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ORIGINAL RESEARCH

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Age-related change of auditory functional connectivity in Human Connectome Project data and tinnitus patients

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Abstract

Background: We reported that tinnitus patients showed reduced levels of auditory functional connectivity (FC) in comparison with normal hearing control subjects, and that we succeeded in objective diagnosis of tinnitus with 86% sensitivity and 74% specificity by focusing only on auditory-related FC. However, the age-related change of auditory FC is not clarified. In this study, we examine age-related change of the auditory FC using the database of Human Connectome Project (HCP) and compared with our database of tinnitus patients.

Method: From the HCP database HCP Lifespan Pilot project, we studied five age groups, 8 to 9 years old, 14 to 15, 25 to 35, 45 to 55, and 65 to 75. We also applied our tinnitus patients' resting-state functional magnetic resonance imaging (fMRI) database, which is divided into three generations; 20 to 40 years old, 40 to 60, and 60 to 80 to compare with the HCP database. The resting state fMRI analyses were performed using the CONN toolbox version 18. As auditory-related regions, Heschl's gyrus, planum temporale, planum polare, operculum, insular cortex, and superior temporal gyrus were set as the regions of interest from our previous reports.

Result: Auditory FC is strongest among adolescents and reduces with age. But the auditory FC of tinnitus patients were significantly less than those of HCP data in each generation.

Conclusion: Although auditory FC decreases with age, tinnitus patients have less auditory FC compared with age-matched controls. The age-matched cutoff values are necessary for an objective diagnosis of tinnitus with resting state fMRI.

KEYWORDS

auditory functional connectivity, resting state functional magnetic resonance imaging, tinnitus

1 | INTRODUCTION

Age-related changes in hearing ability occur at all levels of the auditory system. There are several pieces of evidence for age-related changes in auditory cortex morphology or function.[1] Although substantial variability is seen across individuals, the aging brain shows widespread changes in cortical structure and network dynamics that carry cognitive function.[2] Functional connectivity (FC) refers to the statistical association or dependency between two or more anatomically distinct time series and is measured via imaging modalities such

as resting-state functional magnetic resonance imaging (rs-fMRI) using cross correlation-based techniques.[3] Rs-fMRI is used to study connectivity in the brain by acquiring fMRI data from a subject lying "at rest" in the scanner and is based upon the premise that spontaneous activity patterns in functionally related brain regions are temporally correlated.[4] We previously reported that tinnitus patients with or without hearing loss showed reduced levels of statistically significant auditory related FC in comparison with normal hearing control subjects,[5] and we succeeded in objective diagnosis of tinnitus with 86% sensitivity and 74% specificity by focusing only on auditory-related FC.[6] The prevalence of hearing loss and tinnitus is more common in the older population compared with the younger population.[7] However, age-related changes of auditory FC have not been clarified. In this study, we examined the age-related change in auditory FC using the database of Human Connectome Project (HCP)[8] and compared with our database of tinnitus patients.

2 | METHOD

From the HCP database HCP Lifespan Pilot project,[9] we studied five age groups, 8 to 9 years old (n = 6: three female and three male), 14 to 15 years old (n = 6: five female and one male), 25 to 35 years old (n = 5: three female and two male), 45 to 55 years old (n = 5: two female and three male), and 65 to 75 years old (n = 5: two female and three male). MRI structure images (T1 w) and resting fMRI images were analyzed. The Lifespan-HCP protocol acquires T1w (MPRAGE) structural images at a resolution of 0.8 mm isotropic voxels, and the resting fMRI at a voxel unit of 2 mm, multi-band 8, and TR 720 ms with eyes open by 3 T MRI. The fMRI images were preprocessed with SPM version 12[10] according to typical procedures, including realignment, smoothing, coregistration, segmentation, and normalization. Images were then band-pass filtered from 0.008 to 0.09 Hz, and region of interest (ROI)-based correlation analyses were performed using the CONN toolbox version 18.[11] CONN allowed ROI-based analysis to be performed by grouping voxels into ROIs on the basis of anatomical partitions.[12] Bivariate correlations were calculated between each pair of ROIs to act as measures of connectivity. Fisher-transformed correlation values (beta values) were obtained for each ROI pair, and significance tests (unpaired *t* test) were performed on these beta values. The significance threshold was set at $P < .05$ (false discovery rate-corrected). As auditory-related regions, Heschl's gyrus, planum temporaleale, planum polare, operculum, insular cortex, and superior temporal gyrus were set as the ROI from our previous reports.[5,6]

We used our tinnitus patients' resting fMRI database, whose study was approved by the ethics committee of Keio University, to compare with the HCP database. The inclusion criteria for tinnitus patients were more than 20 years of age, suffering from chronic (more than 3 months) tinnitus and giving written informed consent. The exclusion criteria were the patients who had contraindications for MRI scanning. The median age was 57.5 (21-80) years. Subjects divided into three generations: 20 to 40 years old (n = 6), 40 to 60 (n = 11), and 60 to 80 (n = 11). The average ages of each

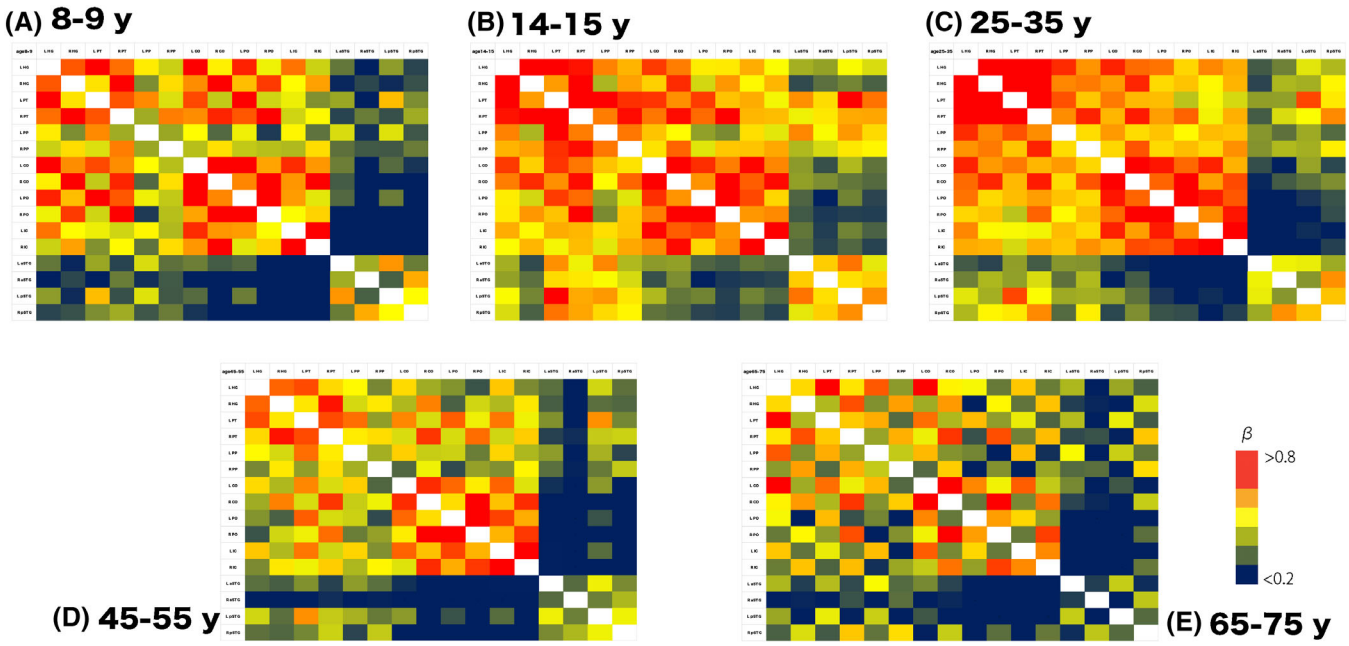

FIGURE 1 Correlation matrix of beta values between auditory related ROIs in the five control age groups (A: 8-9, B: 14-15, C: 25-35, D: 45-55, and E: 65-75). The color map was defined with beta values. The colder (blue-end) boxes represent low correlations between regions, whereas warmer (red-end) boxes represent stronger correlations. aSTG indicates anterior division of superior temporal gyrus; CO, central opercular; HG, Heschl's gyrus; IC, insular cortex; PO, parietal operculum; PP, planum polare; PT, planum temporale; pSTG, posterior division of superior temporal gyrus; ROI, region of interest

generations are 29 ± 5.5, 54 ± 5.6, and 70 ± 5.7 respectively. The average Japanese version of the Tinnitus Handicap Inventory (THI) in each generation were 36.0 ± 27.7, 49.1 ± 19.1, and 48.4 ± 28.0 respectively. In the tinnitus 20 to 40 groups, all patients have normal hearing thresholds at all tested frequencies. In the tinnitus 40 to 60 groups, five patients have normal hearing, five have mild hearing impairment, and one has severe hearing impairment. In the tinnitus 60 to 80 groups, three patients have normal hearing, four have mild hearing impairment, one has moderate hearing impairment, and three have severe hearing impairment. Their functional and anatomical images were acquired on a PHILIPS Achieva 1.5T A-Series singli/G Eco scanner (Philips Medical Systems, Best, The Netherlands). Anatomical images were collected using a three-dimensional isotropic T1-weighted magnetization prepared rapid gradient echo sequence (matrix scan 304, reconstruction 512, voxel size: 0.72 × 0.72 × 4 mm). The rs-fMRI images were obtained using an echo planar sequence (TR 2500 ms, echo time 40 ms, flip angle 90°, field-of-view 220 mm, voxel size 3.44 × 3.44 mm, slice thickness 4 mm, interslice gap 0 mm). Subjects were asked to lie motionless with their eyes open during the rs-fMRI acquisition. The rs-fMRI data analysis was the same as above.

3 | RESULT

Beta values obtained for each auditory-related ROI pair were averaged across subjects in the HCP database and are presented in a matrix with a heat color scale representing connection strength in

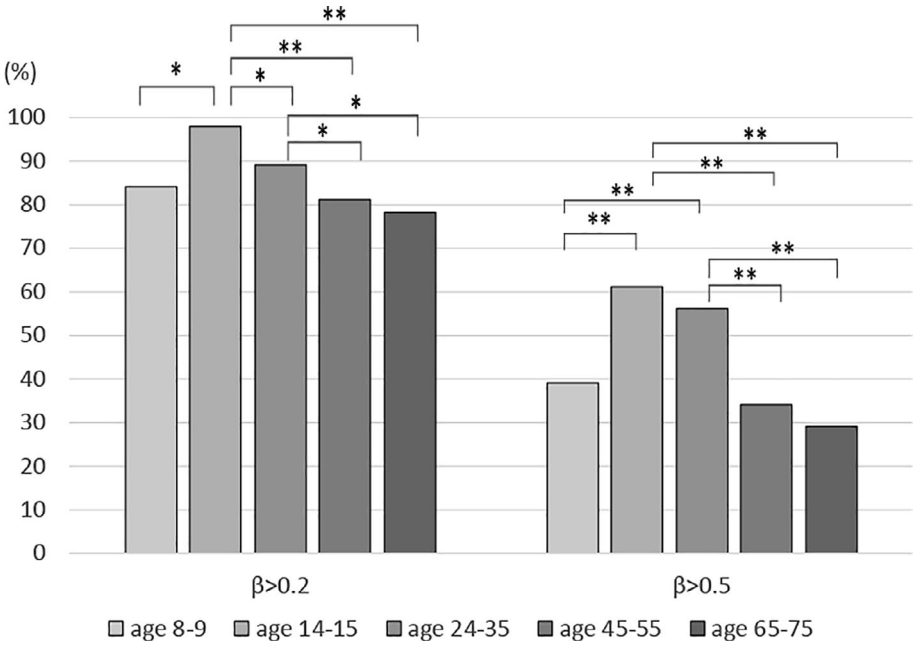

FIGURE 2 The percentage of all possible connections between the auditory related regions. At a beta threshold of more than 0.2 (left), mean percentage score from groups 14 to 15 was significantly higher than that of groups 8 to 9 and 25 to 35. Both groups 14 to 15 and 25 to 35 scored significantly higher than groups 45 to 55 and 65 to 75. When a stricter threshold of beta more than 0.5 was applied (right), both groups 14 to 15 and 25 to 35 scored significantly higher than groups 8 to 9, 45 to 55, and 65 to 75. ANOVA with SNK comparison showed * as $P < .05$ and ** as $P < .01$

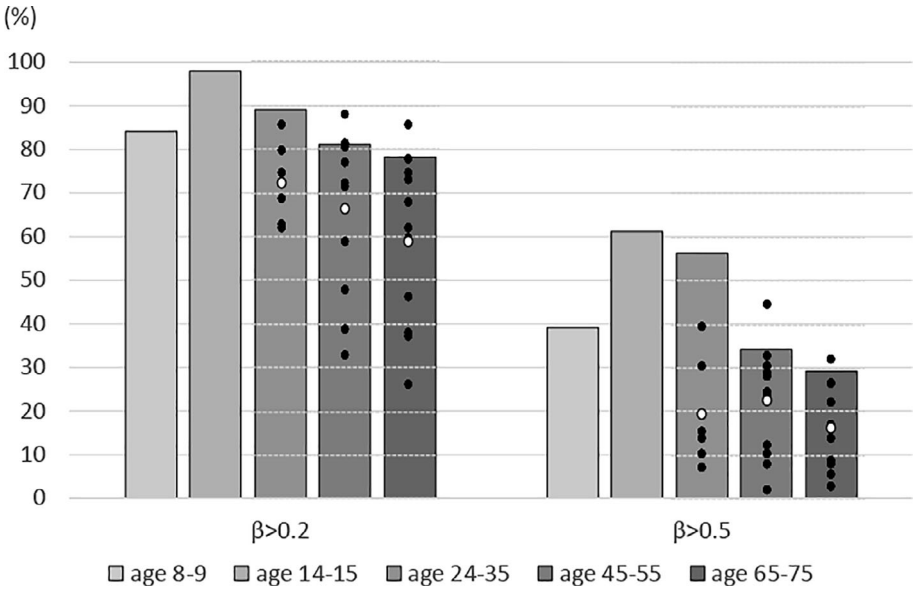

FIGURE 3 The data from tinnitus patients are added to the data from Figure 2. The black circles imply the percentage of each tinnitus patient. The white circles are the average of each age. Unpaired *t* test comparison showed that the auditory functional connectivity of tinnitus patients were significantly lower than that of Human Connectome Project data in each generation at both of the beta threshold of more than 0.2 (left) and 0.5 (right; $P < .05$)

Figure 1. At a beta threshold of more than 0.2, the percentages of all possible connections between the auditory-related ROIs remaining intact in the five age groups (8-9, 14-15, 25-35, 45-55, and 65-75) are 84% ± 8, 98 ± 2, 89 ± 1, 81 ± 6, and 78 ± 2 (Figure 2A). ANOVA with SNK (Student-Newman-Keuls) comparison showed that the mean percentage score from groups 14 to 15 was significantly more than groups 8 to 9 and 25 to 35. Both groups 14 to 15 and 25 to 35 scored significantly higher than groups 45 to 55 and 65 to75. When a stricter threshold of beta greater than 0.5 was applied, the percentages of all possible connections between the auditory-related ROIs remained intact in the five age groups (8-9, 14-15, 25-35, 45-55, and 65-75) are 39% ± 6, 61 ± 8, 56 ± 2, 34 ± 6, and 29 ± 3 (Figure 2B). ANOVA with SNK comparison showed that the mean percentage score from groups 14 to 15 was significantly greater than the score for groups 8 to 9. Both groups 14 to 15 and 25 to 35 scored significantly higher than groups 8 to 9, 45 to 55, and 65 to 75.

To compare auditory FC in tinnitus patients, each generation of tinnitus patients' data was added to the graph shown in Figure 2. The percentages of all possible connections between the auditory-related ROIs remaining intact in the three generation groups (20-40, 40-60, 60-80) are 72% ± 9, 66 ± 19, and 58 ± 19, respectively, at a beta threshold of more than 0.2, and 19% ± 13, 22 ± 13, and 16 ± 10, respectively, at a stricter beta threshold of more than 0.5. Unpaired *t* test comparison showed that the auditory FC of tinnitus patients were significantly lower than that of HCP data in each generation at both of the beta threshold of more than 0.2 and 0.5 (Figure 3).

4 | DISCUSSION

In the current study, auditory FC is strongest among the adolescents and reduced with age. Until adolescence, brain function becomes increasingly focal in some regions as a process of brain maturation. This is consistent with a recent study that found that cortico-cortical connectivity increases during development in children from 7 to 18 years of age.[13] Additional structural changes occur throughout childhood. For example, cortical gray matter thickness peaks in children and generally decreases after adolescence.[14] Synaptogenesis and arborization can result in increasing cross talk between brain regions.[15] After adolescence, the localized brain functions lose specialized characteristics, but other regions provide something useful to neutralize the disruption. This reorganization theory, including dedifferentiation and compensation, can be related to this age-dependent auditory FC change.[16] Dedifferentiation is described as the loss of functional specificity in the brain regions that are engaged during the performance of a task.[17] Dedifferentiation in older listeners may be due to age related declines in peripheral hearing, deficits in phase-locking and timing in brainstem, and changes in cortical anatomy, as well as reductions in FC. The compensation hypothesis in aging states that older adults are able to recruit higher levels of activity in comparison to young subjects in some brain areas to compensate for functional deficits located somewhere else in the brain.[18] Compensation in older listeners was suggested by the upregulation of activity in speech motor regions for decoding impoverished speech representations in adverse listening conditions.[19] According to the previous report, age-dependent FC change can occur not only in auditory-related regions but also in other regions. The common findings of decreased connectivity were reported within the nodes of some of the resting state networks, including the default mode network, and the salience, executive and attention networks.[16,20,21] Disrupted connectivity in aging persists, even when brain atrophy or age-related structural changes are controlled for, and connectivity decreases directly, imply reductions in how information is transferred between different brain regions.

We have reported that the tinnitus patients showed less auditory-related FC compared with the control group.[5] When rs-fMRI positive is defined as less than 9% of all possible connections between auditory-related ROIs with a beta threshold of more than 0.7, the sensitivity of tinnitus diagnosis is 86%, the specificity is 74%.[6] Because the older patients tend to decrease in the objective diagnostic yield for tinnitus, we examined the age-related change of the auditory FC using the HCP database. Although the auditory FC is decreased with age, the tinnitus patients have less auditory FC compared with age-matched controls. The stricter threshold of beta more than 0.5 is more appropriate for objective diagnosis of tinnitus, because there was a further widening of the gaps between the auditory FS of control and tinnitus patients. However, the gaps narrowed with age as the control group showed decreasing auditory FC. Some older patients' auditory FC is close to the control or greater than the control. Therefore, the age-matched cutoff values are necessary for the tinnitus objective diagnosis with the rs-fMRI. As a limitation, first, because HCP database does not include hearing level information, it is not clear how hearing impairment influences auditory-related FC. Second, there are some methodological differences between HCP data and tinnitus patients' data, such as different MRI devise and the age range of each generation. It is reported that the amount of activated voxels do not depend on the system, but the positions of these voxels do.[22] The different MRI scanners between HCP subjects and tinnitus patients might add variability, but the results are comparable, because we evaluated relatively large amount of signals in auditory ROIs. The high-level noise produced by the MRI scanner can induce an overload the posterior cingulate cortex.[23] To reduce the possible influence by high noise levels, the subjects were physically attenuated about 40 dB of noise by using earmuffs and earplugs.[24] Third, the number of sample size is small and statistically underpowered. Further research with presbycusis patients without tinnitus and more number of tinnitus patients should be done.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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