Regional Homogeneity And Homotopic Connectivity Changes In Breast Cancer Survivors With Fear of Cancer Recurrence: A Resting State FMRI Study

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Research Article

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Abstract

Background: Fear of cancer recurrence(FCR) has been one of the most commonly endorsed unmet need for breast cancer survivors, but the neuroimaging mechanism underlying fear of cancer recurrence still remains unclear.

Methods: we recruited 62 breast cancer survivors (31 in high FCR group and 28 in low FCR group) to explore the inter-group differences in neuroimaging findings. All the participants underwent resting-state functional magnetic resonance imaging (rs-fMRI) scan. Regional homogeneity (ReHo) and Voxel-mirrored homotopic connectivity (VMHC) method were applied to analyze the imaging data.

Results: Breast cancer survivors with high and low FCR showed significantly different ReHo in the left caudate nucleus and precuneus, and significantly different VMHC in brain regions in the posterior cerebellar lobe, the superior frontal gyrus, the orbital part, the inferior frontal gyrus, the occipital gyrus, the inferior parietal lobule and the frontal middle gyrus. The left caudate nucleus was negatively correlated with FCR ($p < 0.05$), and the correlation coefficient was -0.501. The right precuneus lobe was positively correlated with FCR scores ($p < 0.05$), and the correlation coefficient was 0.505. Besides, VMHC in bilateral superior occipital gyrus was positively correlated with the total score of FCR ($p < 0.05$), and the correlation coefficient was 0.438

Conclusion: This study suggested that the left caudate nucleus, right precuneus lobe and bilateral superior occipital gyrus were involved in the neuropathology of FCR. ReHo and VMHC in specific regions could be applied as a biomarker to distinguish breast cancer survivors with high FCR from those with low FCR.

Introduction

With the progress of modern medicine and improvement of cancer diagnosis and treatment, the number of cancer survivors has been steadily increasing [1]; therefore, the follow-up treatment of cancer survivors and the need for promoting their quality of life have become important issues that need to be addressed in public health [2]. Among women, breast cancer has become the most commonly diagnosed cancer [3]. Despite the prolonged life span of breast cancer patients because of early diagnosis and treatment, numerous studies have reported breast cancer survivors with impaired quality of life associated with long-term chronic psychological stress and negative emotions such as fear and anxiety [4].

Fear of Cancer Recurrence (FCR), defined as fear, worry, or concern about cancer either recurring or progressing, is increasingly recognized as the most prevalent, persistent, and disruptive problems for breast cancer survivors [5]. Excessive FCR becomes a barrier hampering breast cancer survivors' participation of treatment, but also affects their quality of life and prognosis of the disease, thereby increasing the risk of recurrence [6]. Additionally, previous studies demonstrated that breast cancer survivors with high FCR usually show more medical seeking behavior, thus occupying more medical

resources [7]. Currently, researchers had explored the factors affecting FCR of cancer survivors [8], but the brain responses associated with breast cancer survivors' FCR are still unclear.

In neuroscience, functional magnetic resonance imaging (fMRI) with high spatial resolution and non-invasiveness, has provided insights into the association between brain structure and function [9]. Resting state fMRI can exclude the effects of task on the results, and its effectiveness as a method for examining brain function has been reported [10]. In the rs-fMRI literature, Regional homogeneity (ReHo) and Voxel-Mirrored Homotopic Connectivity (VMHC) are two commonly used measures to detect disease-associated regional activity changes in mental disorder. ReHo can reflect the local synchronization of the time courses of the nearest neighboring voxels (usually 27 voxels) based on a voxel-wise measure [11], thus indicating the changes of temporal neuronal activity in specific regional areas. Meanwhile, VMHC aims at accessing interhemispheric FC via analyzing the homotopy connectivity between a specific voxel in one hemisphere and its mirrored voxel in the other side [12]. Therefore, the two indexes could serve as markers of changes in brain dynamics and function in breast cancer survivors with high FCR.

In the present study, we adopted the ReHo and VMHC frameworks to explore the neural mechanisms of breast cancer survivors with fear of cancer recurrence. We examined the functional differences in brain regions between breast cancer survivors with high FCR and individuals with low FCR. We also performed analysis to clarify the relationships between the VMHC values of the different brain regions and FCR scores. On the basis of previous evidence of fear and anxiety in patients [13, 14], we speculate that FCR are related to brain regions of emotion regulation and cognitive function. We hypothesize that both high and low FCR breast cancer survivors would show disrupted ReHo and VMHC, and there would be different ReHo and VMHC patterns between them, which might serve as underlying imaging markers to discern breast cancer survivors with high FCR from patients with low FCR.

Materials And Methods

Participants

62 breast cancer survivors were recruited from the first affiliated hospital of Army Medical University, China, from May to July, 2017. They were investigated by the Fear of Cancer Recurrence Inventory and screened by the cutting score of 12[15], and the subjects with a score of less than 12 were divided into the low FCR group and that of above 12 in the high FCR group. Participants in this study need to meet the following criteria: (1) over 18 years old; (2) education level of junior high school or above; (3) no history of mental illness, cognitive impairment and brain injury; (4) no psychotropic medication and treatment; (5) volunteered to participate in the study. The exclusion criteria for all participants were: (1) pregnancy; (2) cerebral structure abnormalities following initial MRI scanning; (3) contraindications for MRI scan. The study was approved by the Medical Research Ethics Committee of the Army Medical University, China, which is registered with the Chinese Clinical Trial Registry (ChiCTR-OOC-17012132). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Measurement

The 9-item Fear of Cancer Recurrence Inventory (FCRI) is a short form of the FCRI and corresponds to the severity subscale of the FCRI (42 items), which has high correlation to the total score [16]. All items are rated on a Likert scale ranging from 0 ("not at all" or "never") to 4 ("a great deal" or "all the time"). A higher score indicates a higher level of FCR. In this study, Cronbach's α Coefficient is 0.865.

Image Acquisition

Resting-state functional images were acquired with a Siemens 3.0 T scanner (Germany) in the First Affiliated Hospital of the Army Medical University. All participants were placed in a birdcage head coil fitted with foam padding to reduce head motion. During the scanning, the subjects did not need to perform any task, only needed to be in the supine position, eyes opened, still and awake [17, 18]. In this study, routine clinical T1 weighted and T2 weighted MRI scans were carried out, and on-site diagnosis was carried out by two radiology diagnostic doctors, so as to determine whether there was organic craniocerebral abnormality, and the scanning can be continued only when it was clear that there was no such abnormality. The parameters of scanning EPI sequence were set as follows: repetition time (TR) = 2000 ms, echo time (TE) = 30ms, flip angle = 90 °, field of visual (FOV) = 192 × 192 mm^2, voxel size is (3 × 3 × 3) mm^3, the data matrix was (64 × 64), total volumes = 240, the number of scanning layers was 36, and the layer thickness was 3 mm.

Data preprocessing

R-fMRI data were exported to the MATLAB platform, and then were performed using the Statistical Parametric Mapping (SPM8) and Data processing assistant for DPARSF. Subjects needed to be accustomed to the fMRI scanning noise in the initial stage, so the first 10 volumes of each subject's functional time series data were discarded to ensure the overall quality of the image. All images of the whole brain were corrected and realigned in space to eliminate the interference caused by scanning time and head motion. The preprocessed data was processed by band-pass filtering (0.01 to 0.08 Hz). The smoothing of VMHC was different that the preprocessed data was firstly smoothed by FWHM Gaussian kernel (4 mm), and then the VMHC value was obtained, and finally processed by filtering (0.01 to 0.08 Hz). As factors such as white matter, head movement and cerebrospinal fluid signals may interfere with further analysis, this signal and head movement parameters in 6 directions should be regressed as covariates. Then, data were nomalized to a standard corresponding MNI template.

ReHo analysis

The Kendall Coefficient of Concordance (KCC) was applied to calculate the similarity of the time series in the functional cluster between a single voxel and the surrounding 27 voxels based on ReHo. KCC value is used to measure the consistency and similarity of time series for adjacent voxels. The individual difference of the whole brain signal can be reduced by dividing the KCC value of each voxel with the average KCC value of the whole brain, so as to obtain the average KCC brain map of each subject, which can also be understood as the average ReHo brain map. The Gaussian kernel (4mm) of FWHM was used to smooth the image, so as to improve its signal-to-noise ratio.

After the ReHo brain maps of the two groups were obtained, the difference between the mean values of the two groups was tested by two-sample *t*-test, which was considered to be statistically significant with $p < 0.05$, and Gaussian random field (GRF) correlation was performed ($p < 0.01$, $z > 2.32$). In order to examine whether ReHo value has significant correlation with FCR, the Pearson correlation coefficient analysis was performed on the ReHo value and FCR score.

VMHC analysis

The REST software was applied to perform the VMHC analysis. We calculated the homotopic FC as the Pearson correlation between each voxel's residual time series and that of its interhemispheric mirrored voxel for each subject. The Fisher z-transformation of the coefficients was used to improve normality, and the whole-brain VMHC map of each participant was generated.

Two-sample *t*-test and multiple corrections through GRF method ($p < 0.01$ and $z > 2.32$) were performed to clarify the difference range of VMHC values between high FCR group and low FCR group. Based on this, the difference range between groups was regarded as ROI (region of interest), and the mean value of VMHC intensity in patient ROI was extracted. Pearson correlation analysis was used to analyze the correlation between the average intensity of VMHC in abnormal brain areas and FCR score.

Statistical analysis

Statistical analyses were performed using SPSS version 23. Intergroup differences in age, education level, yearly family income and main clinical characteristics between breast cancer survivors with high FCR and low FCR were determined with ANOVA. A significant difference was defined as a two-tailed *P* value <0.05.

Results

Demographic and clinical characteristics

62 subjects were recruited in the experiment. The data of 3 subjects with low FCR were eliminated because they had not completed all the experiments. Finally the data of 59 subjects were obtained, including 28 in the low FCR group and 31 in the high FCR group.

No statistically significant differences were revealed in age, education level, yearly family income, time since cancer diagnosis, TNM staging and cancer treatment received between high FCR group and low FCR group. The statistics of demographic variables and clinical characteristics were shown in Table 1.

Table 1 Comparison of demographic and clinical characteristics between low FCR group and high FCR group

	Low FCR (n=28)	High FCR (n=31)	χ2 Value	*P* Value (two-tailed)
Age			6.065	0.054
<30	0(0%)	0(0%)		
30≤Age<40	3(10.71%)	6(19.36%)		
40≤Age<50	19(67.86%)	11(35.48%)		
Age≥50	6(21.43%)	14(45.16%)		
Education level			0.797	0.671
junior high school	10(35.71%)	8(25.81%)		
High school	8(28.58%)	9(29.03%)		
University	10(35.71%)	14(45.16%)		
Yearly family income(RMB)			5.070	0.151
<50,000	3(10.71%)	0(0%)		
50,000≤income<100,000	10(35.71%)	8(25.81%)		
100,000≤income<300,000	8(28.58%)	9(29.03%)		
≥300,000	7(25%)	14(45.16%)		
Time since cancer diagnosis			2.156	0.190
Time<2 years	12(42.86%)	17(54.84%)		
2years≤ time< 5years	12(42.86%)	13(41.95%)		
5years≤ time<10years	3(10.71%)	1(3.23%)		
≥10 years	1(3.57%)	0(0%)		
TNM staging			0.594	0.897
I	5(17.86%)	6(19.36%)		
II	21(75%)	24(77.42%)		
III	2(7.14%)	1(3.23%)		
IV	0(0%)	0(0%)		
Cancer treatment received			1.725	0.614
mastectomy	27(96.43%)	27(87.10%)		
Conservative therapy	0(0%)	1(3.23%)		

	Low FCR (n=28)	High FCR (n=31)	χ2 Value	*P* Value (two-tailed)
Mastectomy+ breast construction	1(3.57%)	3(9.67%)		

Group differences in ReHo

The ReHo value in the high FCR group in the left caudate nucleus was higher than those in the low FCR group. The ReHo value in the high FCR group in the right precuneus lobe was lower than those in the low FCR group ($p < 0.01$). The specific results were shown in Figure 1 and Table 2.

Table 2 ReHo differences between high FCR group and low FCR group

Brain region	BA	MNI coordinate			*t value*	Number of voxels(mm^3)
		x	y	z		
left caudate nucleus	47	-12	21	-27	4.548	99
right precuneus lobe	7	21	-78	36	-5.230	93

Note. MNI = Montreal Neurological Institute. BA=Broadmann GRF corrected: $p < 0.01$, $Z > 2.32$

Group differences in VMHC

According to ANOVA analysis, there were significant VMHC differences in the posterior cerebellar lobe, superior frontal gyrus, inferior frontal gyrus, superior occipital gyrus, inferior parietal lobule and middle frontal gyrus between groups.

Relative to low FCR group, high FCR patients displayed significant increased VMHC in the posterior lobe of cerebellum, middle frontal gyrus and inferior frontal gyrus, and decreased VMHC in the superior occipital gyrus and inferior parietal lobule (Table 3 and Figure 2).

Table 3 VMHC differences between high FCR group and low FCR group

Brain regions	BA	MNI coordinate			*t* value	Number of voxels(mm^3)
		x	y	z		
Right posterior cerebellar lobe		57	-60	-39	3.768	102
Left posterior cerebellar lobe		-36	-81	-42	3.690	98
Right superior frontal gyrus	9	12	27	-24	3.400	84
Left superior frontal gyrus	9	-12	27	-24	3.400	84
Left inferior frontal gyrus	13	-36	18	18	3.851	95
Right inferior frontal gyrus	13	36	18	18	3.851	90
Left superior occipital gyrus	19	18	-75	30	-3.103	109
Right superior occipital gyrus	19	-18	-75	30	-3.103	109
Left inferior parietal lobule	40	-42	-33	24	-4.045	87
Right inferior parietal lobule	40	-42	-33	24	-4.045	94
Left middle frontal gyrus	6	-9	0	48	3.166	80
Right middle frontal gyrus	6	15	-9	51	3.452	81

Note. MNI = Montreal Neurological Institute. BA: Broadmann (GRF corrected: $p<0.01$, $Z > 2.32$).

Correlations results

The left caudate nucleus was negatively correlated with FCR ($p < 0.05$), and the correlation coefficient was -0.501. The right precuneus lobe was positively correlated with FCR scores ($p < 0.05$), and the correlation coefficient was 0.505 (Figure 3). Besides, VMHC in bilateral superior occipital gyrus was positively correlated with the total score of FCR ($p < 0.05$), and the correlation coefficient was 0.438 (Figure 4).

Disscussion

To our knowledge, this is the first study to explore the functional changes of regional brain areas in breast cancer survivors with fear of cancer recurrence based on ReHo and VMHC values. ReHo analysis suggests that the brain regions with significant differences between the two groups are mainly the caudate nucleus and precuneus. As a multidimensional emotion characteristic, FCR brought about the enhancement of the temporal consistency of neuronal activity in the left caudate nucleus and the decrease of the temporal consistency of neuronal activity in the right precuneus. Furthermore VMHC results indicates that there was a significant difference in the signal activity and functional connectivity of the two groups in the posterior cerebellar lobe, the superior frontal gyrus, the orbital part, the inferior frontal gyrus, the occipital gyrus, the inferior parietal lobule and the frontal middle gyrus.

ReHo is considered as a data-driven method with high test-retest reliability [19]. This method could measure the instantaneous changes of spontaneous behavior of neurons in local brain area one by one while avoiding the interference of confounding factors of different task paradigm. This study reveals that ReHo value of the left caudate nucleus of breast cancer survivors with high FCR was increased. As an important structure of striatum, caudate nucleus is a key constituent unit of basal ganglia, which plays an important role in reward response [20]. Caudate has non-specific responses to various emotional stimuli, such as responding to reward events or signals, but not to signals without reward. Therefore, it has been considered that the caudate nucleus is an important region to ensure that individuals can respond flexibly to the environment [21]. Additionally, the researchers found that the caudate nucleus plays a crucial role an important component of the emotional regulation circuit in the formation of the neural regulation circuit of cortex-striatum-globus pallidus-thalamus. This circuit cooperates with the limbic system-prefrontal circuit to cooperate with the regulatory mechanism to deal with external positive or negative stimuli. Therefore, if the related functions and structures of caudate nucleus are abnormal, it could lead to the disorder of the whole emotion regulation system and the occurrence of negative emotion [22]. Similar results were obtained in fMRI experiments of animals that the caudate nucleus affected emotional decision-making and pessimism, and the abnormal activity of the caudate nucleus may interfere with dopamine activity to some extent [23]. Therefore, dysfunction and abnormal activity of caudate nucleus may lead to increased sensitivity to cancer related emotional stimuli for breast cancer survivors in their daily life, which easily led to more FCR.

Meanwhile, the right precuneus was found to be a brain region with significant differences between the two groups in the study. As an important part of the default network of the brain, precuneus is distributed in the inner range of the parietal lobe. It is the constituent node of DMN with the most active brain area of neurons in the resting state, and is related to cognitive function, working memory and emotional processing [24, 25]. Our study found that the ReHo value of the right precuneus in patients with high FCR was higher than that in patients with low FCR, and there was a significant positive correlation with FCR. As the key brain region of DMN, if the functional synergy between precuneus and other brain regions of DMN is weakened, it will interfere with the functional synergy (or resource allocation) within DMN and between DMN and other brain networks, resulting in the fear of cancer recurrence.

It is noteworthy that ReHo method only reflects the functional connection of local brain tissue and cannot evaluate the abnormal state of function between the same hemisphere with abnormal ReHo value, VMHC method based on voxel level could make up for the shortcoming [26]. Through rigid calibration, the latter can make both cerebral hemispheres achieve symmetry on the anatomical level, so as to evaluate the timing and connection degree of resting state between allovoxels in the same brain region of both cerebral hemispheres. The results of this study suggest that there are significant differences between the two groups of breast cancer survivors who had high FCR in the posterior cerebellar lobe, superior frontal gyrus, orbital part, inferior frontal gyrus, occipital lobe gyrus, inferior parietal lobule and middle frontal gyrus. The VMHC values of the two groups increase in the posterior cerebellar lobe, the middle frontal gyrus and the inferior frontal gyrus, and the VMHC values in the occipital gyrus and the inferior parietal lobules decrease. The role of frontal lobe in emotional-cognitive activities has been confirmed by a large

number of studies, which is closely related to advanced cognitive activities such as emotional regulation, working memory and executive function. The frontal lobe plays an important role in both the formation and expression of fear and the development of fear [27, 28]. This study also found the changes of VMHC in the frontal lobe of patients with fear of cancer recurrence, indicating the abnormal synergy of bilateral frontal lobe function. In addition, we found that there are differences in occipital and parietal lobe between two groups. This is consistent with the previous research findings that fear threat stimulation could activate the occipital lobe and parietal lobe, and is also involved in the regulation of emotion [29].

Several limitations warrant consideration in this study. First, the sample size is relatively small, which may affect statistical efficiency. Second, the relationship between FCR and brain areas is limited by the cross-sectional design in the present study, so we need to conduct intervention to examine the changes of these brain regions in the future. Third, the causality between such functional abnormality and FCR seems unclear.

Conclusion

This study provides a novel perspective on FCR of breast cancer survivors. Resting-State fMRI could help us better understand the relationships of FCR and brain function of breast cancer survivors. It represents a significant improvement over the previous measurements of self-report questionnaires in the past decades. Furthermore, clarifying the specific changes in brain function activities could provide the target for evaluating the effectiveness of intervention training to reduce the fear of cancer recurrence of breast cancer survivors in future work.

Declarations

Ethical Approval and Consent to participate

The study was approved by the Medical Research Ethics Committee of the Army Medical University, China, which is registered with the Chinese Clinical Trial Registry (ChiCTR-OOC-17012132). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of supporting data

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Li Peng designed the experiment and wrote the main manuscript text; Xiaofei Hu and Yuan Xue conducted the scan and data analysis; Chen Xu and Ju Liu edited the article; Ying Yang, Lin Zhong, Jiannan Chen and Aiping Qi recruited the participants; Min Li guided the whole experiment.

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References

[1]Zhang X, Sun D, Qin N, Liu M, Jiang N, Li X. Factors Correlated with Fear of Cancer Recurrence in Cancer Survivors: A Meta-analysis. Cancer Nurs. 2021; 23.

[2] Luo X, Li W, Yang Y, Humphris G, Zeng L, Zhang Z, Garg S, Zhang B, Sun H. High Fear of Cancer Recurrence in Chinese Newly Diagnosed Cancer Patients. Front Psychol. 2020; 11:1287.

[3]Schapira L, Zheng Y, Gelber SI, Poorvu P, Ruddy KJ, Tamimi RM, Peppercorn J, Come SE, Borges VF, Partridge AH, Rosenberg SM. Trajectories of fear of cancer recurrence in young breast cancer survivors. Cancer. 2021; 6.

[4]Omidi Z, Kheirkhah M, Abolghasemi J, Haghighat S. Effect of lymphedema self-management group-based education compared with social network-based education on quality of life and fear of cancer recurrence in women with breast cancer: a randomized controlled clinical trial. Qual Life Res. 2020; 29(7):1789-1800.

[5]Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncology (Williston Park). 2018; 32(1):32-38.

[6]Kim SJ, Kang D, Kim IR, Yoon SE, Kim WS, Butow PN, Guallar E, Cho J. Impact of fear of cancer recurrence on survival among lymphoma patients. Psychooncology. 2020; 29(2):364-372.

[6]Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for clinical presentation and management. Psychooncology. 2017; 26(10):1444-1454.

[7]Pudkasam S, Polman R, Pitcher M, Fisher M, Chinlumprasert N, Stojanovska L, Apostolopoulos V. Physical activity and breast cancer survivors: Importance of adherence, motivational interviewing and

psychological health. Maturitas. 2018; 116:66-72.

[8]Tauber NM, O'Toole MS, Dinkel A, Galica J, Humphris G, Lebel S, Maheu C, Ozakinci G, Prins J, Sharpe L, Smith AB, Thewes B, Simard S, Zachariae R. Effect of Psychological Intervention on Fear of Cancer Recurrence: A Systematic Review and Meta-Analysis. J Clin Oncol. 2019; 37(31):2899-2915.

[9]Smitha KA, Akhil Raja K, Arun KM, Rajesh PG, Thomas B, Kapilamoorthy TR, Kesavadas C. Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. Neuroradiol J. 2017; 30(4):305-317.

[10] Lei D, Ma J, Du X, Shen G, Tian M, Li G. Spontaneous brain activity changes in children with primary monosymptomatic nocturnal enuresis: a resting-state fMRI study. Neurourol Urodyn. 2012; 31(1):99-104.

[11] Jiang L, Zuo XN. Regional Homogeneity: A Multimodal, Multiscale Neuroimaging Marker of the Human Connectome. Neuroscientist. 2016; 22(5):486-505.

[12] Mancuso L, Costa T, Nani A, Manuello J, Liloia D, Gelmini G, Panero M, Duca S, Cauda F. The homotopic connectivity of the functional brain: a meta-analytic approach. Sci Rep. 2019; 9(1):3346.

[13]Chauret M, Suffren S, Pine DS, Nassim M, Saint-Amour D, Maheu FS. Fear conditioning and extinction in anxious youth, offspring at-risk for anxiety and healthy comparisons: An fMRI study. Biol Psychol. 2019; 148:107744.

[14]Chen Y, Wu Y, Mu J, Qiu B, Wang K, Tian Y. Abnormal fear circuits activities correlated to physical symptoms in somatic anxiety patients. J Affect Disord. 2020; 274:54-58.

[15]Peng L, Huang W, Zhang W, Xu Y, Lu F, Zhong L, Chen X, Xu S, Chen W, Li M. Psychometric Properties of the Short Form of the Fear of Cancer Recurrence Inventory (FCRI) in Chinese Breast Cancer Survivors. Front Psychiatry. 2019; 10:537.

[16] Fardell JE, Jones G, Smith AB, Lebel S, Thewes B, Costa D, Tiller K, Simard S, Feldstain A, Beattie S, et al. Exploring the screening capacity of the Fear of Cancer Recurrence Inventory-Short Form for clinical levels of fear of cancer recurrence. Psychooncology. 2018; 27(2):492-99.

[17] Tang YL, Ji GJ, Yu Y, Wang J, Wang ZJ, Zang YF, Liao W, Ding MP. Altered regional homogeneity in rolandic epilepsy: a resting-state FMRI study. Biomed Res Int. 2014; 2014:960395.

[18] Yuan BK, Zang YF, Liu DQ. Influences of Head Motion Regression on High-Frequency Oscillation Amplitudes of Resting-State fMRI Signals. Front Hum Neurosci. 2016; 10:243.

[19] Liu S, Ma R, Luo Y, Liu P, Zhao K, Guo H, Shi J, Yang F, Tan Y, Tan S, et al. Facial Expression Recognition and ReHo Analysis in Major Depressive Disorder. Front Psychol. 2021; 12:688376.

[20] Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage. 2004; 22(1):394-400.

[21] Villablanca JR. Why do we have a caudate nucleus? Acta Neurobiol Exp (Wars). 2010; 70(1):95-105

[22] Filipovic BR, Djurovic B, Marinkovic S, Stijak L, Aksic M, Nikolic V, Starcevic A, Radonjic V. Volume changes of corpus striatum, thalamus, hippocampus and lateral ventricles in posttraumatic stress disorder (PTSD) patients suffering from headaches and without therapy. Cent Eur Neurosurg. 2011; 72(3):133-7.

[23] Amemori K, Amemori S, Gibson DJ, et al. Striatal Microstimulation Induces Persistent and Repetitive Negative Decision-Making Predicted by Striatal Beta-Band Oscillation. Neuron. 2018; 99(4):829-41.

[24] Deco G, Jirsa VK, McIntosh AR. Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat Rev Neurosci. 2011; 12(1):43-56.

[25] Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain. 2006; 129(3):564-83.

[26] Chen J, Sun D, Shi Y, Jin W, Wang Y, Xi Q, Ren C. Altered static and dynamic voxel-mirrored homotopic connectivity in subacute stroke patients: a resting-state fMRI study. Brain Imaging Behav. 2021; 15(1):389-400.

[27] Killgore WD, Britton JC, Schwab ZJ, Price LM, Weiner MR, Gold AL, Rosso IM, Simon NM, Pollack MH, Rauch SL. Cortico-limbic responses to masked affective faces across ptsd, panic disorder, and specific phobia. Depress Anxiety. 2014; 31(2):150-9.

[28] Spalding KN. The role of the medial prefrontal cortex in the generalization of conditioned fear. Neuropsychology. 2018; 32(1):1-17.

[29] Lai CH. Fear Network Model in Panic Disorder: The Past and the Future. Psychiatry Investig. 2019; 16(1):16-26.

Figures

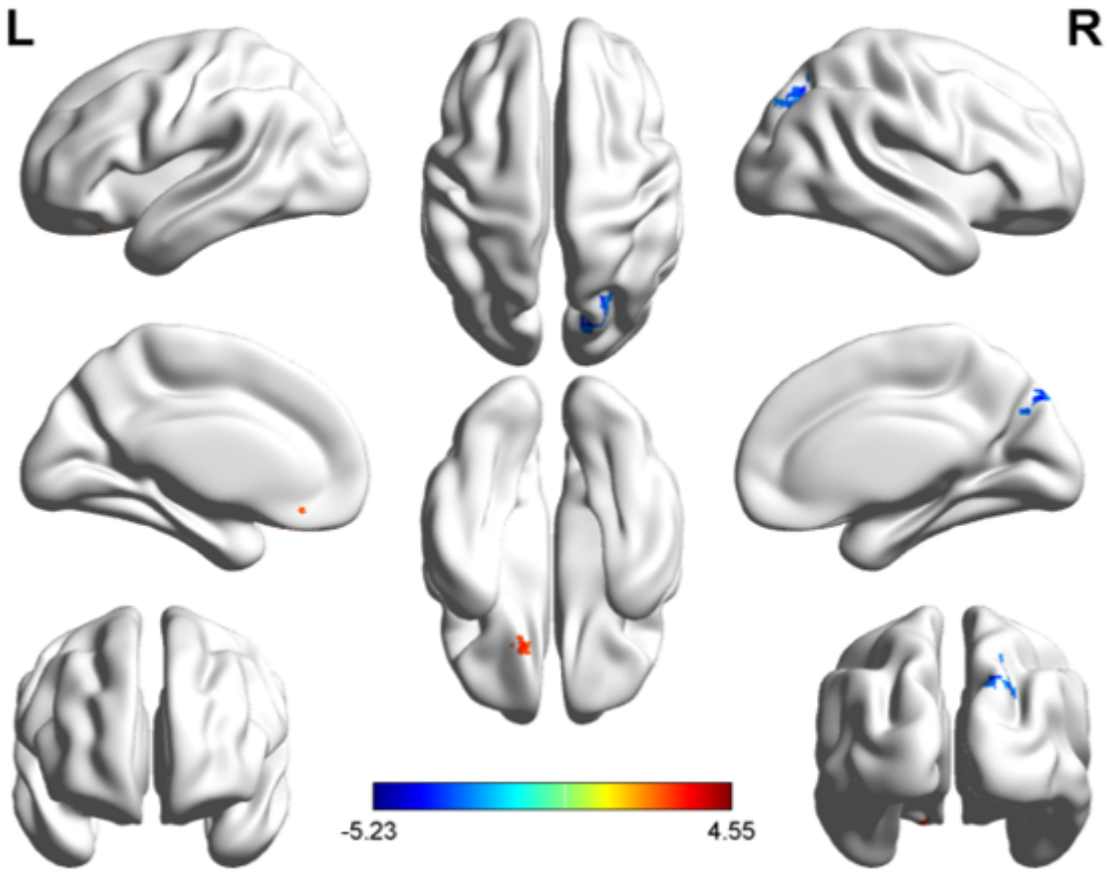

Figure 1

Brain regions with abnormal ReHo between high FCR group and low FCR

group. Red and blue colors denote decreased and increased ReHo. The color bars indicate the *t*-value. Results were GRF corrected.

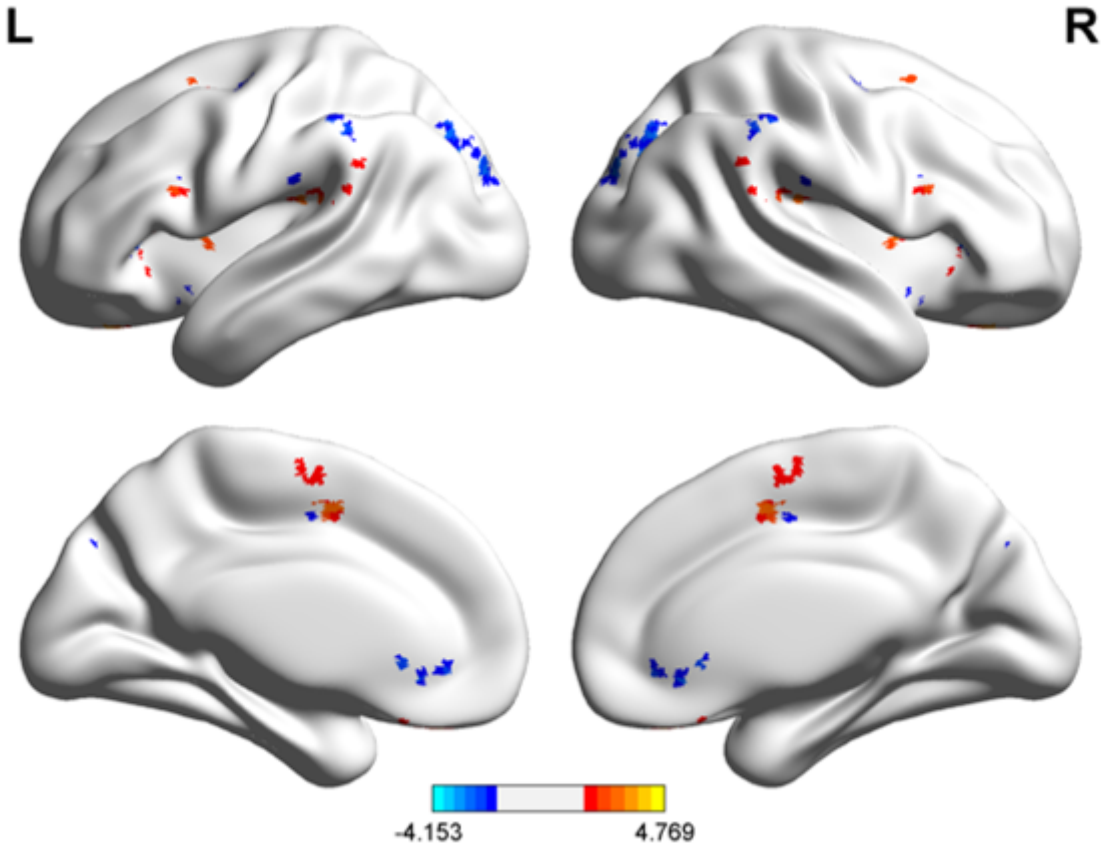

Figure 2

Brain regions with abnormal VMHC between high FCR group and low FCR group. Red and blue colors denote decreased and increased VMHC. The color bars indicate the *t*-value. Results were GRF corrected (GRF corrected: $p<0.05$, $Z > 1.65$).

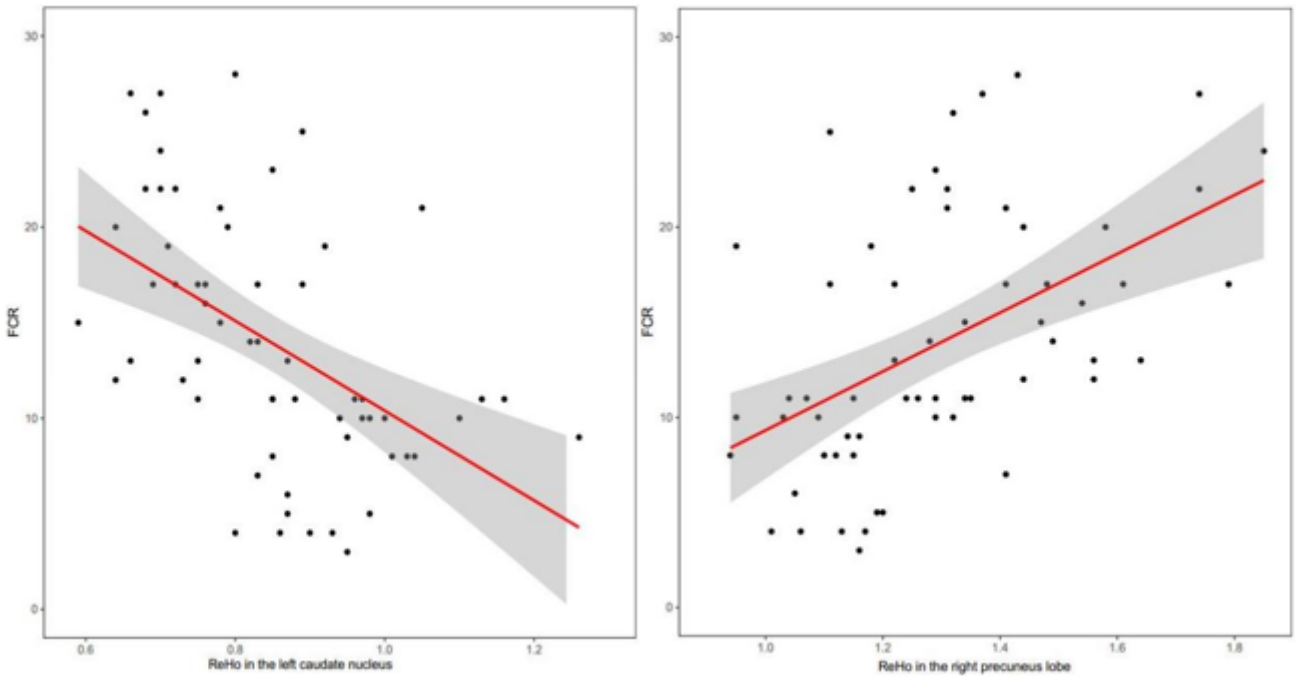

Figure 3

Correlations between the ReHo of abnormal brain regions and FCR scores

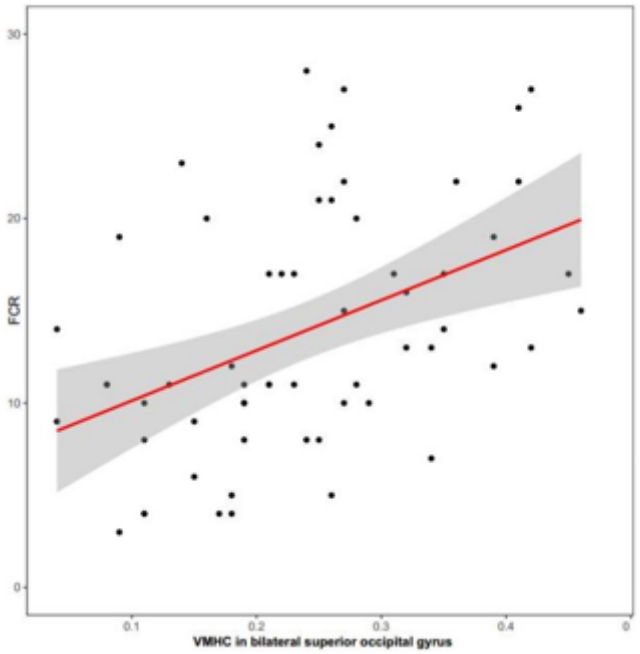

Figure 4

Correlations between the VMHC of abnormal brain regions and FCR scores