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Abnormal regional homogeneity (ReHo) in Congenital Amusia: a resting-state functional MRI study

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Research Article

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Abstract

Congenital amusia (CA) is a disorder of pitch perception, a core function of the human auditory system. A total of seventeen amusics, fitting stringent criteria in Montreal Battery of Evaluation of Amusia (MBEA), and fourteen healthy controls participated in our study. Here, we aimed to characterize a local resting state functional measure, regional homogeneity (ReHo) to evaluate abnormal local consistency of the neurons spontaneous activity in CA group compared with the healthy control group. We focused on potential brain areas with significant differences between the two groups. The partial correlation analyses applied to ReHo values as well as scores of MBEA subtests. The CA group showed a significant decrease ReHo values in the left postcentral gyrus and left middle cingulum cortex when compared to controls. The ReHo values of those two significant regions were both positively correlated with MBEA scores. All in all, this study identified brain regions which were not discussed previously that may partly contribute to or be modulated by CA.

Introduction

Congenital amusia (CA), colloquially labeled tone deaf, is a developmental disorder of the central auditory system that results in behavioral impairments of pitch perception and memory, that cannot be attributed to lack of exposure, intellectual disability, or brain damage after birth(Peretz et al. 2002; Peretz et al. 2007; Ayotte et al. 2002). What characterizes them behaviorally is their difficulty with detecting both their own and others singing out of tune, with distinguishing a familiar tune without the assistance of the lyrics, and with maintaining memory of short tunes(Ayotte et al. 2002). It is widely distributed in the population, accounting for about 4.2% of the total population(Kalmus and Fry 1980), with no obvious gender difference between men and women. Although there is testimony that recovery is possible through training, CA is believed to be innate(Whiteford and Oxenham 2018). While CA is not seriously harmful and does not affect the normal life of the individual, its underlying abnormalities brain structural and/or functional may be important to understand human brain. To nearly everyone, the appeal of music is documented across the lifespan. In this context, lack of musical inclination is bewildering and calls for an analysis of its causes(Peretz 2016). Therefore, characterization of the disorder sheds light on the neuro-cognitive architecture (musical processing) and highlights possible etiologies of disordered brain development at a cognitive and neurobiological level. Systematically investigating the disorder of the neural basis and cognitive has been a relatively recent endeavor.

Recent years studies in amusics suggested that the deficit music ability of CA may be related to emotional information processing disorder. Music can express emotional information via controlling the pitch, tempo, and volume(Dissanayake 2000). Research on the behavioral preferences of CA has shown that the perceptual impairment restricts the level of music appreciation, which is manifested as lower participation in music activities and weaker emotional arousal of music and negative attitude towards music(Arias Gómez 2007). Therefore, the reduction of CA individual's sensitivity to emotional content in music could either result from impaired music procession or emotion processing.

The core performance of CA are the deficits of musical perception and production, especially the significant pitch, expression(Hyde et al. 2011; Foxton et al. 2004) and memory difict(Albouy et al. 2013; Albouy et al. 2015). At present, the Montreal Battery of Evaluation of Amusia (MBEA) (Peretz et al. 2003) is the most widely used tool to diagnose CA which consisting of four sections (melodic, rhythmic, metric, and memory) with six sub-tests. Three sub-tests are under the classification of melodic (violate key, pitch interval, and pitch contour) and one sub-test in every other section.

Individuals of CA have been associated to changes in brain structures and brain functions. The dominant theory of the neural basis of amusia focused on the right inferior frontal gyrus (IFG), right superior temporal gyrus (STG), and the connectivity between them in structure and function in the right hemisphere. Individuals with amusics have been implicated of having a higher grey matter and lower white-matter density in the right IFG(Hyde et al. 2006; Hyde et al. 2007; Albouy et al. 2013), the levels of grey-matter density in the right STG is abnormal(Albouy et al. 2013; Hyde et al. 2007), as well as a decreased arcuate fasciculus to connect the two clusters(Zhao et al. 2016), compared with musically intact subjects. But there is limited research on the left hemisphere of CA: Mandell et al demonstrated the existence of a left fronto-temporal network(Mandell et al. 2007) and Jasmin et al found prominent reductions in functional connectivity between left prefrontal language-related regions and right hemisphere pitch-related regions of CA(Jasmin et al. 2020). Current fMRI resting-state research in CA are also limited to pre-defined resting state networks or seed-voxel correlations(Tillmann et al. 2016; Loui et al. 2009). However, the body of evidence suggests that musical processing is based on a widely distributed neural network and amusia may involve abnormal connectivity and cooperation with the interhemispheric(Schuppert et al. 2000; Peretz 1985; Schurz et al. 2015). Therefore, further study of the whole brain could further improve our understanding of the neural basis of amusia.

In our previous study(Sun et al. 2021), we used the degree centrality (DC) method to discern abnormal functional network centrality and found decreased DC values in the right primary sensorimotor areas in a amusics group compared with healthy control (HC) groups. In our current study, we used Regional Homogeneity (ReHo) to further explore neural networks and discover underlying mechanisms leading to CA. ReHo is a data analysis method of rs-fMRI(Wang et al. 2011; Zang et al. 2004) which is a voxel-based measure of brain activity that evaluates the synchronization/similarity between the time series of a given voxel and its nearest neighbors, and use the Kendall's coefficient of concordance(KCC) as an index(Zang et al. 2004). ReHo mainly reflects the consistency of the local neurons spontaneous activity. The increases in the ReHo value indicate that the local brain area neuron activity tends to be synchronized in the certain time. So the abnormal ReHo value can reflect if neurons are abnormally synchronized. This approach has been used in a variety of mental disorders and has shown to be a promising biomarker(Lai and Wu 2012; Jiang and Zuo 2016; Wu et al. 2009; Tan et al. 2016; Liu et al. 2017; Gao et al. 2015). As far as we know, this is the first article using ReHo to study CA.

In our study we aimed to explore the potential brain biomarkers of congenital amusia in whole brain. We investigated the abnormal consistency of the local neurons spontaneous activity of amusics’ brains at rest compared with healthy controls based on the ReHo method using resting state-functional MRI. In addition, the correlations between the ReHo values in the abnormal brain regions and scores of MBEA with 6 subtests were calculated to investigate the associations between abnormal regions and musical skills in amusics.

Materials And Methods

Participants

19 amusia participants and 19 gender-, education-, and handedness-matched healthy control participants originally were included. All participants came from different colleges and universities with normal intelligence, hearing, and non-musical training experience. They were screened by the online tests and identified by a more accurate face-to-face Montreal Battery of Evaluation of Amusia (MBEA) assessment. Subjects whose scores were 2 standard deviations lower than those of healthy controls were judged to congenital amusia (< 21.5)(Nan et al. 2010). In our assessment, both the rhythmic and melodic assessments use "same-different" discrimination tasks, with the same set of music(Peretz et al. 2003). All stimuli were played by a computer and delivered with a piano sound. The entire test lasting for 2 hours and conducted in a quiet room. In each sub-test interval, the participant can decide whether to rest or not. Exclusion criteria was the history or presence of neurologic or psychiatric disease, drug use in the past 6 months, serious physical diseases, contraindications to MR examination.

Ethical protocol was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. All participants gave their written informed consent.

MR imaging acquisition

All MRI data was collected by a 3T Siemens Skyra MRI equipped with a 20-channel head coil. The protocol included a resting-state functional MRI with echo-planar imaging (EPI) sequences (Time points = 216, TR = 2000ms, TE = 30ms, flip angle = 80°, 32 slices, slice spacing = 1mm, slice thickness = 4mm, FOV = 256×256 mm2, voxel size = 4×4×4mm3, acquisition matrix = 256×256, and a sagittal high-resolution 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 1900ms, TE = 2.03ms, 176 slices, flip angle = 9°, slice thickness = 1mm, FOV = 256×256 mm2, slice spacing = 1mm, voxel size = 1×1×1mm3, acquisition matrix = 256×256. Subjects were placed in a head-first supine position and foam paddings between the head and the head coil were placed to limit their head motions.

Imaging preprocessing and regional homogeneity Calculation

T1-weighted images was visually checked for structural abnormalities, artifacts, and apparent head motion. Images were processed using DPABI (Data Processing & Analysis for Resting-State Brain Imaging, DPABI; http://rfmri.org/dpabi)(Yan et al. 2016). Preprocessing steps were as follows: removing the first 10 time points, slice timing, realigning, reorienting, nuisance covariates regressing, spatial normalization to the MNI (Montreal Neurological Institute) space with re-sampled images (3 mm × 3 mm

× 3 mm), detrending and bandpass filtering (0.01–0.08 Hz). Among nuisance covariates regressing step, head motion(Satterthwaite et al. 2013), signals of white matter and cerebrospinal fluid (CSF) were regressed out. Subjects whose translation or rotation movement of head motion was more than 1.5 mm or 1.5° were excluded. Afterwards, a group mask was generated by overlapping all preprocessed images (the threshold of 90%) to minimize spurious findings due to the variability in head shape and size and coverage differences.

ReHo calculation was also performed by DPABI. A Kendall's coefficient concordance (KCC) map was computed by the following formula: KCC was calculated in a voxel-by-voxel way that was then divided by the mean KCC of the whole brain. KCC maps were then smoothed by a 4mm FWHM Gaussian kernel.

$$KCC = \frac{\sum_{i=1}^{n} (R_i)^2 - n(\overline{R})^2}{\frac{1}{12}K^2 (n^3 - n)}$$

Where R_i is the summed rank of the time point; n is the number of temporal observation in the time series (here n=238); $\overline{R}$ =((n+1)K)/2 represents the mean of the R_i's; K is the number of the time series within a measured cluster (here K=27, including the given center voxel and its 26 nearest neighbors) (Zang et al. 2004);

Statistical analyses

We used the SPSS 21.0 (SPSS, Inc, Chicago, IL, United States) to compare the demographic and MBEA variables between CA group and HC groups. For continuous variables including age, years of education, MBEA scores and head motion, we used the two-sample *t*-test. Fisher's exact test was used to compare the categorical variables such as gender between groups.

Two-sample *t*-test was applied with DPABI to compare the Reho maps between the CA and HC groups on the group mask. We used a permutation test (5000 times) with TFCE (threshold free cluster-enhancement) to control the family-wise error rate (under 5%)(Winkler et al. 2016). Clusters with significant different inter-group Reho value were than obtained and mean Reho values of those clusters of every subject were extracted.

Partial correlation coefficient between MBEA scores including 6 sub-tests and mean Reho values of significant clusters was calculated to assess the relation between abnormal regions and MBEA variables. Age, gender and years of education were taken as covariables. $p < 0.05$ was set as statistical significance.

Results

Demographics and MBEA evaluation

We excluded a total of seven subjects (2 amusics and 5 healthy subjects) because of slightly head motion or artifacts. 17 amusics and 14 healthy controls were remained. Their demographic and MBEA information were showed in Table 1. There were no significant between-groups differences in terms of demographics (gender, age, FD, years of education) but significant differences in terms of each sub-test scores of MBEA assessment between groups. Compared with HC group, a significant decline was found in the group of amusics, including five different aspects of musical ability which are melodic, rhythmic, metric, memory and MBEA mean. For more details, please refer to our previous study(Sun et al. 2021).

Table 1
Characteristics of amusics and controls subjects(Sun et al. 2021).

	Amusics	**Controls**	***p* value**
N (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	19.833 ± 1.631	27.524 ± 0.969	0.000*
*: $p < 0.05$			

Comparison of ReHo values between amusics and healthy controls

As showed in Figure a and Table 2, in comparison to the healthy control group, the amusic group exhibited significantly decreased Reho values in left postcentral gyrus and left middle cingulum cortex according to Anatomic-Automatic-Labeling template (AAL) template (p < 0.05, permutation test with TFCE correction).

Table 2
Significant decreased regional homogeneity regions in amusic group compare to the healthy group.

Brain region (AAL)	Peak *t* value	Cluster Size (voxels)	Peak MNI Coordinates		
			X	Y	Z
Postcentral_L	-5.9129	334	-24	-48	24
Cingulum_Mid_L	-4.2698	285	-3	-6	45
Statistical threshold was p < 0.05 corrected for multiple comparisons by permutation test with TFCE. A combination threshold of cluster size > 209 voxels and p < 0.05 were considered significant; Coordinates are located in MNI space; L, left hemisphere; AAL, Anatomic-Automatic-Labeling template.					

Partial correlation analysis

Taking age, gender and years of education as control variables, we analyzed the partial correlation between the averaged ReHo values of two abnormal clusters and different aspects of MBEA assessment. The partial correlation analyses revealed a positive correlation between ReHo values of the two abnormal clusters (left postcentral gyrus and left middle cingulum cortex) with melodic, rhythm, metric, memory and MBEA mean scores ($p < 0.05$) (Figure b and Table 3).

Table 3
Partial correlation analysis of the left postcentral gyrus and left middle cingulum cortex with different aspects of MBEA assessment.

	left postcentral gyrus		left middle cingulum cortex	
	p value	*r* value	*p* value	*r* value
Melodic	0.040*	0.498	0.010*	0.458
Rhythmic	0.000*	0.596	0.001*	0.582
Metre	0.175	0.251	0.035*	0.379
Memory	0.010*	0.459	0.002*	0.541
MBEA mean	0.002*	0.539	0.001*	0.568
*: $p < 0.05$				

Discussion

In this study, a resting-state fMRI ReHo analysis had been executed to find potential areas with abnormal neuro-function at the voxel-based level in the amusic group. This study revealed that the subjects with CA exhibited decreased ReHo values in the left postcentral gyrus and left middle cingulum cortex. Moreover, altered ReHo in left postcentral gyrus and left middle cingulum cortex were positively correlated with the extent of impairment in musical skills in melodic, rhythmic, memory, metric and MBEA mean. The positive correlation findings supported the credibility and feasibility of considering left postcentral gyrus and left middle cingulate cortex as important abnormal brain areas in CA.

The left postcentral gyrus is an important part in emotion processing(Flaisch et al. 2015; Kassam et al. 2013; Kragel and LaBar 2015). Emotions across different modalities or types share similar neurological characteristics, and studies showed the left postcentral gyrus can (or from where can decode) represent different emotional categories across various stimuli modalities(Gu et al. 2019; Kragel and LaBar 2016). For example, the categories of emotion were successfully deciphered from different perceptual modalities (vocal and face expression) in the left postcentral gyrus(Kragel and LaBar 2016). Based on multivoxel pattern analysis a study showed that the left postcentral gyrus could successfully distinguish three valences (positive, negative and neutral) across different stimulus types (body, face, music or voice)(Gu et al. 2019). In our study, the subjects with CA exhibited decreased ReHo values in the left postcentral gyrus and it is correlated with the music skills. Our findings confirmed prior reports that individuals showed deficit emotional expression(Thompson et al. 2012; Costa et al. 2000; Maher and Berlyne 1982), suggesting that the abnormal synchronization of neurons in the left postcentral gyrus is related to the reduced ability to recognize/distinguish emotion categories thus may cause the music deficits in CA subjects. In summary, the abnormal synchronization of neurons in the left postcentral gyrus of amusics suggest that the left postcentral gyrus may be one of the important pathological brain areas for the onset of CA.

Cingulate cortex integrates input from various sources (evaluation of error, motivation, and representations from emotional networks and cognitive). Research showed that middle cingulate cortex involved cognitive processing: error detection working memory, complex motor control and anticipation of cognitively demanding task(Bush et al. 2000; Carter et al. 1999). In our study, the ReHo value of the left middle cingulum cortex is decreased and positively related to the reduced behaviorally musical ability. We estimate that the decreased consistency of the left middle cingulate cortex spontaneous activity is related to abnormal cognitive processing such as errors detection among CA individuals. Our findings could also be supported by the previous view(Sun et al. 2021) that an auditory feedback disorder prevents individuals of CA from recognizing that they are singing out of tune and to make appropriate corrections. It further confirmed that the changes in the left middle cingulate gyrus of patients is crucial for CA.

Although the findings of our study are encouraging, several limitations must be addressed. Firstly, in our study all participants are between the ages of 18 and 20. There is no comparison at other ages. Secondly, there is a relatively small sample size in our study although the sample was quite homogeneous (all college students) and strict statistical method was derived to control the false positive rate. Thirdly, there were no follow-ups after treatment for CA group. In the future, we will follow up the participants of CA to see if the abnormal brain areas change or return to normal after treatment. On the whole, brain function of amusics at other ages or longitudinal studies of amusics will be a focus in future studies.

In conclusion, our study revealed that the local brain area neuron activity synchronization tends to be disordered in two clusters (left postcentral gyrus and left middle cingulate cortex) in amusics. As far as we know, this is the first study to reveal these two abnormal regions in amusics. Overall, deficit musical emotion perception and disordered auditory feedback perhaps are the underlying neural mechanism in amusics.

Declarations

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Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Junjie Sun, Zhishuai Jin, Ru Yang and Xuan Liao. The first draft of the manuscript was written by Ru Yang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability: The datasets analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request

Ethics approval: This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. All participants gave their written informed consent.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) a and b.

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Figures

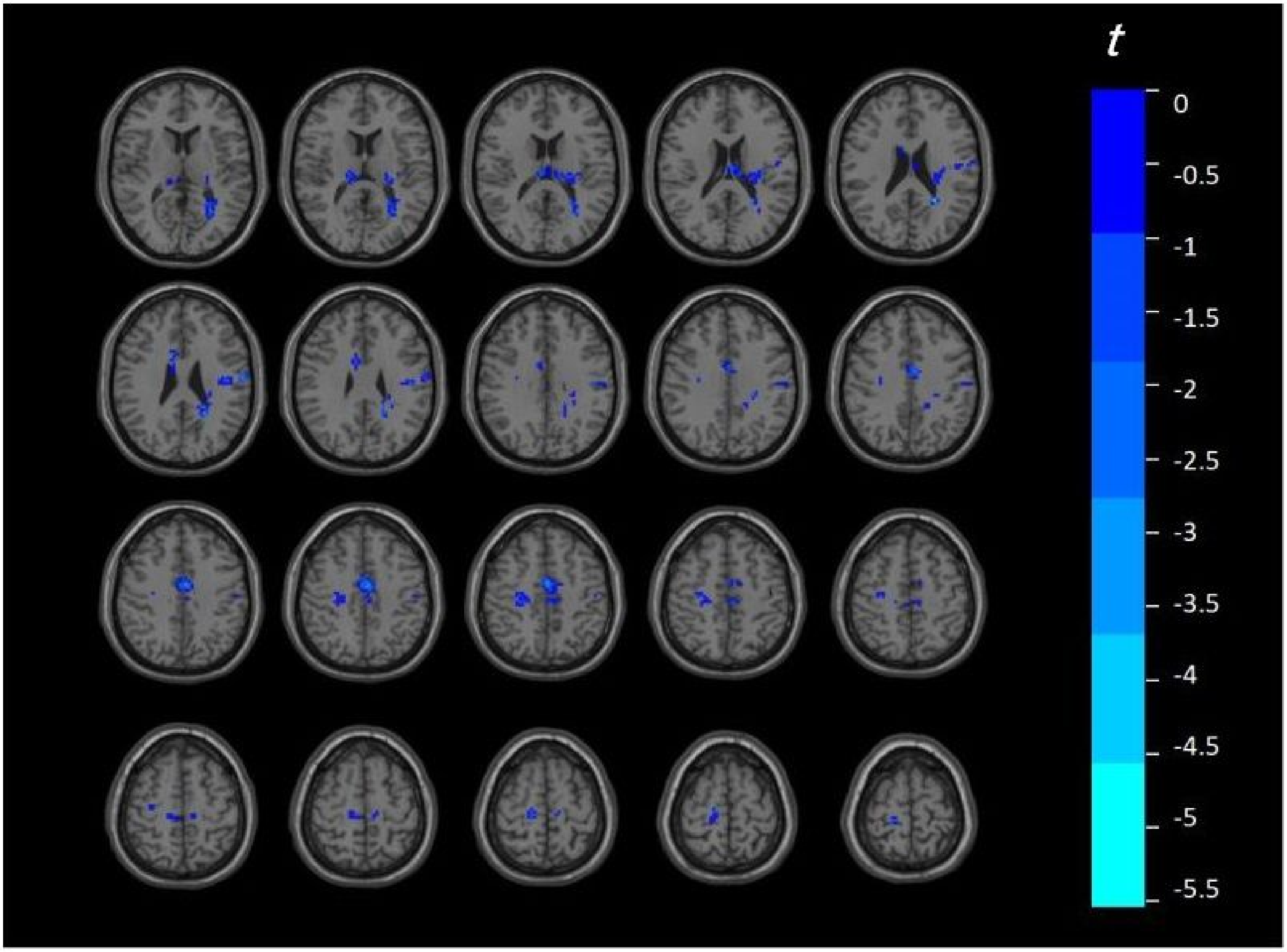

Figure 1

Figure a Significant decreased regional homogeneity regions in amusic group compare to the healthy group. $p<0.05$, permutation test with TFCE correction.

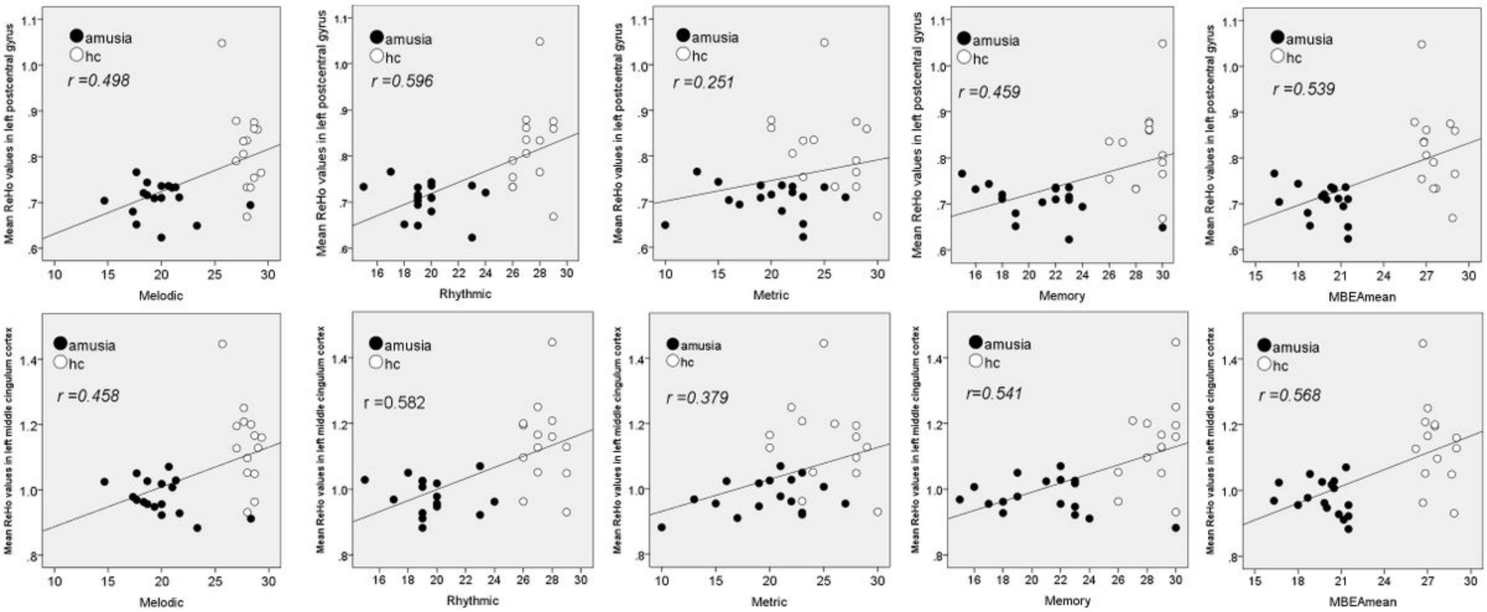

Figure 2

Figure b The mean ReHo values were positively correlated with melodic, rhythmic, metric, memory and MBEA mean scores in the left postcentral gyrus (upper) and left middle cingulum cortex (lower) areas; hc: healthy control.