Is Activity Changes of the DMN an Indicator of Women's Depression After Breast Cancer Surgery?

Jinwen Huang
Zhejiang Chinese Medical University
Luping Zhang
Hangzhou Hospital of Traditional Chinese Medicine
Xiufei Gao
Zhejiang Hospital of Traditional Chinese Medicine
Xiangzhen Zhu
Zhejiang Hospital of Traditional Chinese Medicine
Fan Zhang
Zhejiang Chinese Medical University
Wenwen Song
Zhejiang Hospital of Traditional Chinese Medicine
Maosheng Xu
Zhejiang Chinese Medical University
Zhijian Cao (20001010@zcmu.edu.cn)
Zhejiang Chinese Medical University https://orcid.org/0000-0002-6330-7777

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Abstract

Objective

To investigate the correlation between changes of the brain's default mode network (DMN) activity and clinical scale scores in patients with depression after breast cancer surgery using resting-state functional magnetic resonance imaging (rs-fMRI) based on the amplitude of low frequency fluctuations (ALFF) and the regional homogeneity (ReHo), to explore whether activity changes of the DMN can be an indicator of women's depression after breast cancer surgery.

Methods

The institutional Ethics Committee has approved this prospective study. Twenty-three patients were followed after breast cancer surgery, including 12 cases with postoperative depression and 11 cases without depression. All patients underwent rs-fMRI. The ALFF and ReHo values were obtained and converted to Z values for statistical analysis. Pearson and Spearman correlation analysis were performed to correlate the clinical scale scores with ALFF value and ReHo value. A two sample T-test was conducted for ALFF and ReHo values of patients in two groups.

Results

The ALFF value of the right precuneus was negatively correlated with the Hamilton anxiety scale (HAMA) score ($r = -0.43$, $P < 0.05$). The full-scale attention quotient (FSAQ) score was positively correlated with the ALFF value of the left angular gyrus ($r = 0.44$, $P < 0.05$) and the right supramarginal gyrus ($r = 0.50$, $P < 0.05$). The ReHo value of the right angular gyrus was positively correlated with self-rating depression scale (SDS) score ($r = 0.45$, $P < 0.05$) and HAMA score ($r = 0.49$, $P < 0.05$). There were significant correlations between the clinical scale scores and the ALFF values and ReHo values of the DMN regions in patients after breast cancer surgery, but no statistical difference in ALFF and ReHo values between patients with and without depression after breast cancer surgery.

Conclusions

Activity changes of the DMN in patients were closely related to the attention deficit in depressive disorder and anxiety in patients who had recently undergone breast cancer surgery. Meanwhile, the change of neuronal synchronization in the right angular gyrus may be closely associated with the pathophysiology of anxiety. Rs-fMRI can help to better detect and evaluate depression in patients after breast cancer surgery.

Background

Depressive disorder is a major mental illness characterized by persistent changes in affect, lack of interest and attention deficit, with a lifetime prevalence of about 3.3%.[1] According to the World Health Organization (WHO), at least 350 million people worldwide suffer from depression. Epidemiological research has shown a significant gender preference in depressive disorder, with the prevalence in women being higher than that in men by about 2 times. Female patients with depressive disorder are more likely to be accompanied by somatization and anxiety symptoms, and more likely to commit suicide, which is the leading cause of disability among women globally.[2-3] In recent years, many studies have focused on the clinical symptoms of depression and investigated the specific changes in cortical activity responsible for depressive symptoms. However, the relationship between these changes and the clinical symptoms of depression remained unclear.

On the other hand, breast cancer is one of the most common and threatening malignancies in women, and also the leading cause of cancer-related death.[4] Previous studies have shown an increased prevalence of depressive disorder in patients with breast cancer,[5-6] and the tendency of depression after breast cancer surgery is particularly prominent.[7] It has also been found that the presence of such symptoms increases the probability of cancer recurrence after surgery,[5] directly or indirectly affect the quality of life and treatment outcomes of patients with breast cancer.[8-9] Furthermore, treatment for breast cancer may lead to unintended consequences, such as menopausal symptoms,[10] impaired body image[11] and impaired sexual function,[12] which adversely affect the patient. According to current research, the effect of stress on tumor growth and metastasis has been clearly demonstrated in animal models.[13] In particular, it should be noted that previous studies have noted that successful treatment of mood symptoms following surgery can greatly increase patient follow up in those with metastatic breast cancer.[14] These findings suggest that clinicians should focus on treating both the physiologic and psychologic components of breast cancer for optimal treatment outcome.

For this study, we examined patients with and without depression after breast cancer surgery. This was not only to draw attention to the comorbidity of mood symptoms along with malignancy but also to control for confounding factors as much as possible. Rs-fMRI uses blood oxygen level-dependent signals to observe brain activity noninvasively. In this study, rs-fMRI was used to explore the correlation between changes of cerebral cortical activity and clinical scale scores in patients with depression after breast cancer surgery. In addition, ALFF and ReHo values were expected to be used as indexes in the clinical practice of secondary prevention (early detection, early diagnosis and early treatment) of depressive disorder in patients after breast cancer surgery.

Methods

2.1 Participants

From October 2016 to November 2018, a total of 24 patients after breast cancer surgery (including 12 patients with postoperative depression) were recruited from The First Affiliated Hospital of Zhejiang Chinese Medical University. All patients with postoperative depression met the diagnostic criteria for depression in the fourth edition of the American Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The following exclusion criteria were applied in this study: (a) history of psychiatric disorders such as depression and neuropathy before the diagnosis of breast cancer, (b) history of intracranial organic lesions such as cerebral space-occupying lesions and vascular lesions, (c) history of severe craniocerebral trauma, (d) history of drug or alcohol abuse or dependence, (e) history of prophylactic medication within one year, (f) having contraindications to MRI such as metal implants and claustrophobia, and head motion more than 1.0 mm or 1.0° during MR imaging. All subjects were informed of the contents and methods of the experiment before the examination and signed written consent. This project was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang Chinese Medical University (2016-K-100-01).

2.2 Data collection

All subjects self-identified as right-handed and completed evaluation of relevant clinical scales before MR imaging; including the Hamilton depression scale (HAMD), Hamilton anxiety scale (HAMA), self-rating depression scale (SDS), self-rating anxiety scale (SAS) and full-scale attention quotient (FSAQ). All patients were then evaluated by psychiatrists. Patients were divided into two groups, with those having a HAMD score above 7 as showing post-operative depression.

The fMRI data was acquired using a 3-T MR Scanner (Discovery 750, GE, America) with a 12-channel phased array head coil. Foam padding was placed between the head and the coil to minimize motion artifacts. All subjects were instructed to keep still their eyes closed while avoiding specific thought. However, subjects were instructed to remain awake and scanning commenced once they were comfortable with their surroundings. Routine scans (T1WI, T2WI and DWI) were performed to rule out intracranial organic lesions such as cerebral space-occupying lesions and vascular lesions. Functional data was collected by using a gradient-echo echo-planar sequence with the following parameters: axial slices = 30, repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle (FA) = 90°, field of view (FOV) = 256×256 mm, 64×64 matrix, thickness / gap = 4.0 mm / 1.0 mm. The scanning time was 6 minutes and 180 phases were collected.

2.3 Data processing

The data preprocessing procedures were carried out using the Data Processing Assistant for Resting-state fMRI (DEPRSF) program on the Matlab R2016b platform, which is based on the Statistical Parametric Mapping tool (SPM) and Resting-state fMRI data analysis Toolkit (REST). The first 10 time points were discarded to remove the possible effects of the uneven magnetic field and patient factors at the start of the scan. Slice timing and head motion correction were then performed. The data from one participant was excluded at this point due to excessive head motion (over 1.0 mm of translation or over 1.0° rotation). The diffeomorphic anatomical registration through exponential lie algebra (DARTEL) template was used for spatial normalization.

Covariates such as head movement parameters (Friston 24), cerebrospinal fluid (CSF) signal, white matter signal and linear drift were removed. A band-pass filter (0.01-0.08 Hz) of the functional data as performed to remove reduced low-frequency drifts and high-frequency physiological noise. The ALFF and ReHo values were obtained and converted to a Z score for statistical analysis.

2.4 Statistical analyses

By using the Statistical Product and Service Solutions (SPSS, version 26.0), the normality of demographic data and clinical scale scores were tested and a two-tailed independent sample t-test was conducted to compare differences between patients with postoperative depression and those without after breast cancer surgery. The results were shown as mean ± standard deviation and difference was considered statistically significant at $p < 0.05$. Additionally, the correlation between ALFF and ReHo values and clinical scale scores was examined using the Pearson or Spearman correlation analysis. All results were considered statistically significant at $p < 0.05$.

A Two sample T-test was performed for ALFF and ReHo values of patients with and without postoperative depression after breast cancer surgery by using SPM12. The results were corrected by GRF (Gaussian Random Field Theory correction). The statistical threshold was set as a single voxel $p < 0.001$ and cluster size > 50 voxels. After the Family Wise Error (FEW) multiple corrections, the values were considered statistically significant at $p < 0.05$.

Results

3.1 Participant characteristics

One patient was excluded by head motion correction. Eventually, 12 patients with postoperative depression (mean age±standard deviation, 49.50 years ± 9.73) and 11 patients without depression after breast cancer surgery (mean age±standard deviation, 46.18 years ± 8.47) were included in the final data analysis. All subjects were female, and no significant difference was found in the age in patients with and without depression after breast cancer surgery ($P > 0.05$). There were significant differences ($P < 0.05$) in clinical scale scores between the two groups. Demographic and clinical data were shown in Table 1.

Table 1. Demographics and Clinical Data			
Parameter	+ Depression after breast cancer surgery (n =12)	- Depression after breast cancer surgery (n =11)	P value
Age (y)	49.50±8.52	46.18±8.47	0.360
HAMD	17.83±10.37	3.82±1.99	<0.001
HAMA	15.83±6.38	6.45±2.81	<0.001
SDS	49.92±11.29	34.73±6.78	0.001
SAS	43.17±9.88	32.64±6.65	0.007
FSAQ	77.33±26.14	99.64±6.27	0.012

Note: Data represented as mean ± standard deviation.

Abbreviations: FSAQ: full scale attention quotient; HAMA: Hamilton anxiety scale; HAMD：Hamilton depression scale; SAS: self-rating anxiety scale; SDS: self-rating depression scale.

3.2 Correlation between ALFF/ ReHo value and clinical scale score

There was a negative correlation between the ALFF value of the right precuneus (PCUN_R) and HAMA score (r = -0.43, *P = 0.039*, Figure 1a) in patients after breast cancer surgery. The FSAQ score was also found to be positively correlated with the ALFF value of the left angular gyrus (ANG_L) (r = 0.45, *P = 0.033*, Figure 1b) and the right supramarginal gyrus (SMG_R) (r = 0.50, *P = 0.015*, Figure 1c).

The ReHo value of the right angular gyrus (ANG_R) was positively correlated with SDS score (r = 0.45, *P = 0.033*, Figure 2a) and HAMA score (r = 0.49, *P = 0.018*, Figure 2b) in patients after breast cancer surgery.

3.3 Comparison of ALFF/ ReHo value between postoperatively depressed patients and non-depressed patients and normal templates

There was no statistical difference in ALFF and ReHo values between patients with depression after breast cancer surgery and those without. However, as shown in Figure 3, significant differences in cerebral cortical activity of patients with post-operative depression were found by comparison with the original template in SPM12. The ALFF value of the right precuneus, the left angular gyrus and the right supramarginal gyrus decreased in patients with depression, while the ReHo value of the right angular gyrus increased. This finding correlated with the clinical scale scores.

Discussion

When local neurons of the brain are excited, the oxygen saturation of blood increases in the corresponding region. Rs-fMRI reflects the change of local brain activity by detecting the change of local oxygen saturation in the brain. ALFF reflects the fluctuation of regional cerebral blood flow signal, which is an index to reflect the strength of spontaneous activity of neurons.[15] By calculating the Kendall's concordance coefficient of the time series between a voxel and its adjacent voxels, ReHo suggests the synchronization of the time series of neural activity among adjacent voxels in the brain region, reflecting the consistency of spontaneous activity of neurons in this brain region.[16] ReHo analysis assumes that the hemodynamic characteristics of voxels are similar in functionally in similar clusters and are dynamically synchronized. Therefore, an abnormal ReHo score can suggest a local functional imbalance.[17] ReHo has also shown sensitivity to various neuropsychiatric disorders associated with cognitive and emotional changes,[18] such as depression and social anxiety.

The concept of DMN was put forward by Raichle et al. in 2001. It is believed that some brain regions maintain a high level of activity in the quiet and awake state (i.e. resting state) despite there being no active task. When stimulated, these brain regions are then inhibited due to decreased functional activity during task execution.[19] These regions include the medial prefrontal cortex, cingulate gyrus, precuneus and inferior parietal lobule (including angular gyrus and supramarginal gyrus) which participate in episodic memory extraction, environmental awareness and self-related processing,[20] and regulate attention and cognition in a wider range.[21-22] Contrary to purposeful thinking activities related to external tasks, the DMN is involved in self-referential internal thinking activities, and tasks that require attention often lead to a reduction in DMN activities.[23-24]

The precuneus, angular gyrus and supramarginal gyrus are all important components of the DMN. The precuneus is involved in advanced cognitive processes, including visuospatial image processing, episodic memory retrieval, self-related processing and consciousness.[25-27] It participates in self-related mental representation at rest and shows greater activity at rest than when computing external tasks.[26-28] Both the angular gyrus and supramarginal gyrus are components of the inferior parietal lobule and are involved in visuospatial attention,[29] episodic memory,[30] mathematical cognition[31] and language.[32]

The results showed that the ALFF value of the precuneus was negatively correlated with the HAMA score. That is, patients with a lesser degree of spontaneous precuneus activity had greater levels of anxiety. The ALFF value of the inferior parietal lobule (angular gyrus and supramarginal gyrus) was positively correlated with the FSAQ score. Patients with lesser spontaneous activity of the inferior parietal lobe had a lower FSAQ score, indicating decreased attention.

These results were consistent with the clinical symptoms of patients with depression, wherein patients with greater attention deficits and anxiety showed decreased spontaneous activity of the precuneus and the inferior parietal lobule (angular gyrus and supramarginal gyrus) in the resting state. Contrary to the spontaneous activity enhancement in the DMN of normal people, the spontaneous activity in the DMN of patients with depression decreases in the resting state. This may weaken the ability of patients with depression to retrieve episodic memory, assess the surrounding environment, conduct self-related processing and self-referential internal thinking activities. These findings can result in clinical symptoms such as depression, anxiety, abnormal increase of self-attention and attention deficit.

In addition, it was also found that the ReHo value of the right angular gyrus was positively correlated with the SDS score and the HAMA score. This means that patients with a stronger synchronization of neuronal activity in the right angular gyrus showed more severe anxiety and self-conscious depression. A growing body of evidence shows that the bilateral angular gyrus is strongly involved in mental activity and the right angular gyrus is related to the disturbance of action consciousness. [33-35] As such, patients with lesions involving the right angular gyrus will have changes in autonomous behavior consciousness, affecting the predictive control of voluntary behavior.[36-37] In this study, the abnormal enhancement of neuronal synchronization in the right angular gyrus was positively correlated with the degree of self-evaluated depression, but not with the score of depression scale evaluated by others. This finding was attributed to the change of autonomous behavior consciousness, rendering the self and external evaluations inconsistent.

From previous research studies, it is known that anxiety is the most common concomitant symptom of depression.[38] Furthermore, both depression and anxiety are common in breast cancer patients.[4] Disordered emotional and cognitive processes are considered to be an important part of the pathophysiology of anxiety disorder.[39] In this study, the positive correlation between the synchronization of neuronal activity in the right angular gyrus and the degree of anxiety in patients suggested that the angular gyrus may affect the ability to integrate and cope with negative emotions such as fear and anxiety. Disorders in the angular gyrus would hamper patients' understanding of situational information and self-cognition, contributing to a state of anxiety and depression.

Depressive disorder has a variety of suggested origins. Post-operative patients following breast cancer surgery were chosen to explore the changes in cerebral cortex activity by rs-fMRI. Results suggested that the changes in the cortical activity of multiple functional brain regions, especially components of the DMN, were closely related to the attention deficit in depressive disorder and closely associated with anxiety. We found that the change of neuronal activity synchronization in the right angular gyrus was related to the degree of anxiety in patients after breast cancer surgery, suggesting that the right angular gyrus may be involved in the generation of anxiety. Future studies should examine the changes and role of the right angular gyrus in patients with depression and anxiety.

The values of ALFF and ReHo obtained by rs-fMRI can be used as a quantitative parameter to evaluate the changes of brain activity in patients with depression, which can help to eliminate confounding factors, and achieve a more objective evaluation of depression state in combination with clinical scale scores, in order to help better identify depressive disorder in patients after breast cancer surgery and further improve the quality of life and prognosis of those patients.

The most important limitation is lack of sample size, which may directly lead to no significant difference in the ALFF and ReHo values between two groups. But this study attempted to break the limitation of routine grouping antitheses, the correlation between cerebral cortex activity and clinical scale scores of patients after breast cancer surgery was directly analyzed in the form of non-grouping to avoid setting normal standards for the analysis software, and found that the cerebral cortex activity of patients with depression after breast cancer surgery was significantly related to the clinical scale scores, demonstrating an obvious correlation trend between them.

Future studies will continue to increase the sample size and follow up these patients to conduct a comparative study of changes before and after treatment. Further studies should also examine the cortical activity in the corresponding brain regions after an improvement of clinical symptoms. Taken together, these improvements may be used to further confirm the claim that activity changes of the DMN can be used as an index to evaluate the severity and therapeutic effect in patients suffering from depression.

Conclusion

In the resting state, changes in the activity of the default mode network (DMN) and neuronal synchronization in the right angular gyrus were closely related to depressive symptoms in post-operative patients after breast surgery. The associated cortical changes may be responsible for the characteristic clinical symptoms of depressive disorder, such as attention deficits, flattened affect and anxiety.

Abbreviations

ALFF: amplitude of low frequency fluctuations; ANG_L: left angular gyrus; ANG_R: right angular gyrus; CSF: cerebrospinal fluid; DARTEL: diffeomorphic anatomical registration through exponential lie algebra; DEPRSF: data processing assistant for resting-state fMRI; DMN: default mode network; DSM-IV: American diagnostic and statistical manual of mental disorders; FA: flip angle; FEW: family wise error; FOV: field of view; FSAQ: full scale attention quotient; GRF: Gaussian random field theory correction; HAMA: Hamilton anxiety scale; HAMD：Hamilton depression scale; PCUN_R: right precuneus; ReHo: regional homogeneity; rs-fMRI: resting-state functional magnetic resonance imaging; REST: resting-state fMRI data analysis toolkit; SAS: self-rating anxiety scale; SDS: self-rating depression scale; SMG_R: right supramarginal gyrus; SPM: statistical parametric mapping; SPSS: statistical product and service solutions TE: echo time; TR: repetition time; WHO: world health organization;

Declarations

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Authors' contributions

JH: image acquisition, data processing, data analysis, data interpretation, literature search, manuscript draft. LZ: image acquisition, data processing, data analysis, literature search. XG: case collection, information acquisition, data analysis, XZ: scale scoring, statistical analysis, data interpretation. FZ: data processing, figures and tables. WS: statistical analysis, literature search. ZC and MX: study design and review of the final draft. All authors have read and approved the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang Chinese Medical University (2016-K-100-01). Written informed consent to participate in the study was obtained from each patient.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Author details

[1]The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang, China. [2]Department of Radiology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang, China. [3]Department of Radiology, Hangzhou Ding Qiao Hospital, Hangzhou 310021, Zhejiang, China. [4]Department of Breast, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang, China. [5]Department of Mental Health, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang, China

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Figures

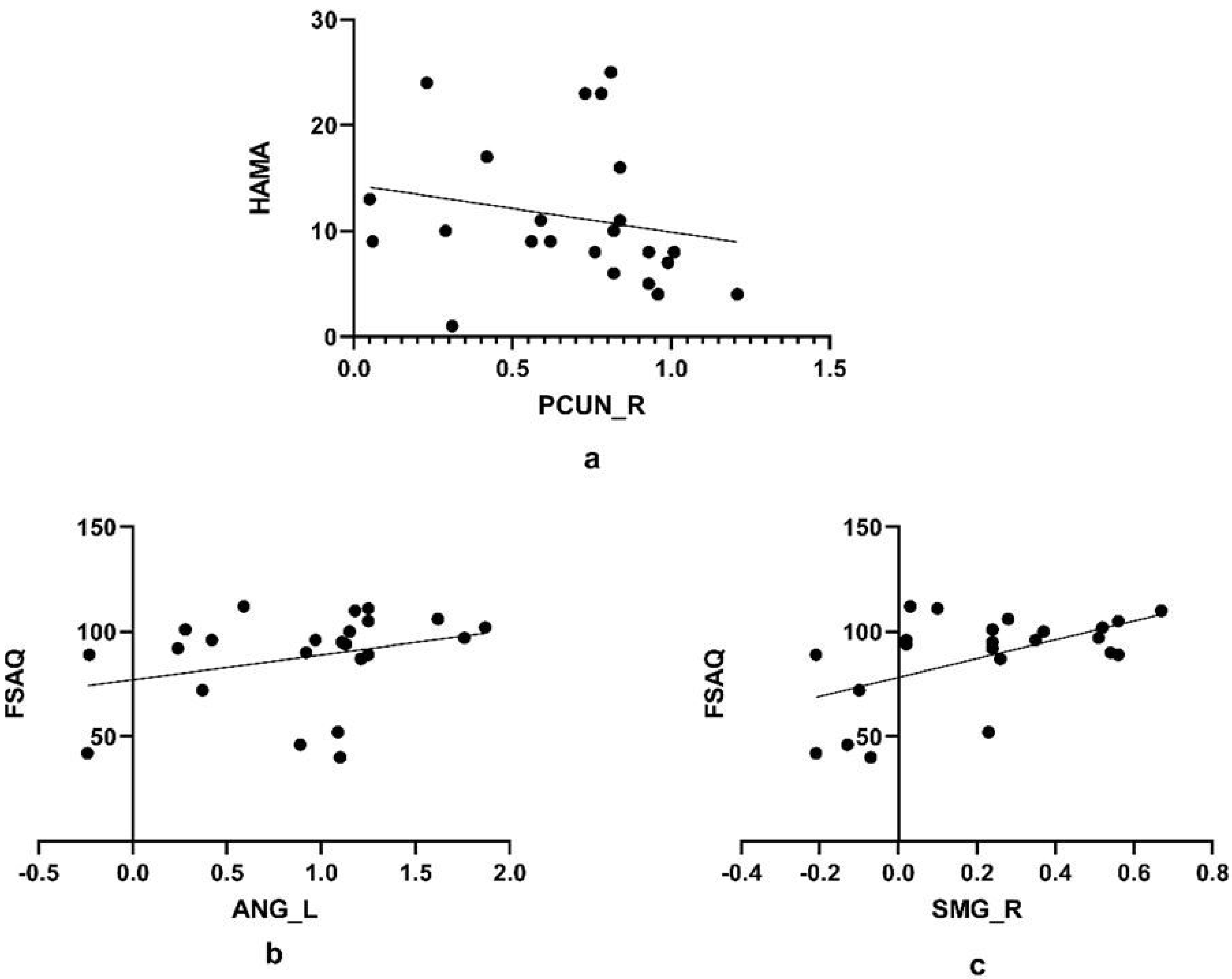

Figure 1

a) The scatter plot of the correlation between ALFF value in PCUN_R with HAMA score (r = -0.43, P = 0.039); b) The scatter plot of the correlation between ALFF value in ANG_L with FSAQ score (r = 0.44, P = 0.033). c) The scatter plot of the correlation between ALFF value in SMG_R with FSAQ score(r = 0.50, P = 0.015).

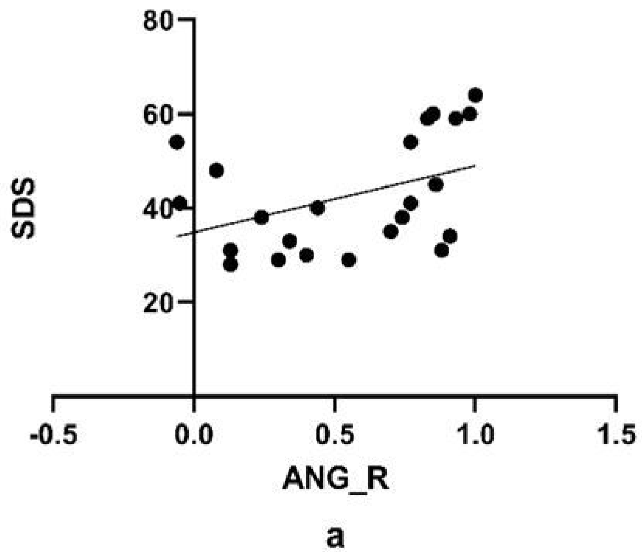

Figure 2

Results of correlation analysis between ReHo value and clinical scale scores: a) The scatter plot of the correlation between ReHo value in ANG_R with SDS score (r = 0.45, P = 0.033); b) The scatter plot of the correlation between ReHo value in ANG_R with HAMA score (r = 0.49, P = 0.018).

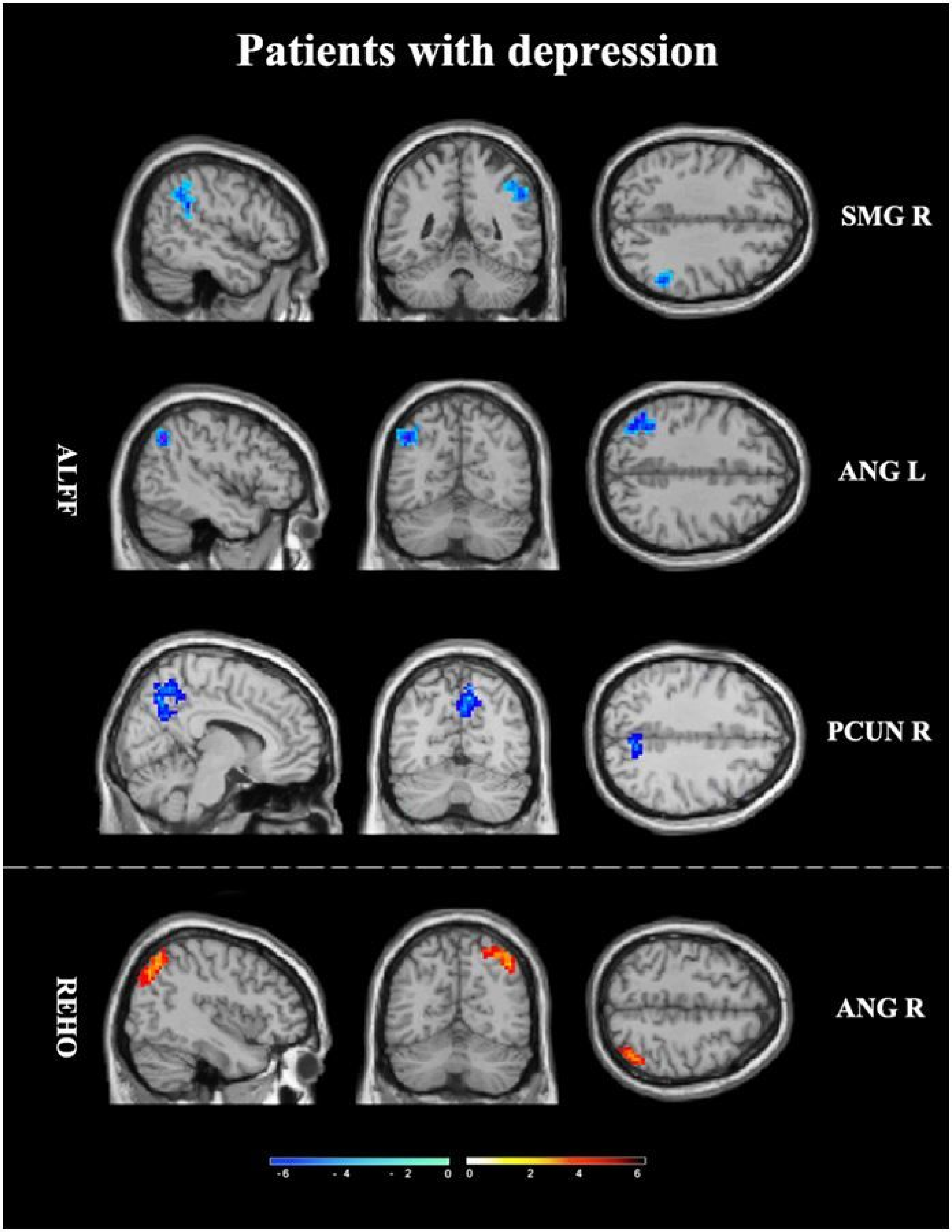

Figure 3

Brain regions with decreased ALFF or increased ReHo in patients with depression after breast cancer surgery. The ALFF value of PCUN_R, ANG_L and SMG_R decreased in patients with depression, while the ReHo value of ANG_R increased.