study by our observations of the relationships between the laterality of functional connectivity and clinical variables in the tinnitus cohort.

## Limitations

In this study, most patients with tinnitus did not have normal hearing, while the control subjects did. We did not exclude patients with hearing loss in the tinnitus group. Therefore, it is unclear whether the differences in functional connectivity between the patients and controls were related to the tinnitus itself or to hearing problems. An additional limitation was that we did not attempt a discovery of all lateralization differences in an attempt to assess all functional networks, without an *a priori* concept. Instead, this study looked for lateralization differences in only six networks that were previously identified as being tinnitus-related networks. ICA analysis of functional connectivity has its limitations in terms of anatomical connections and the direction of information from one area to another. Therefore, our study results do not prove why regions showing significant different laterality should present with altered lateralization in the tinnitus patients. Further studies with a more sophisticated analysis method will be needed before a definitive conclusion can be drawn.

In conclusion, we provided rs-fMRI evidence that the fundamental laterality of the networks of the auditory and non-auditory cortical regions can be altered in chronic tinnitus. This finding suggests that the extent and strength of the functional connectivity might be differentially affected by tinnitus on the right and left sides, according to the dominance of the networks. This finding also explains the psychological distress associated with tinnitus, which might be related to the extent of functional connections within the dominant and non-dominant sides of the networks, and is therefore helpful in providing a comprehensive understanding of network changes in tinnitus patients.

### Conflict of Interest

We declare that we have no conflict of interest.

### Acknowledgments

This work was supported by a grant from Kyung Hee University in 2016 (KHU-20160695), and by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (2017R1D1A1B03028952).

## REFERENCES

1. Vigneau M, Beaucousin V, Herve PY, et al. What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. Neuroimage 2011;54:577-593
2. Thiebaut de Schotten M, Dell'Acqua F, Forkel SJ, et al. A lateralized brain network for visuospatial attention. Nat Neurosci 2011;14:1245-1246
3. Su L, An J, Ma Q, Qiu S, Hu D. Influence of resting-state network on lateralization of functional connectivity in mesial temporal lobe epilepsy. AJNR Am J Neuroradiol 2015;36:1479-1487
4. Zhan J, Gao L, Zhou F, et al. Decreased regional homogeneity in patients with acute mild traumatic brain injury: a resting-state fMRI study. J Nerv Ment Dis 2015;203:786-791
5. Saleh S, Bagce H, Qiu Q, et al. Mechanisms of neural reorganization in chronic stroke subjects after virtual reality training. Conf Proc IEEE Eng Med Biol Soc 2011;2011:8118-8121
6. Luo C, Zhang X, Cao X, et al. The lateralization of intrinsic networks in the aging brain implicates the effects of cognitive training. Front Aging Neurosci 2016;8:32
7. Geven LI, de Kleine E, Willemsen AT, van Dijk P. Asymmetry in primary auditory cortex activity in tinnitus patients and controls. Neuroscience 2014;256:117-125
8. Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 2007;49:669-679
9. Schecklmann M, Landgrebe M, Poeppl TB, et al. Neural correlates of tinnitus duration and distress: a positron emission tomography study. Hum Brain Mapp 2013;34:233-240
10. Newman CW, Jacobson GP, Spitzer JB. Development of the tinnitus handicap inventory. Arch Otolaryngol Head Neck Surg 1996;122:143-148
11. Watkins KE, Paus T, Lerch JP, et al. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Cereb Cortex 2001;11:868-877
12. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 2001;14:140-151
13. Himberg J, Hyvarinen A, Esposito F. Validating the independent components of neuroimaging time series via clustering and visualization. Neuroimage 2004;22:1214-1222
14. Erhardt EB, Rachakonda S, Bedrick EJ, Allen EA, Adali T, Calhoun VD. Comparison of multi-subject ICA methods for analysis of fMRI data. Hum Brain Mapp 2011;32:2075-2095
15. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106:13040-13045
16. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 2006;103:13848-13853
17. Agcaoglu O, Miller R, Mayer AR, Hugdahl K, Calhoun VD. Lateralization of resting state networks and relationship to age and gender. Neuroimage 2015;104:310-325
18. Tomasi D, Volkow ND. Laterality patterns of brain functional connectivity: gender effects. Cereb Cortex 2012;22:1455-1462

19. Swanson N, Eichele T, Pearlson G, Kiehl K, Yu Q, Calhoun VD. Lateral differences in the default mode network in healthy controls and patients with schizophrenia. Hum Brain Mapp 2011;32:654-664
20. Chen YC, Xia W, Feng Y, et al. Altered interhemispheric functional coordination in chronic tinnitus patients. Biomed Res Int 2015;2015:345647
21. Burton H, Wineland A, Bhattacharya M, Nicklaus J, Garcia KS, Piccirillo JF. Altered networks in bothersome tinnitus: a functional connectivity study. BMC Neurosci 2012;13:3
22. Maudoux A, Lefebvre P, Cabay JE, et al. Auditory resting-state network connectivity in tinnitus: a functional MRI study. PLoS One 2012;7:e36222
23. Duquette P. Increasing our insular world view: interoception and psychopathology for psychotherapists. Front Neurosci 2017;11:135
24. Sikora M, Heffernan J, Avery ET, Mickey BJ, Zubieta JK, Pecina M. Salience network functional connectivity predicts placebo effects in major depression. Biol Psychiatry Cogn Neurosci Neuroimaging 2016;1:68-76
25. Barrett LF, Quigley KS, Hamilton P. An active inference theory of allostasis and interoception in depression. Philos Trans R Soc Lond B Biol Sci 2016;371
26. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349-2356
27. Michalka SW, Kong L, Rosen ML, Shinn-Cunningham BG, Somers DC. Short-term memory for space and time flexibly recruit complementary sensory-biased frontal lobe attention networks. Neuron 2015;87:882-892
28. Zhang J, Chen YC, Feng X, et al. Impairments of thalamic resting-state functional connectivity in patients with chronic tinnitus. Eur J Radiol 2015;84:1277-1284
29. Ueyama T, Donishi T, Ukai S, et al. Brain regions responsible for tinnitus distress and loudness: a resting-state FMRI study. PLoS One 2013;8:e67778
30. Carpenter-Thompson JR, Schmidt SA, Husain FT. Neural plasticity of mild tinnitus: an fMRI investigation comparing those recently diagnosed with tinnitus to those that had tinnitus for a long period of time. Neural Plast 2015;2015:161478