Observational Study

Medicine®

OPEN

Comparison of functional dorsal attention network alterations in breast cancer survivors before and after chemotherapy

Chao-Yu Shen, MD, PhD[a,b], Yuan-Hsiung Tsai, MD, PhD[c,d], Vincent Chin-Hung Chen, MD, PhD[c,e], Ming-Chih Chou, MD, PhD[a,f], Roger S. McIntyre, MD[g,h,i], Jun-Cheng Weng, PhD[e,j,k,*]

Abstract

Breast cancer is the leading type of cancer among women worldwide, and a high number of breast cancer patients are suffering from psychological and cognitive disorders. This cross-sectional study used resting-state functional magnetic resonance imaging (rs-fMRI) and clinical neuropsychological tests to evaluate the possible underlying mechanisms.

We enrolled 32 breast cancer patients without chemotherapy (BC), 32 breast cancer patients within 6 to 12 months after the completion of chemotherapy (BC_CTx) and 46 healthy controls. Participants underwent neuropsychological tests and rs-fMRI with mean fractional amplitude of low-frequency fluctuation and mean regional homogeneity analyses. Between groups whole-brain voxel-wise rs-fMRI comparisons were calculated using two-sample *t* test. rs-fMRI and neuropsychological tests correlation analyses were calculated using multiple regression. Age and years of education were used as covariates. A false discovery rate-corrected *P*-value of less than .05 was considered statistically significant.

We found significantly alteration of mean fractional amplitude of low-frequency fluctuation and mean regional homogeneity in the frontoparietal lobe and occipital lobe in the BC group compared with the other 2 groups, indicating alteration of functional dorsal attention network (DAN). Furthermore, we found the DAN alteration was correlated with neuropsychological impairment.

The majority of potential underlying mechanisms of DAN alteration in BC patients may due to insufficient frontoparietal lobe neural activity to drive DAN and may be related to the effects of neuropsychological distress. Further longitudinal studies with comprehensive images and neuropsychological tests correlations are recommended.

Abbreviations: BC = breast cancer patients without chemotherapy, BC_CTx = breast cancer patients after chemotherapy, DAN = dorsal attention network, mfALFF = mean fractional amplitude of low-frequency fluctuation, mReHo = mean regional homogeneity, rs-fMRI = resting-state functional magnetic resonance imaging.

Keywords: breast cancer, chemotherapy, dorsal attention network, resting-state functional MRI

1. Introduction

Breast cancer is the leading type of cancer among women worldwide. Fortunately, current outstanding comprehensive therapies have increased the patient survival time. However, a high number of breast cancer patients are suffering from psychological and cognitive disorders, and thus life quality of breast cancer patients is becoming an important issue.[1–7] A term "chemo-brain" was created to describe cognitive impairment

Editor: Hyunjin Park.

YHT and CYS contributed equally to this work.

This study was supported by the research programs MOST107-2221-E-182-054-MY3 and MOST110-2221-E-182-027, which were sponsored by the Ministry of Science and Technology, Taipei, Taiwan. This study was also supported by grants (NMRPD1H0101~3) from Chang Gung University, Taoyuan, Taiwan, and grants (CORPG6G0101~3, CORPG6G0121~3) from Chang Gung Memorial Hospital, Chiayi, Taiwan.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Institute of Medicine and School of Medicine, Chung Shan Medical University, Taichung, Taiwan, [b] Department of Medical Imaging, Chung Shan Medical University Hospital, Taichung, Taiwan, [c] School of Medicine, Chang Gung University, Taoyuan, Taiwan, [d] Department of Diagnostic Radiology, Chang Gung Memorial Hospital, Chiayi, Taiwan, [e] Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi, Taiwan, [f] Division of Thoracic Surgery, Department of Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan, [g] Mood Disorder Psychopharmacology Unit, University Health Network, Department of Psychiatry, University of Toronto, Toronto, ON, Canada, [h] Institute of Medical Science, University of Toronto, Toronto, ON, Canada, [i] Departments of Psychiatry and Pharmacology, University of Toronto, Toronto, ON, Canada, [j] Department of Medical Imaging and Radiological Sciences, Bachelor Program in Artificial Intelligence, Chang Gung University, Taoyuan, Taiwan, [k] Medical Imaging Research Center, Institute for Radiological Research, Chang Gung University and Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan.

[*] Correspondence: Jun-Cheng Weng, Department of Medical Imaging and Radiological Sciences, Chang Gung University, No. 259, Wenhua 1st Rd., Guishan Dist., Taoyuan City 33302, Taiwan (e-mail: jcweng@mail.cgu.edu.tw).

How to cite this article: Shen CY, Tsai YH, Chen VH, Chou MC, McIntyre RS, Weng JC. Comparison of functional dorsal attention network alterations in breast cancer survivors before and after chemotherapy. Medicine 2021;100:33(e27018).

Received: 23 April 2021 / Received in final form: 14 July 2021 / Accepted: 3 August 2021

http://dx.doi.org/10.1097/MD.0000000000027018

experienced by patients after receiving chemotherapy.[7,8] A recent review study included more than 50 published neuropsychological associated breast cancer researches found that executive function, memory, processing speed, and also attention were the most commonly affected cognitive functions in breast cancer patients and may be related to chemotherapy.[9]

Brain magnetic resonance imaging (MRI) has been widely used to examine the effects of breast cancer and its associated treatments to approach the underlying mechanism of cognitive dysfunction. By structural approaches using voxel-based morphometry and diffusion tensor imaging (DTI) analyses, recent MRI studies revealed reduced brain gray and white matter volume in frontal, temporal, thalamus, cerebellar regions, and decreased white matter integrity in frontal, parietal, and occipital lobes in breast cancer patients after chemotherapy.[10,11] Compared with structural MRI studies, functional MRI (fMRI) can detect brain activities by measuring blood oxygen level-dependent signal changes, which shows more sensitive to evaluate brain cognitive function and being widely used to assess diseases associated with cognitive impairments.[12–20] Using task-based fMRI and resting-state functional magnetic resonance imaging (rs-fMRI) approaches, recent studies revealed alteration of working memory-related activation, functional connectivity, global and local efficiency, and majorly involving frontal lobes in breast cancer patients after chemotherapy and these changes may have an association with attention function.[17,20–23]

In our previous breast cancer study, by using rs-fMRI with mean fractional amplitude of low-frequency fluctuations (mfALFF) analysis, correlated with neuropsychological tests and compared with healthy controls, we revealed alterations in the dorsal attention network (DAN) in patients with breast cancer within 6 months after completion of chemotherapy and may be related to the effects of both chemotherapy and neuropsychological distress.[24]

Although majority of previous structural and functional MRI studies focused on chemo-brain change and showed cognitive associated brain alterations[25]; however, more and more recent studies have suggested that cognitive alterations in patients with breast cancer can occur before undergoing chemotherapy. These findings indicated and enhanced that neuropsychological distress rather than the effects of chemotherapy alone may play an important role in breast cancer-related cognitive impairments.[4,26–31] To better understand and distinguish the effects of chemotherapy and neuropsychological distress of breast cancer patients, this cross-sectional study compared breast cancer patients without chemotherapy, breast cancer patients after the completion of chemotherapy and healthy controls and correlated these groups with neuropsychological tests by using rs-fMRI to clarify the possible underlying mechanisms.

2. Materials and methods

2.1. Participants

All participants were recruited from the Chang Gung Memorial Hospital, Chiayi, Taiwan and were separated into 3 groups, including breast cancer patients without chemotherapy (BC), breast cancer patients within 6 to 12 months after the completion of chemotherapy (anthracyclines, such as doxorubicin, epirubicin, and taxanes, such as paclitaxel, docetaxel) (BC_CTx) and sex-matched healthy controls (HC). The inclusion criteria of breast cancer patients included age 20 to 55 female with pathological proved primary breast cancer. The exclusion criteria of breast cancer patients included end-stage of the breast cancer, underwent treatment for other cancer, post-radiation therapy before investigation, evidence of brain metastasis or other brain insults, any known neuropsychiatric disorder or substance used and unable to have an MRI scan. The same exclusion criteria were used for HC in addition to having no evidence of breast cancer. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Chiayi, Taiwan (Nos. 104-5082B, 201700256B0, 201702027B0), and the written informed consent was obtained from all patients.

2.2. Neuropsychological tests

All neuropsychological tests were evaluated by an experienced psychotherapist. The Mini-Mental State Examination (MMSE) was used to assess cognitive function (our MMSE quote number is W36019); it features tests of orientation (both time and place), attention, calculation, registration of words, word recall, and also visual and language construction. The scores range from 0 to 30, with higher values indicating a higher cognitive function.[32,33] The Cognitive and Affective Mindfulness Scale-Revised (CAMS-R) was used to assess mindful qualities; it is designed with 12-item measurements for capture a broad conceptualization of mindfulness, with higher values reflecting greater mindful qualities.[34] The Hospital Anxiety and Depression Scale (HADS) was used to assess possible anxiety and depression symptoms; it is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety, and the other 7 relate to depression. Scores range from 0 to 21, and higher values reflect greater anxiety and depression symptoms.[35] The Impact of Event Scale-Revised (IES-R) was used to assess subjective distress caused by potential traumatic events; it is a self-report measurement with totally 22 items, with higher values reflecting greater levels of life distress.[36]

2.3. MRI scan acquisition

Brain MRI examinations of all participants were performed using a 3.0-T MRI scanner (Magnetom Verio, Siemens Medical Systems, Erlangen, Germany) with a standard 8-channel head coil. For rs-fMRI measurements, a gradient echo–echo planar imaging sequence with 31 axial slices per volume was used and totally 300 volumes were recorded with a temporal resolution of 2 seconds (TR: 2000 millisecond, TE: 30 millisecond, and FA: 90°; voxel size = 3.4 mm × 3.4 mm × 4.0 mm). All participants were taught to close their eyes, keep relaxed, and motionless but awake in the absence of goal-directed attention during the examination. Besides, head cushions and earmuffs were used in all participants for motion and scanner noise reduction.

2.4. Resting-state functional MRI data preprocessing

Data were collected, preprocessed, and analyzed similarly as described in our previous study.[24] In brief, the preprocessing of rs-fMRI data was performed using Statistical Parametric Mapping 8 (SPM8, Wellcome Department of Cognitive Neurology, London, UK) based on MATLAB 2013 (MathWorks, Natick, MA). Initially, the first 10 volumes of each participant were discarded to allow for the magnetization equilibrium and saturation effects. Then slice-timing correction were performed for the remaining 290 consecutive volumes. For

head motion correction, only participants with head motion less than ±1 mm in the *x*, *y*, *z* direction and less than ±1° rotation about each axis were included. For data normalization, Montreal Neurological Institute was used as standard space, after affine transformation, data were resampled to isotropic 3-mm voxels, followed by using a 6-mm full width at half maximum Gaussian kernel for spatially smoothing to get a better signal-to-noise ratio gain. Thereafter, Nuisance regression was performed to remove the physiological noise by using 6 head motion parameters as covariates and whole brain, white matter, and cerebrospinal fluid as masks. To minimize the effects of low-frequency drifts and physiological signals, linear detrending and bandpass temporal filtering were calculated on the time series of each voxel by using the Resting-State Data Analysis toolkit v1.8 (REST v1.8, Center for Cognition and Brain Disorders, Hangzhou Normal University, Zhejiang, China). According to the previously published studies and our own study experience, 0.01 to 0.12 Hz were selected as frequency range to cover dominant physiological information and minimize the effect of both high-frequency physiological noise and low-frequency drift.[19,23,37,38]

The mfALFF with frequency range of 0.01 to 0.12 Hz was evaluated. Using fast Fourier transform, the time series was converted to the frequency domain for a given voxel. The square root of the power spectrum was calculated, averaged, and normalized across a predefined frequency interval at the given voxel.[39,40] To analyze regional homogeneity (ReHo), each individual ReHo map was generated by calculating the Kendall's coefficient of concordance, which measured the neural synchronization of a given voxel with its 26 neighboring voxels.[41] A mask was then used to remove nonbrain tissues and noise on the ReHo maps, and the individual ReHo maps were divided by their own mean Kendall's coefficient of concordance within the mask for standardization purposes to compute the mean regional homogeneity (mReHo).

2.5. Data analysis

To explore group differences in demographic data and neuropsychological tests, normal distribution was tested first, followed by one-way ANOVA with Bonferroni-adjusted post hoc test using SPSS version 22. A *P*-value of less than .05 was considered statistically significant. To explore group differences in rs-fMRI mfALFF and mReHo between the BC, BC_CTx, and HC groups, a whole-brain voxelwise comparison was performed using two-sample *t* test in SPM8. To explore the relationship between the mfALFF and mReHo with neuropsychological tests, the correlation between mfALFF with the MMSE, CAMS-R, HADS (Anxiety and Depression), and IES-R and the correlation between mReHo with the MMSE, CAMS-R, HADS (Anxiety and Depression), and IES-R were calculated using multiple regressions in SPM8. Age and years of education were used as covariates. A false discovery rate-corrected *P*-value of less than .05 was considered statistically significant. Finally, T1-weighted Montreal Neurological Institute template was used to create the underlying map for result viewing.

3. Results

3.1. Participants

A total of 110 participants were recruited. Thirty-two participants were in the BC group, mean age: 48.6 ± 6.7 years; years of education: 12.7 ± 4.3; breast cancer stage (according to the 8th edition American Joint Committee on Cancer): 0 (n = 19), I (n = 10), II (n = 2), and III (n = 1). Thirty-two participants were in the BC_CTx group, mean age: 49.9 ± 6.3 years; years of education: 11.4 ± 3.8; breast cancer stage: I (n = 5), II (n = 18), III (n = 7), and IV (n = 2). Forty-six participants were in the HC group, mean age: 43.5 ± 7.0 years; years of education: 13.3 ± 3.0. Significant differences were noted in the age comparison (ANOVA: *P*-value < .01), between the BC and HC groups (post hoc test: *P*-value = .02) and between the BC_CTx and HC groups (post hoc test: *P*-value < .01) (Table 1).

3.2. Neuropsychological tests

All participants, including 32 BC, 32 BC_CTx, and 46 HC participants, underwent the HADS test, and both anxiety and depression domains showed no significant difference among the groups. Only the BC and BC_CTx groups underwent the MMSE and CAMS-R tests, and the results showed no significant difference between the groups. All participants underwent the IES-R test and

Table 1

Summary of characteristics of demographic data and neuropsychological tests.

	Breast cancer patients without chemotherapy (n = 32)		Breast cancer patients after chemotherapy (n = 32)		Healthy controls (n = 46)		ANOVA	A	B	C
Characteristics	Mean or count	SD	Mean or count	SD	Mean or count	SD	*P*-value*			
Age (yrs)	48.6	6.7	49.9	6.3	43.5	7.0	<.01	.44	.02	<.01
Education (yrs)	12.7	4.3	11.4	3.8	13.3	3.0	.09	.28	.29	.23
Breast ca stage: (0, I, II, III, IV)	(19,10,2,1,0)	N/A	(0,5,18,7,2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MMSE	28.5	1.7	28.6	1.7	N/A	N/A	N/A	.94†	N/A	N/A
CAM-R	36.7	6.3	34.9	7.4	N/A	N/A	N/A	.35†	N/A	N/A
HADS										
Anxiety	6.2	4.7	5.1	4.3	5.0	4.8	.40	.26	.20	.88
Depression	4.6	4.5	3.1	3.8	4.3	3.4	.25	.16	.76	.17
IES-R	13.2	20.5	11.8	16.4	3.4	8.3	<.01	.88	.03	.01

A = post hoc test between breast cancer patients without and after chemotherapy; B = post hoc test between breast cancer patients without chemotherapy and healthy controls; C = post hoc test between breast cancer patients after chemotherapy and healthy controls; CAM-R = Cognitive and Affective Mindfulness Scale-Revised; HADS = Hospital Anxiety and Depression Scale; IES-R = Impact of Event Scale-Revised; MMSE = Mini-Mental State Examination; N/A = not applicable; SD = standard deviation.

* *P*-value < .05 indicating significant difference.

† Two sample *t* test.

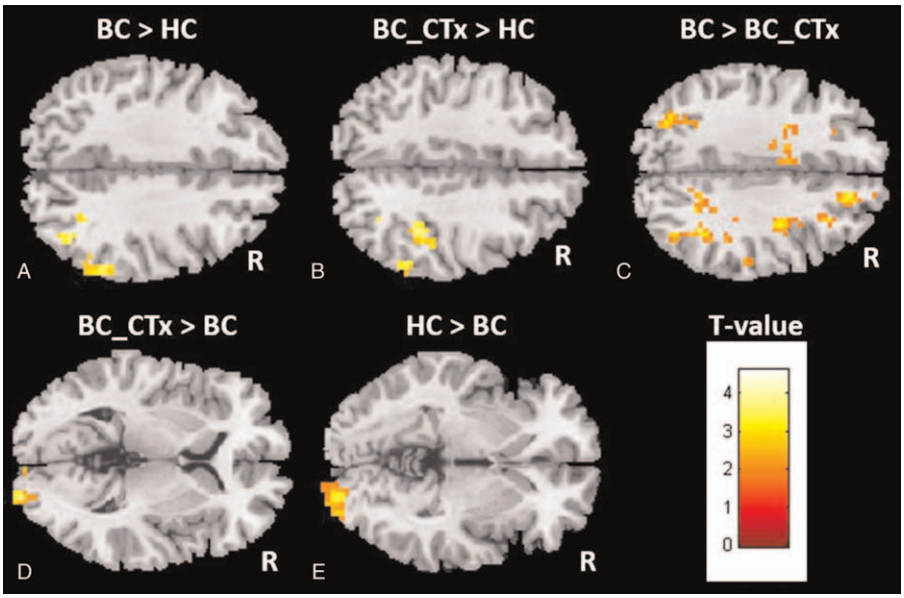

Figure 1. The mfALFF analysis. Both the (A) BC and (B) BC_CTx groups showed significantly increased mfALFF in the frontoparietal lobe compared with that of the HC group. (C) The BC group showed significantly increased mfALFF in the frontoparietal lobe compared with that of the BC_CTx group. Both the (D) BC_CTx and (E) HC groups showed increased mfALFF in the occipital lobe compared with that of the BC group. BC = breast cancer patients without chemotherapy; BC_CTx = breast cancer patients within 6 to 12 mo after the completion of chemotherapy; HC = sex-matched healthy controls.

significant differences were noted among the groups (ANOVA: *P*-value < .01) and both the BC and BC_CTx groups showed significant differences compared to the HC group (post hoc test: *P*-value = .03 between the BC and HC groups; post hoc test: *P*-value = .01 between the BC_CTx and HC groups) (Table 1).

3.3. mfALFF analysis

Both the BC and BC_CTx groups showed significantly increased mfALFF in the frontoparietal lobe compared with that of the HC group. The BC group showed significantly increased mfALFF in the frontoparietal lobe compared with that of the BC_CTx group. Both the BC_CTx and HC groups showed increased mfALFF in the occipital lobe compared with that of the BC group. No significant difference of mfALFF in the occipital lobe was found between the BC_CTx and HC groups. In brief, in the frontoparietal lobe, the BC group showed greater mfALFF than the BC_CTx group, and the BC_CTx group showed greater mfALFF than the HC group. In the occipital lobe, the HC and BC_CTx groups showed no significant mfALFF difference, but both showed greater mfALFF than the BC group (Fig. 1).

3.4. mReHo analysis

The HC group showed significantly increased mReHo in the frontoparietal lobe compared with that of the BC and BC_CTx groups. The BC_CTx group showed significantly increased mReHo in the frontoparietal lobe compared with that of the BC group. In brief, in the frontoparietal lobe, the HC group showed greater mReHo than the BC_CTx group, and the BC_CTx group showed greater mReHo than the BC group (Fig. 2).

3.5. Neuropsychological tests correlation analysis

In mfALFF with neuropsychological test correlation analysis, both the MMSE and CAMS-R scores showed a positive

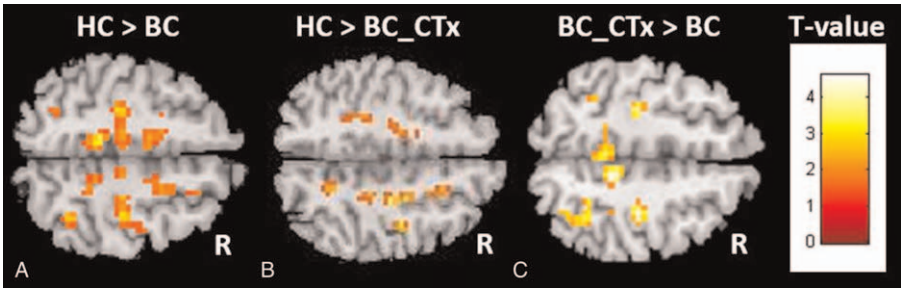

Figure 2. The mReHo analysis. (A and B) The HC group showed significantly increased mReHo in the frontoparietal lobe compared with that of the BC and BC_CTx groups. (C) The BC_CTx group showed significantly increased mReHo in the frontoparietal lobe compared with that of the BC group. BC = breast cancer patients without chemotherapy; BC_CTx = breast cancer patients within 6 to 12 mo after the completion of chemotherapy; HC = sex-matched healthy controls; mReHo = mean regional homogeneity.

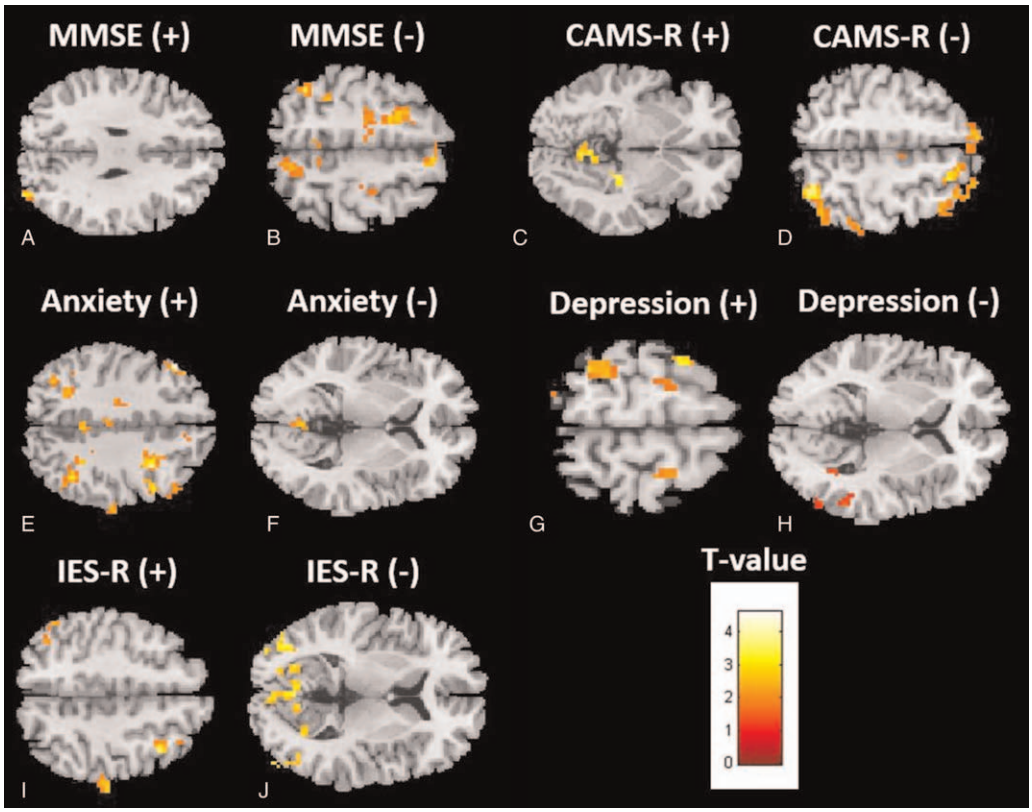

Figure 3. The mfALFF with neuropsychological test correlation analysis. (A and B) MMSE and the (C and D) CAMS-R showed a positive correlation in the occipital lobe and a negative correlation in the frontoparietal lobe. In contrast, the (E and F) Anxiety and (G and H) Depression and the (I and J) IES-R showed a positive correlation in the frontoparietal lobe and a negative correlation in the occipital lobe. Anxiety and Depression = Hospital Anxiety and Depression Scale; CAMS-R = Cognitive and Affective Mindfulness Scale-Revised; IES-R = The Impact of Event Scale-Revised; MMSE = Mini-Mental State Examination; mfALFF = mean fractional amplitude of low-frequency fluctuation.

correlation in the occipital lobe and a negative correlation in the frontoparietal lobe. In contrast, the HADS (Anxiety and Depression) and IES-R scores showed a positive correlation in the frontoparietal lobe and a negative correlation in the occipital lobe (Fig. 3). In mReHo with neuropsychological tests correlation analysis, both the MMSE and CAMS-R scores showed a positive correlation in the frontoparietal lobe. In contrast, the HADS (Anxiety and Depression) and IES-R scores showed a negative correlation in the frontoparietal lobe (Fig. 4).

4. Discussion

In this study with cross-sectional design, we used mfALFF for detecting the regional intensity of spontaneous fluctuations and mReHo for detecting the synchronization of spontaneous local brain neuronal activities to evaluate possible rs-fMRI signal differences among breast cancer patients without chemotherapy, breast cancer patients after the completion of chemotherapy and sex-matched healthy controls. Furthermore, we evaluated the correlation between alterations in brain functional connectivity and neuropsychological tests. Our results showed increased mfALFF and decreased mReHo in the frontoparietal lobe and decreased mfALFF in the occipital lobe in the BC group compared with the HC and the BC_CTx groups. The majority of involved brain area were located in functional DAN. The DAN is derived from the frontoparietal lobe and reacting at the occipital lobe, which playing important role in voluntary control of attention with top-down direction in the human brain.[42,43] Therefore, in the BC group, increased mfALFF but decreased mReHo in frontoparietal lobe may indicated insufficiently increased neural activity to drive attention network, and decreased mfALFF in occipital lobe may indicated poor attention network reaction.

Recent studies have recognized an important role of alteration of attention in cognitive impairments in cancer survivors and recommended that the perceive problems with memory may be associated to early-stage deficits of information processing and related to attention impairment.[44,45] Furthermore, several recent MRI studies using arterial spin labeling perfusion, task-based fMRI and rs-fMRI showed alterations in cerebral blood flow and the functional connectivity associated with DAN in breast cancer patients after chemotherapy.[17,21,22,46–48] By combined functional and structural approaches, Mo et al used rs-fMRI and DTI to evaluate post-chemotherapy breast cancer patients and found a decrease of ReHo mainly in the frontal lobe in rs-fMRI evaluation and a decrease of fractional anisotropy (FA) in the superior fronto-occipital fasciculus, a part of visuospatial attention network in DTI evaluation.[49] In addition, in our previous study using rs-fMRI with mfALFF analysis in correlation with cognitive tests, we found that functional DAN alteration may play a crucial role in cognitive impairment in breast cancer patients.[24] Similar to these studies, our results showed alterations in the DAN among the patients with breast cancer not only in the BC_CTx group but also in the BC group. In

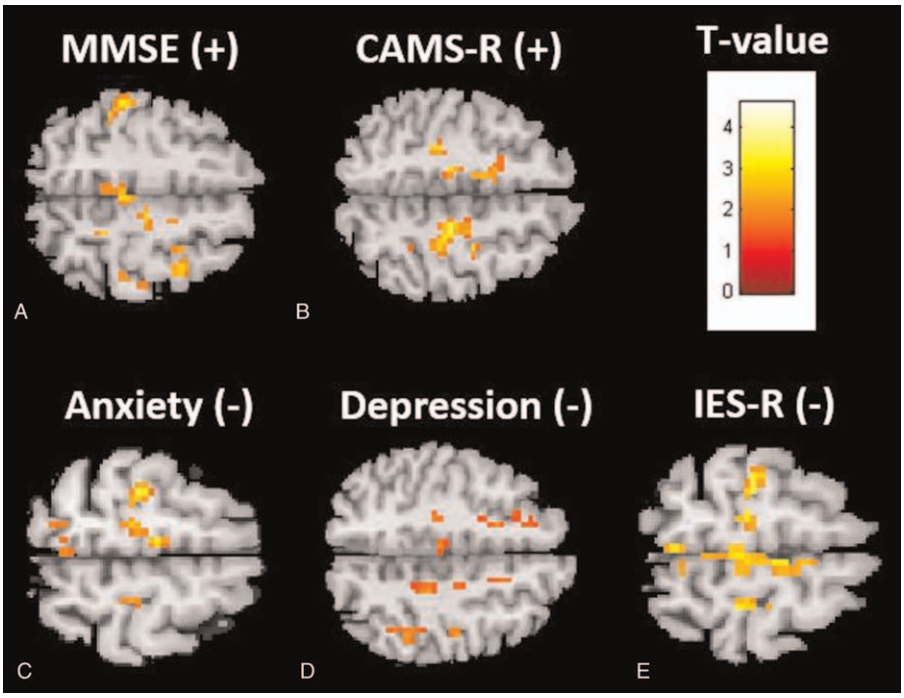

Figure 4. The mReHo with neuropsychological test correlation analysis. The (A) MMSE and the (B) CAMS-R showed a positive correlation in the frontoparietal lobe. In contrast, the (C) Anxiety, (D) Depression, and the (E) IES-R showed a negative correlation in the frontoparietal lobe. Anxiety and Depression = Hospital Anxiety and Depression Scale; CAMS-R = Cognitive and Affective Mindfulness Scale-Revised; IES-R = The Impact of Event Scale-Revised; MMSE = Mini-Mental State Examination); mReHo = mean regional homogeneity.

addition, when we compared the BC group with the BC_CTx group, the BC group showed significantly increased DAN alteration compared with that of the BC_CTx group. Therefore, the result cannot be well explained by the effect of chemotherapy alone.

Indeed, several recent published studies with clinical and MRI approaches have suggested that breast cancer patients can suffer from cognitive impairments, including compromised attention function before chemotherapy, which may associated with stress disorder.[26–30] A recent prospective longitudinal study with clinical assessments suggested that the symptoms of stress disorder affected more than 80% of breast cancer patients after the disease was diagnosed, even before any treatment, such as mastectomy or chemotherapy, and the symptoms may gradually recover within 1 year.[50] Furthermore, in a recent controlled, longitudinal, multisite study, Hermelink et al found that breast cancer patients, both before and 1 year after chemotherapy, compared with healthy controls, showed lower accuracy in attention tests and cognitive decline and the effects were significantly associated with stress disorder.[30] These previous results help us to explain why breast cancer patients without brain metastasis or those who underwent systemic chemotherapy still showed DAN alterations and the alterations may gradually recover even after chemotherapy.

In neuropsychological tests correlation analysis, we found alterations in mfALFF in the frontoparietal lobe and occipital lobe and alterations in mReHo in the frontoparietal lobe, which indicates that alterations in the DAN may play an important role in neuropsychological impairments. These findings may be explained by compensatory mechanisms, a concept suggested by several recent studies that brain has capability to recruit normal area to maintain cognitive performance when functional alterations occur and this alternative adaptive mechanism has been observed in cancer survivors.[17,51–53] In addition, we found significant differences in IES-R scores in both the BC and BC_CTx groups compared to the HC group. Therefore, we suggest that the effects of neuropsychological distress may play a key role in DAN alterations in breast cancer patients, especially without chemotherapy, and we recommend that early intervention with neuropsychological therapy, such as mindfulness-based interventions for the patient who diagnosed with breast cancer may help to reduce and minimize the degree of post-diagnosis neuropsychological distress.[54,55]

However, our study has several limitations worth noting. First, a relatively small number of participants were included, and not all of the neuropsychological tests were performed in the HC group, which may have caused the results of significant age difference among the 3 study groups and some of the results of the neuropsychological tests among group comparisons to show only trends or nearly significant differences. Future research involving a larger sample size of participants, including breast cancer patients and healthy controls, who will undergo more detailed and comprehensive neuropsychological tests that consisted with more subscale measurements of different cognitive functions is recommended.[56,57] Second, the cross-sectional design did not allow us to detect the possible longitudinal effects of both neuropsychological stress and chemotherapy in the same breast cancer and further longitudinal studies are required to verify such effects. Third, during data processing with head motion correction, although only the participant's data with translational or rotational parameters less than ± 1 mm and $\pm 1°$ were included and all the participants fulfilled the criteria. However,

we did not calculate the frame-wise displacements (FD) in this study. FD measurement can reflect the volume-to-volume changes in head position and we recommend to use FD measurement in future studies to help optimal handling of rs-fMRI data with consequence of motion artifact.[58–60]

5. Conclusions

Comparing with HC group, we found alterations in mfALFF and mReHo in the DAN of breast cancer patients before and within 6 to 12 months after chemotherapy in this cross-sectional rs-fMRI study. We suggest the majority of possible underlying mechanisms may due to insufficient frontoparietal lobe neural activity to drive DAN and may be related to the effects of neuropsychological distress. We recommend that further prospective longitudinal studies using comprehensive images with neuropsychological tests correlations to delineate clearer picture of relationship between the decline of specific cognitive functions and rs-fMRI changes in breast cancer patients and even other cancer patients are necessary.

Acknowledgments

The authors would like to thank Xuan-Ru Zhang for her assistance in experimental preparation.

Author contributions

Conceptualization: Chao-Yu Shen, Vincent Chin-Hung Chen.
Data curation: Yuan-Hsiung Tsai, Vincent Chin-Hung Chen.
Formal analysis: Chao-Yu Shen.
Funding acquisition: Yuan-Hsiung Tsai, Vincent Chin-Hung Chen, Jun-Cheng Weng.
Investigation: Chao-Yu Shen, Yuan-Hsiung Tsai, Vincent Chin-Hung Chen.
Methodology: Chao-Yu Shen, Jun-Cheng Weng.
Project administration: Jun-Cheng Weng.
Software: Yuan-Hsiung Tsai, Jun-Cheng Weng.
Supervision: Jun-Cheng Weng.
Validation: Jun-Cheng Weng.
Visualization: Chao-Yu Shen, Yuan-Hsiung Tsai.
Writing – original draft: Chao-Yu Shen, Yuan-Hsiung Tsai.
Writing – review & editing: Vincent Chin-Hung Chen, Ming-Chih Chou, Roger S. McIntyre, Jun-Cheng Weng.

References

[1] DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. CA: Cancer J Clin 2017;67:439–48.
[2] Society ACBreast Cancer Facts & Figures 2017–2018. Atlanta: American Cancer Society, Inc; 2017.
[3] Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Med [Review] 2015;13:195.
[4] Jim HS, Phillips KM, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol 2012;30:3578–87.
[5] Vardy J. Cognitive function in breast cancer survivors. Cancer Treat Res [Review] 2009;151:387–419.
[6] Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer [Clinical Trial Clinical Trial, Phase III Randomized Controlled Trial] 2004;100:2292–9.
[7] Hermelink K. Chemotherapy and cognitive function in breast cancer patients: the so-called chemo brain. J Natl Cancer Inst Monogr [Research Support, Non-US Gov't Review] 2015;2015:67–9.
[8] Wang XM, Walitt B, Saligan L, Tiwari AF, Cheung CW, Zhang ZJ. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. Cytokine 2015;72:86–96.
[9] Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. Curr Neurol Neurosci Rep [Review] 2012;12:267–75.
[10] McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res Treat 2010;123:819–28.
[11] Deprez S, Amant F, Smeets A, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J Clin Oncol 2012;30:274–81.
[12] Sanz-Arigita EJ, Schoonheim MM, Damoiseaux JS, et al. Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PLoS One [Research Support, Non-U S Gov't] 2010;5:e13788.
[13] Lynall ME, Bassett DS, Kerwin R, et al. Functional connectivity and brain networks in schizophrenia. J Neurosci: the official journal of the Society for Neuroscience [Research Support, N I H, Extramural Research Support, Non-U S Gov't] 2010;30:9477–87.
[14] Nakamura T, Hillary FG, Biswal BB. Resting network plasticity following brain injury. PLoS One [Research Support, N I H, Extramural] 2009;4:e8220.
[15] Wang L, Zhu C, He Y, et al. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp [Research Support, Non-U S Gov't] 2009;30:638–49.
[16] Conroy SK, McDonald BC, Smith DJ, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res Treat 2013;137:493–502.
[17] McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study. J Clin Oncol 2012;30:2500–8.
[18] Jung MS, Zhang M, Askren MK, et al. Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis. Brain Imaging Behav 2017;11:86–97.
[19] Dumas JA, Makarewicz J, Schaubhut GJ, et al. Chemotherapy altered brain functional connectivity in women with breast cancer: a pilot study. Brain Imaging Behav 2013;7:524–32.
[20] Deprez S, Vandenbulcke M, Peeters R, et al. Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. J Clin Oncol [Comparative Study Research Support, Non-U S Gov't] 2014;32:2031–8.
[21] Miao H, Chen X, Yan Y, et al. Functional connectivity change of brain default mode network in breast cancer patients after chemotherapy. Neuroradiology [Controlled Clinical Trial] 2016;58:921–8.
[22] Wang L, Yan Y, Wang X, et al. Executive function alternations of breast cancer patients after chemotherapy: evidence from resting-state functional MRI. Acad Radiol 2016;23:1264–70.
[23] Xuan H, Gan C, Li W, et al. Altered network efficiency of functional brain networks in patients with breast cancer after chemotherapy. Oncotarget 2017;8:105648–61.
[24] Shen C-Y, Chen VC-H, Yeh D-CY, et al. Association of functional dorsal attention network alterations with breast cancer and chemotherapy. Sci Rep 2019;9:104.
[25] Pomykala KL, de Ruiter MB, Deprez S, McDonald BC, Silverman DH. Integrating imaging findings in evaluating the post-chemotherapy brain. Brain Imaging Behav [Comparative Study Review] 2013;7:436–52.
[26] Jim HS, Donovan KA, Small BJ, Andrykowski MA, Munster PN, Jacobsen PB. Cognitive functioning in breast cancer survivors: a controlled comparison. Cancer [Comparative Study Research Support, N I H, Extramural] 2009;115:1776–83.
[27] Cimprich B, Reuter-Lorenz P, Nelson J, et al. Prechemotherapy alterations in brain function in women with breast cancer. J Clin Exp Neuropsychol [Research Support, Non-US Gov't] 2010;32:324–31.
[28] Berman MG, Askren MK, Jung M, et al. Pretreatment worry and neurocognitive responses in women with breast cancer. Health Psychol: official journal of the Division of Health Psychology, American Psychological Association [Research Support, NIH, Extramural Research Support, US Gov't, Non-PHS] 2014;33:222–31.

[29] Scherling C, Collins B, Mackenzie J, Bielajew C, Smith A. Pre-chemotherapy differences in visuospatial working memory in breast cancer patients compared to controls: an FMRI study. Front Hum Neurosci 2011;5:122.
[30] Hermelink K, Buhner M, Sckopke P, et al. Chemotherapy and post-traumatic stress in the causation of cognitive dysfunction in breast cancer patients. J Natl Cancer Inst [Clinical Trial] 2017;109:djx057.
[31] Hermelink K, Voigt V, Kaste J, et al. Elucidating pretreatment cognitive impairment in breast cancer patients: the impact of cancer-related post-traumatic stress. J Natl Cancer Inst 2015;107:djv099.
[32] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975;12:189–98.
[33] Kurita GP, Sjogren P, Ekholm O, et al. Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: a multinational study. J Clin Oncol 2011;29:1297–303.
[34] Feldman G, Hayes A, Kumar S, Greeson J, Laurenceau J-P. Mindfulness and emotion regulation: the development and initial validation of the Cognitive and AffectiveMindfulness Scale-Revised (CAMS-R). J Psychopathol Behav Assess 2007;29:177–90.
[35] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[36] Weiss DS, Marmar CR. Wilson JP, Keane TM. The impact of eventscale —revised. Assessing Psychological Trauma and PTSD: A Handbook for Practitioners New York: Guilford Press; 1997;399–411.
[37] Hosseini SM, Hoeft F, Kesler SR. GAT: a graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks. PLoS One 2012;7:e40709.
[38] Bruno J, Hosseini SM, Kesler S. Altered resting state functional brain network topology in chemotherapy-treated breast cancer survivors. Neurobiol Dis 2012;48:329–38.
[39] Deprez S, Kesler SR, Saykin AJ, Silverman DHS, de Ruiter MB, McDonald BC. International cognition and cancer task force recommendations for neuroimaging methods in the study of cognitive impairment in non-CNS cancer patients. J Natl Cancer Inst 2018;110:223–31.
[40] Zou QH, Zhu CZ, Yang Y, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J Neurosci Methods [Research Support, Non-US Gov't] 2008;172:137–41.
[41] Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. NeuroImage [Clinical Trial Research Support, Non-U S Gov't] 2004;22:394–400.
[42] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci [Research Support, Non-U S Gov't Research Support, U S Gov't, P H S Review] 2002;3:201–15.
[43] Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist: a review journal bringing neurobiology, neurology and psychiatry [Research Support, Non-U S Gov't Review] 2014;20:150–9.
[44] Root JC, Ryan E, Barnett G, Andreotti C, Bolutayo K, Ahles T. Learning and memory performance in a cohort of clinically referred breast cancer survivors: the role of attention versus forgetting in patient-reported memory complaints. Psycho-oncology 2015;24:548–55.
[45] Ahles TA, Hurria A. New challenges in psycho-oncology research IV: cognition and cancer: conceptual and methodological issues and future directions. Psycho-oncology [Editorial] 2018;27:3–9.
[46] Chen X, He X, Tao L, et al. The attention network changes in breast cancer patients receiving neoadjuvant chemotherapy: evidence from an arterial spin labeling perfusion study. Sci Rep 2017;7:42684.
[47] Piccirillo JF, Hardin FM, Nicklaus J, et al. Cognitive impairment after chemotherapy related to atypical network architecture for executive control. Oncology [Clinical Trial Research Support, N I H, Extramural Research Support, Non-U S Gov't] 2015;88:360–8.
[48] Tao L, Lin H, Yan Y, et al. Impairment of the executive function in breast cancer patients receiving chemotherapy treatment: a functional MRI study. Eur J Cancer Care 2017;26:e12553.
[49] Mo C, Lin H, Fu F, et al. Chemotherapy-induced changes of cerebral activity in resting-state functional magnetic resonance imaging and cerebral white matter in diffusion tensor imaging. Oncotarget 2017;8:81273–84.
[50] Voigt V, Neufeld F, Kaste J, et al. Clinically assessed posttraumatic stress in patients with breast cancer during the first year after diagnosis in the prospective, longitudinal, controlled COGNICARES study. Psycho-oncology 2017;26:74–80.
[51] Asher A. Cognitive dysfunction among cancer survivors. Am J Phys Med Rehabil [Review] 2011;90(Suppl 1):S16–26.
[52] de Ruiter MB, Schagen SB. Functional MRI studies in non-CNS cancers. Brain Imaging Behav [Review] 2013;7:388–408.
[53] Von Ah D, Storey S, Jansen CE, Allen DH. Coping strategies and interventions for cognitive changes in patients with cancer. Semin Oncol Nurs [Research Support, Non-U S Gov't] 2013;29:288–99.
[54] Andersen BL. Psychological interventions for cancer patients to enhance the quality of life. J Consult Clin Psychol 1992;60:552–68.
[55] Xunlin NG, Lau Y, Klainin-Yobas P. The effectiveness of mindfulness-based interventions among cancer patients and survivors: a systematic review and meta-analysis. Support Care Cancer 2020;28:1563–78.
[56] Saykin AJ, de Ruiter MB, McDonald BC, Deprez S, Silverman DH. Neuroimaging biomarkers and cognitive function in non-CNS cancer and its treatment: current status and recommendations for future research. Brain Imaging Behav [Introductory Research Support, N I H, Extramural Research Support, Non-U S Gov't] 2013;7:363–73.
[57] Arnaboldi P, Riva S, Crico C, Pravettoni G. A systematic literature review exploring the prevalence of post-traumatic stress disorder and the role played by stress and traumatic stress in breast cancer diagnosis and trajectory. Breast Cancer (Dove Med Press) [Review] 2017;9:473–85.
[58] Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 2012;59:2142–54.
[59] Liu F, Guo W, Liu L, et al. Abnormal amplitude low-frequency oscillations in medication-naive, first-episode patients with major depressive disorder: a resting-state fMRI study. J Affect Disord 2013;146:401–6.
[60] Lu FM, Zhou JS, Wang XP, Xiang YT, Yuan Z. Short- and long-range functional connectivity density alterations in adolescents with pure conduct disorder at resting-state. Neuroscience 2017;351:96–107.