Research Article

Changes in sensorimotor regions of the cerebral cortex in congenital amusia: a case-control study

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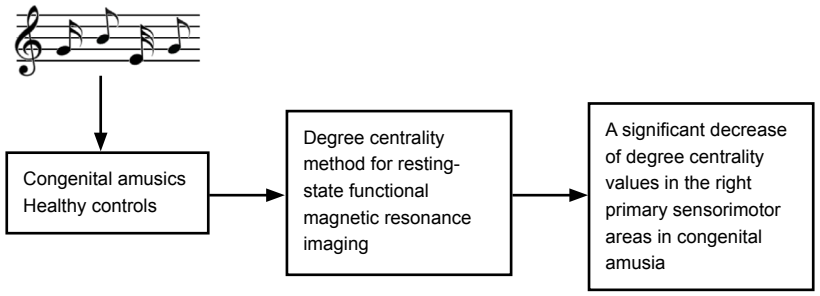
Graphical Abstract *Abnormal degree centrality in congenital amusia*



Abstract

Perceiving pitch is a central function of the human auditory system; congenital amusia is a disorder of pitch perception. The underlying neural mechanisms of congenital amusia have been actively discussed. However, little attention has been paid to the changes in the motor rain within congenital amusia. In this case-control study, 17 participants with congenital amusia and 14 healthy controls underwent functional magnetic resonance imaging while resting with their eyes closed. A voxel-based degree centrality method was used to identify abnormal functional network centrality by comparing degree centrality values between the congenital amusia group and the healthy control group. We found decreased degree centrality values in the right primary sensorimotor areas in participants with congenital amusia relative to controls, indicating potentially decreased centrality of the corresponding brain regions in the auditory-sensory motor feedback network. We found a significant positive correlation between the degree centrality values and the Montreal Battery of Evaluation of Amusia scores. In conclusion, our study identified novel, hitherto undiscussed candidate brain regions that may partly contribute to or be modulated by congenital amusia. Our evidence supports the view that sensorimotor coupling plays an important role in memory and musical discrimination. The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, China (No. WDX20180101GZ01) on February 9, 2019.

Key Words: congenital amusia; degree centrality; lifelong impairment; local functional connectivity; music discrimination; primary motor area; primary sensorimotor area; primary sensory area; resting-state functional magnetic resonance imaging; voxel-based analysis

Chinese Library Classification No. R445.2; R741; B842.1

Introduction

Congenital amusia (CA), a lifelong developmental learning impairment and colloquially labelled "tone deaf", is characterized by difficulty in music perception, production, memory without hearing loss, brain damage, and cognitive deficits (Ayotte et al., 2002; Peretz et al., 2002). This disorder affects about 4% of the population (Kalmus and Fry, 1980). CA-afflicted individuals are unable to detect small pitch variations and are unaware when they (or others) sing out of tune. Psychophysically, these individuals cannot consciously discriminate fine-grained pitches (Peretz et al., 2002). The Montreal Battery of Evaluation of Amusia (MBEA) assessment is the main diagnostic tool for CA, and comprises six sub-tests in four sections that assess melodic, rhythmic, metric, and memory skills. Discrimination is usually measured by three sub-tests in the melodic category (violations of key, pitch contour, and pitch interval) and one sub-test in the rhythmic section (Peretz et al., 2003).

Behavioral studies have linked the music perception and production impairment of CA to deficits in pitch perception

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(Foxton et al., 2004; Albouy et al., 2016) and pitch memory (Tillmann et al., 2016), which have been associated with changes in brain structure and/or function. Previously, cerebral substrates of CA have been implicated in abnormal activity in the right frontotemporal network, which plays a major role in music perception and memory, particularly for processing pitch-related dimensions (Albouy et al., 2013). CA has been associated with a reduced white matter concentration in the right inferior frontal gyrus and right superior temporal gyrus (Hyde et al., 2006; Albouy et al., 2013), as well as a diminished arcuate fasciculus connecting the two areas (Loui et al., 2009; Zhao et al., 2016), compared with musically intact subjects. Anomalies in the auditory cortices and inferior frontal gyrus, as well as their connectivity, have been revealed via resting-state magnetic resonance imaging (MRI) (Leveque et al., 2016), functional MRI (Hyde et al., 2011), and magnetoencephalography studies (Peretz et al., 2002; Albouy et al., 2015). Recent CA studies have indicated that impaired encoding of rapid pitch information underlies perception and memory deficits (Albouy et al., 2016). CA-associated damage first occurs in the right auditory cortex as opposed to the frontotemporal network.

Mandel et al. (2007) reported that the left frontal and temporal cortices were impaired in subjects with amusia, and proposed that CA is an auditory-motor feedback disorder. Other researchers have also reported CA-related anomalies in the right or left frontal and temporal cortex (Mandell et al., 2007; Leveque et al., 2016; Wang et al., 2017), without supportive evidence of motor system impairment. A recent meta-analysis of neuroimaging in healthy people reported that passive music-listening selectively activated the motor system, even without movement (Gordon et al., 2018). The general complaint associated with CA is not fine-grained pitch discrimination, but singing out of tune. Usually, singing in tune is achieved through a repetitive process of learning and correcting mistakes. The auditory-sensorimotor feedback system receives information from the auditory cortex and then feeds it back to the auditory cortex through the sensorimotor system. However, no studies have examined the involvement of motor areas in CA. Functional MRI resting-state studies of CA have only assessed pre-defined resting-state networks or seed-voxel correlations (Loui et al., 2009; Leveque et al., 2016). Thus, more advanced approaches are needed to further explore the neural networks and underlying mechanisms of CA. We hypothesized that CA is an auditory-motor feedback disorder. To address this in the present study, we examined functional changes in the auditory-motor feedback loop in people with CA.

The graph theory method for analyzing brain functional networks has been widely used in various neuropsychiatric diseases. Among the graph theory methods, the degree centrality (DC) method, which is voxel-based, has recently gained attention because it uses a simple and directive description of centrality and prioritizes nodes in the network. In the DC method, the voxels in the brain are thought of as nodes, and the connections between the voxels as edges. DC can reflect functional connectivity density without requiring delineation of the predetermined target by computing the temporal correlations for every pair of neighboring voxels in the entire brain (Tomasi and Volkow, 2010; Zhou et al., 2019). Greater DC values indicate that voxels contain a higher density of functional connections. The voxel-based DC method can surpass the limitations of seed-based approaches to anomaly detection (Zhou et al., 2019). The purpose of this study was to detect changes in cerebral functional connectivity in amusia to examine the auditory-motor system impairment hypothesis.

Participants and Methods

Participants

The whole study was conducted in Second Xiangya Hospital of Central South University from November 2018 to August 2019. Nineteen participants with CA and 19 healthy controls without amusia, matched for age, sex, education, and handedness, participated in a functional MRI scanning. All participants were Chinese college students from Changsha, Hunan Province, China, with normal intelligence, normal hearing, and no musical training. Participants gave written informed consent (**Additional file 1**). The Ethics Committee of the Second Xiangya Hospital, Central South University approved our research protocol (No. WDX20180101GZ01) on February 9, 2019 (**Additional file 2**). This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (**Additional file 3**).

We collected basic information (age, sex, years of education, handedness, health conditions), and participants completed the Wechsler Intelligence Scale (Wechsler, 2008) as well as a pure tone audiometry test. Then, participants who had identified themselves as singing out of tune were confirmed as amusic individuals via a face-to-face MBEA assessment (Peretz et al., 2003). The controls were matched to the amusic participants in terms of basic demographics, except that their MBEA assessments demonstrated intact musical perception ability. The inclusion criteria were 1) a score above 85 on the Wechsler Intelligence Scale, which indicates normal intelligence, and 2) the ability to hear at least 25 decibels, as measured by pure tone audiometry. The exclusion criteria were 1) a self-reported presence or history of psychiatric or neurologic disease, 2) serious physical disease, 3) drug use history in the past 6 months, 4) hearing loss, and/or 5) contraindications to MRI examination. The recruitment process is shown in **Figure 1**.

In the MBEA assessment, subjects who had scores that were two standard deviations below the mean score of healthy controls were considered to have CA. The melodic and rhythmic sub-tests of the MBEA use “same–different” discrimination tasks, with the same set of novel music. All stimuli were delivered with a piano sound and played on a computer. The test took around 2 hours to complete, and was conducted in a quiet, sound-proof room. Participants were given the option to rest between each sub-test.

MRI acquisition

All MRI data were obtained using a 3T Siemens Skyra MRI scanner (Magnetom Skyra, Siemens, Munich, Germany) equipped with a 20-channel head coil. Our protocol included a resting-state functional MRI with echo-planar imaging sequences (repetition time = 2000 ms, echo time = 30 ms, flip angle = 80°, 32 slices, slice thickness = 4 mm, slice spacing = 1 mm, field of view = 256 mm × 256 mm, acquisition matrix = 64 mm × 64 mm, voxel size = 4 mm × 4 mm × 4 mm), and a sagittal high-resolution 3D magnetization-prepared rapid gradient echo sequence (repetition time = 1900 ms, echo time = 2.03 ms, flip angle = 9°, 176 slices, slice thickness = 1 mm, slice spacing = 1 mm, field of view = 256 mm × 256 mm, acquisition matrix = 256 × 256, voxel size = 1 mm × 1 mm × 1 mm). Scanning was conducted while subjects were in the

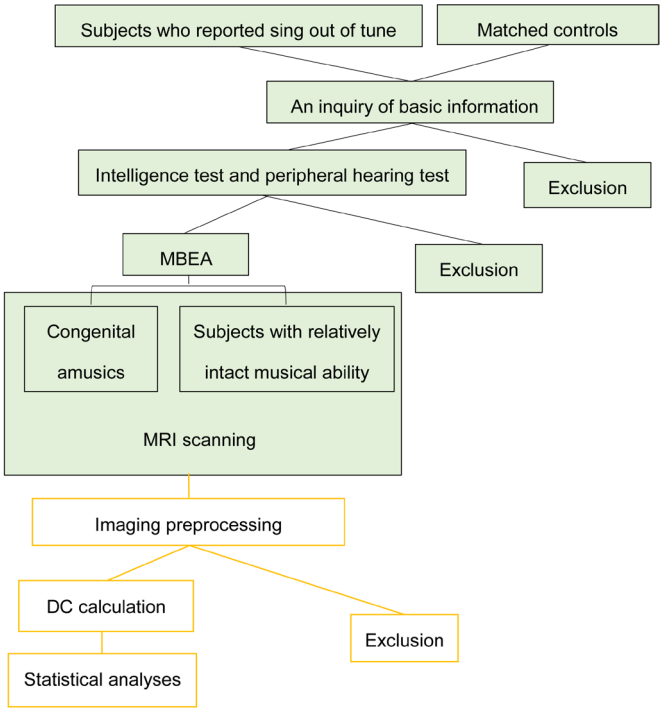

Figure 1 | **Flow chart of the study.**
MBEA: Montreal Battery of Evaluation of Amusia; MRI: magnetic resonance imaging.

supine position, and foam padding was placed between their head and the head coil to minimize head motion.

Imaging preprocessing and DC calculation

The quality of scanned images was visually checked for artifacts, structural abnormalities, or apparent head motion. Imaging preprocessing was performed on a toolbox for Data Processing & Analysis of Brain Imaging (DPABI; http://rfmri.org/dpabi) based on Statistical Parametric Mapping (SPM8; https://www.fil.ion.ucl.ac.uk/spm). The processing steps were as follows: removal of the first 10 time points, slice timing, head motion correction, reorientation, regression of nuisance covariates, spatial normalization to the Montreal Neurological Institute space with re-sampled images (3 mm × 3 mm × 3 mm), detrending, and bandpass filtering (0.01–0.08 Hz). To reduce the influence of nuisance variables, head motion and white matter and cerebrospinal fluid signals were regressed out. In addition, we created a group mask to minimize spurious findings caused by variability in head size and shape and coverage differences (the threshold was set to 90%).

DC analysis was carried out using the same DPABI software. First, we extracted the time course of each voxel within a default mask. Subsequently, we computed the Pearson correlation coefficients between the time course of any two voxels to obtain a correlation matrix. After thresholding each correlation at $r > 0.25$, correlation coefficients with an $r > 0.25$ were summed for each voxel, and we then computed the DC as the sum of connections (weighted) for each voxel. To fit a normal distribution, the resulting voxel-wise DC map was divided by the global mean DC. Then, the standardized DC map was converted into a Z-score map by subtracting the global mean DC and dividing by the standard deviation (SD) of the whole-brain DC. Notably, smoothing (Gaussian kernel with a full-width at half maximum = 4 mm) was performed after DC calculation rather than in the preprocessing steps to prevent the possible introduction of automatically local artifactual correlations (Zuo et al., 2012).

Statistical analyses

We compared demographic data and MBEA variables between the CA and healthy control groups using SPSS 21.0 (SPSS, Inc., Chicago, IL, United States). To eliminate artifacts in small structures, such as pulsatile effects from the vasculature and partial volume effects in boundary regions, subjects with any slight head motion (a translation movement of more than 1.5 mm, or a rotation more than 1.5°) were excluded. Furthermore, we calculated the mean framewise displacement of each subject to control micro-scale head motion. Levene's test was used if all variances satisfied homogeneity of variance. A two-sample *t*-test was used to perform between-group comparisons in continuous variables (e.g., age, years of education, framewise displacement, MBEA scores), and the Fisher's exact test was used to perform between-group comparisons of categorical variables (e.g., sex). Within DPABI, a two-sample *t*-test was applied to compare the Z-score maps between the CA group and the healthy control group. Then, to achieve the best balance between the family-wise error rate (under 5%) and test-retest reliability, we used a permutation test with threshold-free cluster-enhancement (TFCE; permutation with 5000 times) to identify clusters showing statistically significant differences (Winkler et al., 2016). Additionally, we used an image calculator module to overlap the identified clusters with statistically significant inter-group differences with brain regions in the Anatomical Automatic Labeling template. This enabled us to identify the brain regions represented by the clusters. The averaged eigenvalues of DC for each subject were computed from these brain regions. A two-sample *t*-test was used to compare the differences in mean DC values in identified brain regions between the two groups. To further assess the relationship between DC values and MBEA scores, we implemented a two-tailed Pearson's correlation analysis. The threshold for statistical significance for the two-sample *t*-test, Fisher's exact test, multiple comparison correction, and Pearson's correlation analyses was set at 0.05.

Results

Demographics and MBEA evaluation of the CA and healthy control groups

We excluded seven subjects, two from the CA group and five from the healthy control group, after checking MRI images and head motion. One subject from each group was excluded because of slight head motion. The other five subjects were excluded because of artifacts. This resulted in 17 participants in the CA group (12 males, 5 females) and 14 participants in the healthy control group (7 males, 7 females) (**Figure 1**). All subjects were right-handed. Demographic information (sex, age, and years of education), framewise displacement, and MBEA scores are presented in **Table 1**. There were no significant between-group differences in sex ($P = 0.288$), age ($t = –1.588$, $P = 0.123$), framewise displacement ($t = –0.267$, $P = 0.791$), or years of education ($t = –0.257$, $P = 0.799$) A significant inter-group difference was observed in each sub-test MBEA score ($P = 0.000$). Compared with the healthy control group, the CA group had lower scores for four different aspects of musical ability, namely melodic discrimination, rhythmic discrimination, meter, and memory (all $P < 0.001$, except for meter, which was $P = 0.001$).

Comparison of DC values between the CA and healthy control groups, and correlation analyses

According to the Anatomical Automatic Labeling template, the

Table 1 | **Characteristics of the CA and healthy controls groups**

	Congenital amusics	Healthy controls	*P*-value
Number (male/female)	17 (12/5)	14 (7/7)	0.288*
Age (yr)	18.294±0.588	18.642±0.633	0.123†
Framewise displacement	0.056±0.221	0.583±0.295	0.791†
Education (yr)	13.176±0.393	13.214±0.426	0.799†
Melodic discrimination			
Violate key	18.824±2.921	27.571±1.697	0.000†
Pitch contour	20.353±3.141	28.429±1.399	0.000†
Pitch interval	19.529±3.044	27.857±1.657	0.000†
Mean scores	19.510±2.169	27.953±0.941	0.000†
Rhythmic discrimination	19.647±2.178	27.357±1.151	0.000†
Metre	19.765±4.409	25.296±3.338	0.001†
Memory	20.882±3.638	28.643±1.447	0.000†
MBEA mean scores	19.833±1.631	27.524±0.969	0.000†

Data are expressed as the mean ± SD, except for number data. All variables conformed to homogeneity of variance. Fisher's exact test (*) and two-sample *t*-tests (†) were used to test between-group differences in categorical and continuous variables, respectively. MBEA: Montreal Battery of Evaluation of Amusia; violate key, pitch contour, pitch interval, rhythm, meter, and memory: subscales of the MBEA.

CA group exhibited significantly decreased clusters in the right precentral and postcentral gyrus, namely, the primary sensory and motor areas ($P < 0.05$, permutation with TFCE-corrected), compared with the healthy control group (**Figures 2** and **3A**). The changes in cluster size and peak value were greater in the sensory area than in the motor area (**Table 2**). In addition, as shown in **Figure 3B** and **C**, the mean DC values of significantly decreased clusters in primary sensory and motor areas were significantly lower in the CA group than in the healthy control group ($P < 0.001$). The correlation analyses revealed a positive correlation between the averaged DC values of two changed clusters (sensory area, motor area) and four aspects (melody, rhythm, meter, and memory) of the MBEA assessment ($P < 0.001$), except for the metric test ($P > 0.05$). The correlation results are presented in **Figure 3C**.

Discussion

In our study, a resting-state functional MRI DC analysis was performed to identify regions with neuro-functional abnormalities at the voxel-based level in the CA group compared with the healthy control group. We found that the subjects with CA exhibited lower DC values in the right primary sensorimotor regions than the healthy control group. In addition, averaged DC values in the brain regions with significant intergroup differences were positively correlated with the averaged total melodic scores and the average scores from the rhythmic and memory subtests. Furthermore, the CA group had significantly lower melodic discrimination, rhythmic discrimination, and memory scores than the healthy control group.

We found that in addition to reduced pitch perception and memory, the patients with CA received lower scores on the other music perception tests compared with the control group. Our findings support the idea that pitch perception and memory impairment are hallmarks of CA (Albouy et al., 2016; Tillmann et al., 2016). Interestingly, individuals with CA for whom English is their mother tongue mainly present with selective pitch perception disorder (Hyde et al., 2006; Albouy et al., 2013), while those for whom Chinese is their first language are more likely to be diagnosed with extensive pitch perception disorders (Chen et al., 2015; Jiang et al., 2019).

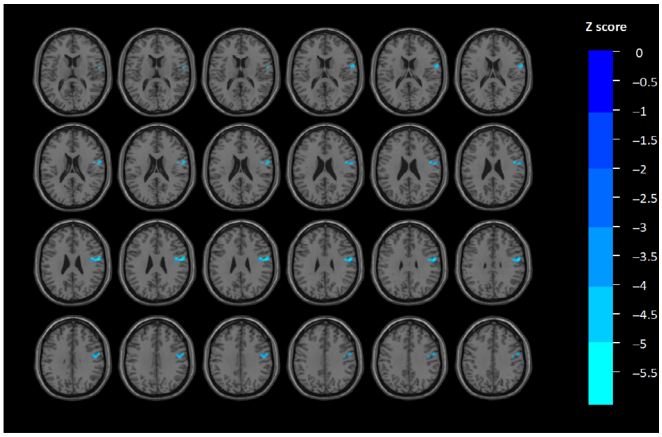

Figure 2 | **Clusters that significantly varied in terms of DC values in amusics *versus* controls.**
The CA group had significantly lower degree centrality values in changed clusters, which are expressed as a Z-score, than the healthy control group ($P < 0.05$; corrected for permutation with threshold-free cluster-enhancement). CA: Congenital amusia; DC: degree centrality.

Table 2 | **Abnormal functional hubs located by cluster peak information in the CA group assessed by degree centrality indices**

Brain region	Peak *t*-value	Cluster size (voxels)	Peak MNI coordinates		
			X	*Y*	*Z*
Precentral_R	–4.196	15	51	3	24
Postcentral_R	–5.36	54	54	–6	27

The significance level was set at $P < 0.05$ (corrected for permutations with threshold-free cluster-enhancement). CA: Congenital amusia; MNI: Montreal Neurological Institute; R: right.

To our knowledge, this study is the first to reveal that individuals with CA demonstrate reduced degree centrality in the right primary sensorimotor regions compared with controls. A decrease in the centrality of the right primary sensorimotor areas represents a decrease in the global connectivity as well as in its importance in the whole brain (Zhou et al., 2019). The recent study revealed CA impairment begins right auditory cortex (Albouy et al., 2016), while our study found a decreased global connectivity in right primary sensorimotor areas. Amusia has been associated with abnormalities in the auditory cortices and inferior frontal gyrus, as well as their connectivity, but there is no evidence of CA-associated anomalies in the sensorimotor system. This is the first report of a specific CA-associated sensorimotor anomaly. Our data support previous findings indicating that CA-associated abnormalities might be related to auditory-motor disorders (Mandell et al., 2007). Specifically, our findings indicate that an auditory-motor feedback disorder prevents those with amusia from identifying that they are singing out of tune and making appropriate corrections.

Altered DC in right primary sensorimotor areas was positively correlated with the degree of impairment in musical skill, mainly in melodic ability, rhythmic discrimination, and memory recognition. For amusics, lower DC values in the right primary sensorimotor areas were correlated with decreased musical ability. A wide range of brain areas has been implicated in the neural network involved in memory recognition and musical discrimination, including the primary motor cortex, premotor areas, supplementary motor area, Broca's area, anterior insula, primary and secondary somatosensory cortices, and the superior temporal gyrus and sulcus. Our findings support the view that auditory-sensorimotor coupling plays an important role in musical discrimination and memory

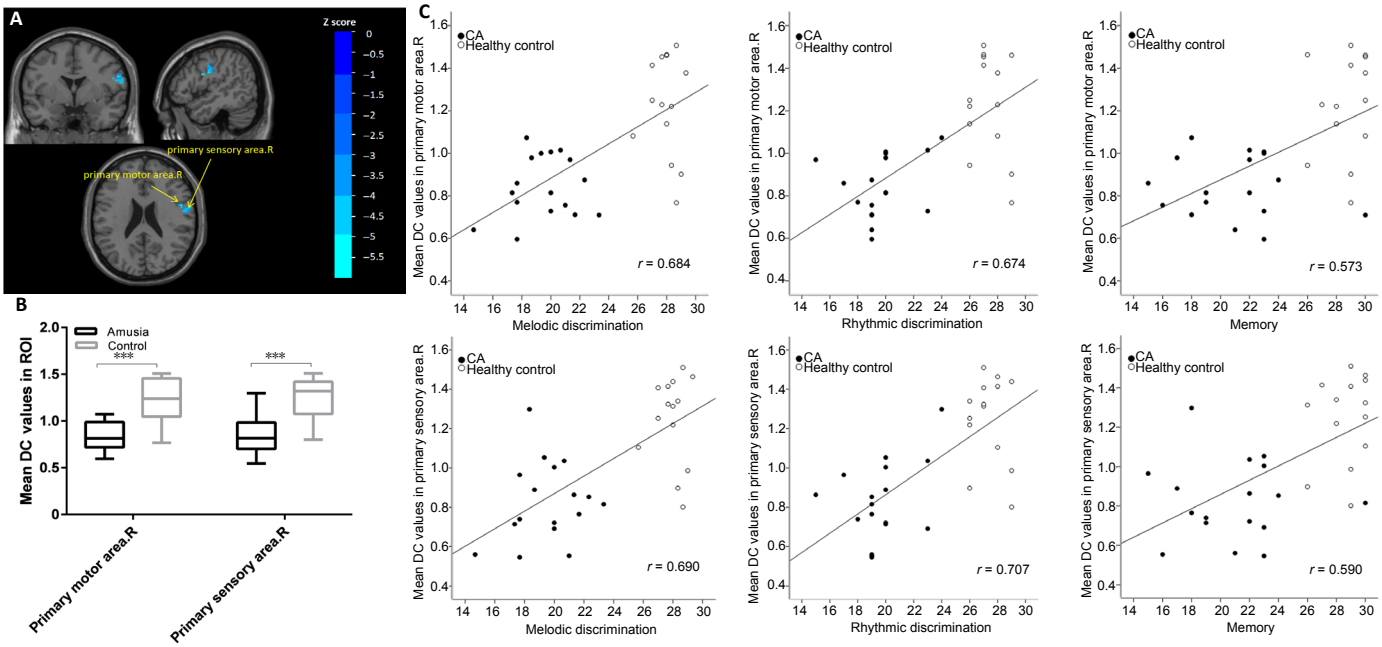

Figure 3 | **Degree centrality (DC) changes marked by the Anatomical Automatic Labeling (AAL) template in the CA group.**
(A) The brain regions identified by the AAL template exhibited a significant decrease in DC values for the CA group. The change in DC values is denoted with a Z-score. The brain regions showing AAL template denoted with a Z-score. (B) In the primary sensory and motor area, the mean DC values were computed and compared between the CA and healthy control groups (***$P < 0.001$). (C) In the primary motor (upper) and sensory (lower) areas denoted in Figure 2A, the mean DC values were positively correlated with melodic, rhythmic and memory subtest scores. CA: Congenital amusia; R: right; ROI: region of interest.

(Keough et al., 2013; Marvel et al., 2019). Our correlation analysis revealed similar DC values in the primary sensory and motor areas, with a closely functional relationship. This demonstrates the feasibility and credibility of considering the primary sensorimotor area as an integral whole. Reduced spontaneous connections in primary sensorimotor regions are indicative of decreased centrality in the primary sensorimotor area within the auditory-sensorimotor system.

Much like the cerebral hemispheres, the auditory cortex is functionally asymmetrical (Jamison et al., 2006). Neuroimaging studies have suggested that the right auditory cortex is key in sequential pitch processing (Patterson et al., 2002), and that it has a higher resolution in the pitch domain (Jamison et al., 2006) and is more sensitive to small pitch changes (Jamison et al., 2006) relative to the left. Previous studies on CA have reported abnormal functioning of the right auditory cortex (Hyde et al., 2006; Loui et al., 2009). Consistent with auditory cortex abnormalities in amusics, we found sensorimotor abnormalities located in the right hemisphere. When we considered the auditory-sensorimotor system as a whole, we found lateralization for fine pitch resolution. Additionally, we noticed that, in the sensory area, the decreased cluster size and peak value were greater than those in the motor area. Music processing is a cognitive process that involves the flow of information from perception (external information), to cognition (central processing unit), and then to movement/behavior (Bubic et al., 2010). The sensory system needs to gather as much information as possible and activate more regions to form precise movements. A deficit in music perception is the major complaint associated with CA, and this sensory deficit is more pronounced than off-key singing (movement-related). Therefore, it is understandable that we found more abnormalities in sensory areas compared with motor areas in individuals with amusia.

Our study has some limitations that should be noted. First, we concentrated on the detection of abnormal changes and did not investigate the link between the auditory cortex and sensorimotor area. Thus, we only identified candidate areas of abnormality, and did not obtain direct evidence of reduced functional connectivity between the auditory cortex and primary sensorimotor regions. Second, unlike in previous studies, we did not find abnormalities in the auditory cortex, but only in the right primary sensorimotor areas. It is possible that different research methods have varying sensitivities to nerve impairments. Third, the sample size was relatively small, although similar studies also used small samples (Hyde et al., 2006; Loui et al., 2009; Chen et al., 2018). The sample was quite homogeneous, as all participants were college students. In future research, we plan to expand our sample sizes and to examine both static and dynamic functional connectivity in the auditory-sensorimotor systems in individuals with CA. Given that plastic changes occur in the brain of musicians, we are also interested in cerebralplastic changes after musical interventions in individuals with CA.

In conclusion, using a resting-state functional MRI DC analysis, we identified new candidate brain regions, i.e., the right primary sensorimotor areas, implicated in CA. Disordered auditory-motor feedback may be the underlying neural mechanism of CA, and may specifically affect music learning. Further research could examine the exact roles of these brain regions in the expression of this learning deficit, or examine potential neural targets for treatment. There is evidence that sensory substitution devices can be used to convert lost perceptual information into alternative sensory forms in sensory-deprived subjects (Nau et al., 2015). Further research could examine whether the brain regions with reported abnormal functional could be useful in the development of strategies for sensory substitution training in individuals with CA.

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parameters.

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Institutional review board statement: *The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, China (No. WDX20180101GZ01) on February 9, 2019.*

Declaration of participant consent: *The authors certify that they have obtained all appropriate participant consent forms from the conscious participants. In the forms, the participants have given their consent for their images and other clinical information to be reported in the journal. The participants understood that their names and initials will not be published.*

Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.*

Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of the Second Xiangya Hospital, Central South University, China.*

Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

Open peer reviewer: *Lei Gao, Zhongnan Hospital of Wuhan University, China.*

Additional files:

Additional file 1: *Informed consent (Chinese).*

Additional file 2: *Hospital ethics approval (Chinese).*

Additional file 3: *STROBE chechlist.*

Additional file 4: *Open peer review report 1.*

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	2
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*2*
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3
		(*b*) Describe any methods used to examine subgroups and interactions	3
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	2
		(*e*) Describe any sensitivity analyses	3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	3

		included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	2-3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*3*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	3
		(*b*) Report category boundaries when continuous variables were categorized	3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4-5
Generalisability	21	Discuss the generalisability (external validity) of the study results	4-5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.