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Original Article

The dorsolateral prefrontal cortex is selectively involved in chemotherapy-related cognitive impairment in breast cancer patients with different hormone receptor expression

Haijun Chen[1*], Ke Ding[1*], Jingjing Zhao[1*], Herta H Chao[2,3], Chiang-Shan R Li[4], Huaidong Cheng[1*]

[1]Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui, China; [2]Cancer Center, VA Connecticut Healthcare System, West Haven, CT 06516, USA; Departments of [3]Internal Medicine, [4]Psychiatry, Yale University School of Medicine, New Haven, CT 06520, USA. [*]Equal contributors.

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Abstract: To investigate chemotherapy-related cognitive impairment (CRCI) in breast cancer patients with different hormone receptor (HR) expression and its neural mechanisms, forty BC patient were enrolled in this study and were divided into two groups. HR+ group was composed of twenty-one patients with Estrogen Receptor (ER)+/ Progesterone Receptor (PR) +, HR- group included nineteen patients with ER-/PR-. A battery of neuropsychological tests and resting-state functional magnetic resonance imaging (rs-fMRI) examinations were administered to all subjects. The functional connectivity of the dorsolateral prefrontal cortex (DLPFC) of the patients was calculated from the resting-state fMRI data, and the correlation between the DLPFC's connectivity and the neuropsychological test was analyzed. The functional connectivity (FC) of the left dorsolateral prefrontal cortex (DLPFC) with the left precuneus (PCU), the right DLPFC with the right precuneus and the right superior frontal gyrus (SFG) of the HR- group were significantly increased compared to the HR+ group. Meanwhile, a significant positive correlation was found between the post-chemotherapy prospective memory (PM) score and the functional connectivity of the left DLPFC with the left precuneus in the HR- group. These findings suggest that different hormone receptor expression in patients with breast cancer may be associated with CRCI and provide evidence that the DLPFC functional connectivity (FC) strength may be selectively involved in CRCI in HR- group breast cancer patients, especially in regard to the subjective prospective memory.

Keywords: Breast cancer, chemotherapy, cognitive impairment, functional connectivity

Introduction

It has been reported in many recent studies that breast cancer (BC) patients frequently experience cognitive impairment following chemotherapy [1, 2]. Chemotherapy-related cognitive impairment (CRCI) is the decline of memory, learning ability, attention, reasoning ability, executive function, information processing speed and visual space function that occurs in cancer patients during or after chemotherapy [3-5]. The study showed that breast cancer patients were affected by CRCI for a long period of time after standard treatment and 45.2% of breast cancer patients showed changes in cognitive function after treatment, while only 10% of healthy control group showed changes in cognitive function [6]. The research believes that CRCI is widespread, involving memory, executive function, information processing speed and other aspects, and there is no significant change in the early stage and it is not easy to be detected [7]. Pinto et al. found that the improvement of breast cancer treatment technology led to an increase in the number of long-term survival of breast cancer patients, and cognitive changes such as memory disorder, insomnia and depression were the most important factors affecting the quality of life after chemotherapy [8-10]. However, the specific mechanisms underlying chemotherapy-related cognitive impairment (CRCI) are still not well understood.

However, neuroimaging studies have found that changes in brain structure and function in

breast cancer patients were associated with chemotherapy-related cognitive impairment [11-13]. Structural changes in both gray matter (GM) and white matter (WM) are evident in breast cancer patients after chemotherapy [14]. The gray matter structure of corresponding brain regions was changed and the damage of axons and demyelinating lesion of local white matter in breast cancer patients are related to the damage of cognitive function [15-18]. The neurotoxicity of chemotherapy affects both the structure and function of the brain, especially the frontal lobe and the cognition processes [19]. In recent years, the improvement of rs-fMRI technology provides a relatively more direct and objective means for us to study brain network changes. Of course, this technique was also applied in the research of traditional central nervous system diseases, and soon some scholars applied it to explore the brain network generation mechanism of CRCI in breast cancer. Bruno studied the network of breast cancer patients after chemotherapy, and found that the brain network in the frontal lobe, temporal lobe and striatum area showed obvious abnormalities, and its clustering coefficient was significantly lower than that of healthy people. The conclusion was that the increase of the shortest path and the decrease of the clustering coefficient in the frontal lobe, temporal lobe and other regions of breast cancer patients after chemotherapy suggested that the abnormal brain network in the frontal lobe and temporal lobe, which are related to cognitive function, may be one of the important mechanisms of the occurrence of CRCI in breast cancer [20]. Similarly, Kesler pointed that patients may suffer damage of DMN after chemotherapy, which will further affect brain function and cause decline in learning, memory and other cognitive abilities [21]. Miao used anterior cingulate cortex (ACC) as the seed point and found that functional connectivity of left superior frontal gyrus, left medial frontal gyrus, left middle temporal gyrus, and right superior frontal gyrus had significantly decreased in breast cancer patients after chemotherapy, and the decreased connectivity of these areas was significantly correlated with cognitive dysfunction, especially the executive function [22].

Molecular classification of breast cancer has become one of the most important direction in the field of breast cancer research. Due to molecular genetic changes, there is a high degree of heterogeneity at the molecular level, which leads to a great difference in the prognosis and response to treatment of breast cancer. Several studies have shown heterogeneity within CRCI among breast cancer survivors [23, 24]. However, the specific mechanisms driving the heterogeneity of CRCI in breast cancer patients is not obvious. A study indicated that the different hormone receptor expression in BC patients may be related to the heterogeneity of CRCI [25]. The prognosis is different for BC patients with different hormone receptor expression, but the relationship between the occurrence of CRCI in breast cancer and the expression of hormone receptors remains unclear. Currently, few neuroimaging studies have investigated how alterations in the resting state functional connectivity within specific brain regions are related to cognitive function in BC patients with different hormone receptor expression. Therefore, the current study aims to explore the alterations of functional connectivity in BC patients with different hormone receptor expression by using resting-state fMRI. The dorsolateral prefrontal cortex (DLPFC), which is in the middle frontal gyrus, is involved functions including working memory, prospective memory and executive function [26]. We chose the DLPFC as the seed region and computed its functional connectivity with the whole brain at resting-state and then analyzed the relationship between the functional connectivity of the DLPFC network and neuropsychological performance of BC patients with different hormone receptor expression.

Materials and methods

Participants

Forty patients with breast cancer, before and after chemotherapy, were enrolled in this study in the Department of Oncology of the Affiliated Second Hospital of Anhui Medical University from September 2016 to February 2018. The patients were divided into two groups. The HR+ group was composed of twenty-one patients with ER+/PR+ status, and the HR- group included nineteen patients with ER-/PR- status. The study was approved by the Research Ethics Committee of the Affiliated Second Hospital of

Anhui Medical University, and all subjects provided their informed consent.

The inclusion criteria for the participants were as follows: (1) Postoperative pathological tissue and immune-histochemical diagnosis of breast cancer patients; (2) Standard-dose chemotherapy treatment with doxorubicin (40 mg/m^2) and paclitaxel (175 mg/m^2) for each chemotherapy cycle for 6 cycles; (3) Mini-Mental State Examination (MMSE) score ≥24; (4) Karnofsky Performance Scale (KPS) score ≥80; (5) No impairment in vision, hearing or language. Patients with breast cancer were excluded if the following conditions were present: (1) treatment with hormone- or radiation-therapy; (2) anxiety, depression, delusion and other mental symptoms; (3) a history of alcohol or drug dependence; (4) distant metastasis and advanced cachexia (5) other physical and mental disorders that can lead to cognitive impairment.

Neuropsychological background tests

A series of neuropsychological background tests were administered within one week before chemotherapy and within one month after chemotherapy to assess the general cognitive function, working memory and executive functions in patients with breast cancer. The neuropsychological assessment was performed on the same day as the MRI examination.

The MMSE (mini-mental state examination) was to assess the general cognitive, including memory, orientation, executive function, visual and spatial ability. The scale consists of 30 questions, one point for each question, and one point for correct answer, no point are awarded for wrong answer or unknown answer. The total score reflects the general cognitive function. The higher the score, the better the cognitive function; the lower the score, the worse the cognitive function.

The VFT (verbal fluency test) widely used for spontaneous speech generation, in which subjects are asked to generate a word in response to a prompt, reflecting the ability of patients to retrieve key words related to the content of the prompt from their own long-term memory. VFT requires subjects to list as many examples as possible within a specified time (1 min). The commonly used ranges include country, place names, schools, daily necessities, fruits, vegetables, animals, vehicles, and last names, and one point will be given for each answer.

The DST (digit span test) assessed participants' short-term memory and concentration, including digits forward or backward. When performing a number breadth order test, subjects are asked to repeat the number read by the operator. For example, the researchers read out five numbers: 11, 12, 13, 14, 15. The subjects repeated 11, 12, 13, 14, 15. The score for the last retelling of the correct string is 8. To do the number span backwards test, subjects were asked to repeat the number the researchers had read backwards. For example, the researchers read out five numbers: 11, 12, 13, 14, 15, and the subjects returned the five numbers: 15, 14, 13, 12, 11. According to the order set by the scale, digits backward was carried out, and the score was the corresponding score of the last backward correct string, with the highest score being 8 points.

Prospective memory (PM) and retrospective memory (RM) questionnaires

The PM/RM questionnaires (PRMQ) consisted of 16 items, 8 testing for PM disorders, and 8 for RM disorders. Patients were required to rate the degree of their memory failure on a 4-point Likert scale for each item: 4: very often, 3: sometimes, 2: rarely, 1: never. Total scores for RM or PM ranged from 8 to 32, with higher scores indicating greater memory impairment. All the tests were conducted in a quiet room without interference and were completed in 10 minutes.

Image acquisition

The image data was obtained by a Siemens Verio 3.0 Tesla scanner (Siemens, Erlangen, Germany) with 16-channel head coil at the Affiliated Second Hospital of An Hui Medical University. The whole MRI scan was about 15 min. The resting-state functional connectivity fMRI (R-fMRI) images were obtained by a gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence. The R-fMRI data was obtained as following parameters: TR = 2000 ms, TE = 25 ms, FA = 90°, acquisition matrix = 64 × 64, FOV = 240 × 240 mm, thickness = 4.0 mm, gap = 0 mm, NEX = 1.0, number of slices = 36, time points = 240. The T1-weighted 3D Spoiled

Gradient Recalled Echo (3D-SPGR) images were obtained with the following parameter settings: repetition time (TR) = 1900 ms, echo time (TE) = 2.48 ms, flip angle (FA) = 9°, acquisition matrix = 256 × 256, field of view (FOV) = 240 × 240 mm, thickness = 1.0 mm, gap = 0 mm, number of slices = 176, number of excitations (NEX) = 1.0. During the data scans, all participants were instructed to keep their eyes closed and to avoid falling asleep or getting distracted during the scanning.

Image preprocessing

The fMRI data were preprocessed by using a SPM12 toolkit (http://www.fil.ion.ucl.ac.uk/spm) and MATLAB version 8.0 (The Math Works, Inc., Natick, MA, USA). First, the first ten volumes of the scanning session were discarded for T1 equilibration effects. The remaining 230 volumes were corrected for slice timing, realigned, and subsequently spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template using the default settings. All the normalized images were resliced by 3.0 × 3.0 × 3.0 mm^3 voxels. To further reduce the effects of confounding factors, six motion parameters, the global mean signal, white matter (WM) signal, and cerebrospinal fluid (CSF) signal were removed from the data through linear regression. The head motion in each direction over 2 mm or rotation angle exceed 2° were excluded. We also calculated the framewise displacement (FD), which reflects the mismatch of volume to volume head position [27, 28]. There was no significant difference in the FD among groups ($P > 0.05$), and the mean FD was also applied as a covariate in the imaging analyses. Moreover, a bandpass filter was applied to maintain low-frequency fluctuations within a frequency range of 0.015-0.1 Hz. Lastly, the images were smoothed by a 6 mm full width at half maximum Gaussian kernel. After preprocessing, the individual data were used for further connectivity analyses.

Statistical analysis

Demographic and neuropsychological data: The Statistical Package for Social Sciences (SPSS) 16.0 was used for all statistical analyses. Differences in questionnaire scores that were obtained before and after chemotherapy were analyzed by means of paired-samples t-tests. Comparisons between groups were assessed using independent samples t-tests. In addition, the categorical variables such as pathological pattern and stage of tumor in the groups were assessed by the chi-square (χ^2) test. All statistical tests were two-tailed with the level of significance set at $P < 0.05$.

Analysis of resting-state functional connectivity: We used an anatomical region-of-interest (ROI) method to extract the bilateral DLPFC as the seed region. Data from the bilateral DLPFC regions over time were extracted from functional EPI images of each subject. The mean time course of the signal in each DLPFC region was used as the seed time course, and cross-correlation was used to correlate the time course of all brain voxels. Then, the Pearson correlation coefficient (r) was subjected to a Fisher z transform to obtain variables approximating a normal distribution [$m = 0.5 \ln (1 + r)/(1-r)$]. Finally, the data were spatially normalized to MNI space, resampled to 3 mm isotropic voxels, and smoothed with a Gaussian kernel (6-mm full width at half maximum).

Partial correlation analysis: To explore whether the DLPFC functional connectivity alterations were associated with the cognitive performances of the breast cancer patients. The correlation between the change of neuropsychological test and the change of DLPFC functional connectivity in breast cancer patients was analyzed. The correlation analyses were also conducted separately in the HR+ and HR- group breast cancer patients.

Results

Demographic characteristic and clinical data

As illustrated in **Table 1**, there were no significant differences in the demographic information, including the age, the level of education, and the menstrual status, as well as in clinical information such as the Karnofsky performance status (KPS), pathological pattern and tumor stage between the HR+ and HR- groups ($P > 0.05$).

Neuropsychological assessment and memory questionnaire results

Table 2 shows the performance of the breast cancer patients before and after chemotherapy on the neuropsychological tests and memory

Table 1. Comparison of demographic characteristics and clinical data of breast cancer between the HR+ group and the HR- group

	HR+ (n=21)	HR- (n=19)	t/χ^2	P
Age (years)	52.29±7.27	48.47±7.62	1.618	0.114
Education (years)	7.76±3.67	8.16±3.29	-0.358	0.722
KPS	89.52±5.90	87.89±5.35	0.911	0.368
Pathological pattern (cases)				
Invasive ductal carcinoma	16	13	0.302	0.583
Invasive lobular carcinoma	5	6		
Stage (cases)				
I	4	5	0.311	0.856
II	10	8		
III	7	6		
Menstrual status				
Premenopausal	8	10	0.852	0.356
Postmenopausal	13	9		

Notes: Data are presented as mean ± SD. Abbreviations: SD, standard deviation; KPS, Karnofsky performance status; HR+, breast cancer patients with ER+/PR+ status; HR-, breast cancer patients with ER-/PR- status.

Table 2. Comparison of neuropsychological tests and memory performance in patients with breast cancer before and after chemotherapy

Parameters	CB (n=40)	CA (n=40)	t	P
MMSE	29.10±0.87	25.03±2.37	9.781	0
VFT	11.55±2.29	6.30±1.47	12.774	0
DST	6.38±0.87	4.78±1.21	7.495	0
PM	10.90±1.74	20.18±4.01	-14.153	0
RM	10.15±1.56	19.65±2.67	-20.782	0

Notes: Data are presented as mean ± SD. Abbreviations: SD, standard deviation; MMSE, mini-mental state examination; DST, digit span test; VFT, verbal fluency test; PM, prospective memory; RM, retrospective memory; CB, breast cancer patients before chemotherapy; CA, breast cancer patients after chemotherapy.

questionnaires. There were significant differences in the total scores on the MMSE ($t = 9.781$, $P < 0.01$), VFT ($t = 12.774$, $P < 0.01$), DST ($t = 7.495$, $P < 0.01$), PM ($t = -14.153$, $P < 0.01$), and RM ($t = -20.782$, $P < 0.01$). In **Table 3**, it suggested that the general cognitive function on MMSE ($t = 3.381$; $P < 0.01$), VFT ($t = 3.205$; $P < 0.01$), DST ($t = 2.101$; $P < 0.05$), PM ($t = -2.207$; $P < 0.05$) and RM ($t = -4.006$; $P < 0.01$) had significant differences between the HR+ group and the HR- group breast cancer patients after chemotherapy.

However, there were no significant differences on the neuropsychological tests and memory questionnaires between the HR+ group and the HR- group breast cancer patients before chemotherapy.

Functional connectivity

There was a significant difference in the functional connectivity in the bilateral DLPFC network in the BC patients after chemotherapy (**Figure 1** and **Table 4**). Compared to before chemotherapy, there was a significant increase in the functional connectivity in the BC patients after chemotherapy in the following areas: the left DLPFC with the left precuneus ($t = -2.789$, $P < 0.01$), the right DLPFC with the right precuneus ($t = -3.086$, $P < 0.01$), and the right superior frontal gyrus ($t = -3.442$, $P < 0.01$). In addition, the functional connectivity of the left DLPFC with left precuneus ($t = -2.247$, $P < 0.05$), the right DLPFC with the right precuneus ($t = -2.034$, $P < 0.05$), and the right superior frontal gyrus ($t = -2.337$, $P < 0.05$) in the HR- group were significantly increased in comparison with those in the HR+ group (**Figure 2**).

Correlation

A significant positive correlation was observed between the FC of the left DLPFC-left precuneus and the PM score in the HR- group breast cancer patients after chemotherapy ($r = 0.444$, $P = 0.02$) (**Figure 3**). No significant correlation was observed between the other neuropsychological performances and the FC alteration.

Discussion

In the present study, we found that BC patients with different hormone receptor expression have different levels of CRCI. Specifically, BC patients with an ER-/PR-status have poorer scores on memory and the DS tests than patients with an ER+/PR+ status. In addition, BC patients in the HR- group had more serious chemotherapy-induced PM and RM impairment than patients in the HR+ group. This is consis-

Table 3. Comparison of neuropsychological tests and memory questionnaires between the HR+ group and the HR- group breast cancer patients before and after chemotherapy

Parameters	Before				After			
	HR+ (n=21)	HR- (n=19)	t	P	HR+ (n=21)	HR- (n=19)	t	P
MMSE	29.14±0.91	29.05±0.85	0.323	0.748	26.10±1.92	23.84±2.29	3.381	0.002
VFT	11.76±2.76	11.32±1.67	0.626	0.536	6.95±0.86	5.58±1.68	3.205	0.004
DST	6.29±0.85	6.47±0.90	-0.679	0.501	5.14±0.98	4.37±1.34	2.101	0.042
PM	10.86±1.85	10.95±1.65	-0.162	0.872	18.90±3.97	21.58±3.66	-2.207	0.033
RM	10.14±1.59	10.16±1.57	-0.030	0.976	18.29±2.22	21.16±2.32	-4.006	0.000

Notes: Data are presented as mean ± SD. Abbreviations: SD, standard deviation; MMSE, mini-mental state examination; DST, digit span test; VFT, verbal fluency test; PM, prospective memory; RM, retrospective memory; HR+, breast cancer patients with ER+/PR+ status; HR-, breast cancer patients with ER-/PR- status.

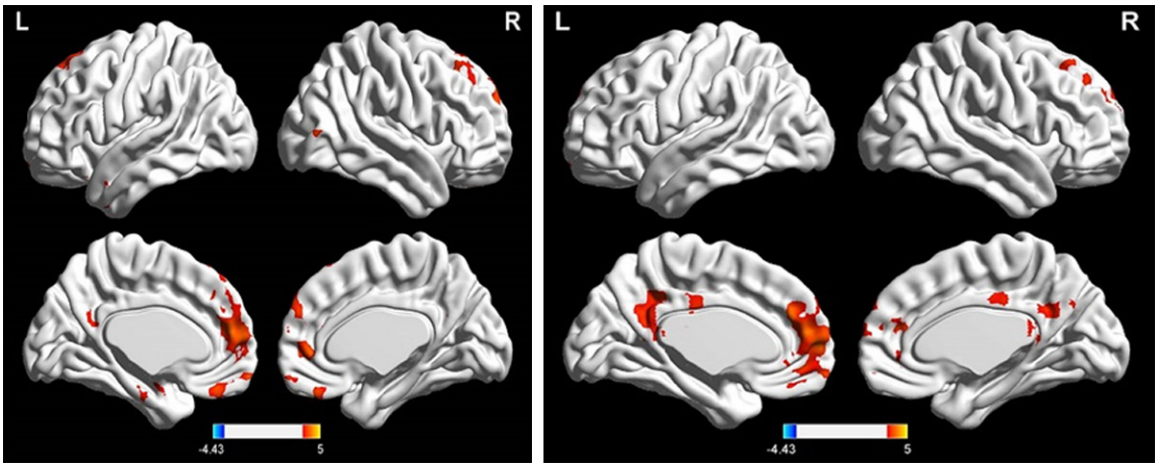

Figure 1. The resting state analysis of functional connectivity of bilateral DLPFC networks in breast cancer patients before and after chemotherapy. (Warm color represents the increase of FC value after chemotherapy, while cool color represents the decrease of FC value. After 3 d clustsim correction, P=0.005, α=0.05, cluster size >35).

Table 4. Analysis results of functional connectivity of bilateral DLPFC networks in breast cancer patients after chemotherapy

Brain region	BA	Cluster size	MNI Coordinate (RAI)			Peak (Z value)	t	P
			X	Y	Z			
Left DLPFC FC networks								
Left Precuneus	7	39	-12	-57	72	3.35	-2.789	0.007
Right DLPFC FC networks								
Right SFG	8	66	27	30	51	3.35	-3.442	0.001
Right Precuneus	7	36	3	-57	69	3.73	-3.086	0.003

Abbreviations: MNI, Montreal Neurological Institute; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; SFG, superior frontal gyrus.

tent with a previous study that showed that the expression of different hormone receptors may be related to the heterogeneity of CRCI in breast cancer [25].

In this study, we found that breast cancer patients with different hormone receptor expression receiving chemotherapy displayed change of functional connectivity in the bilateral DLPFC networks, and that the correlation analysis within the HR- group also indicated that the altered functional connectivity between the left DLPFC and left PCU was significantly correlated with the prospective memory (PM) in HR- group.

There is evidence that estrogen and progesterone play an important role in the regulation of cognition [29]. In clinical, estrogen is useful in the treatment of menopause and age-related

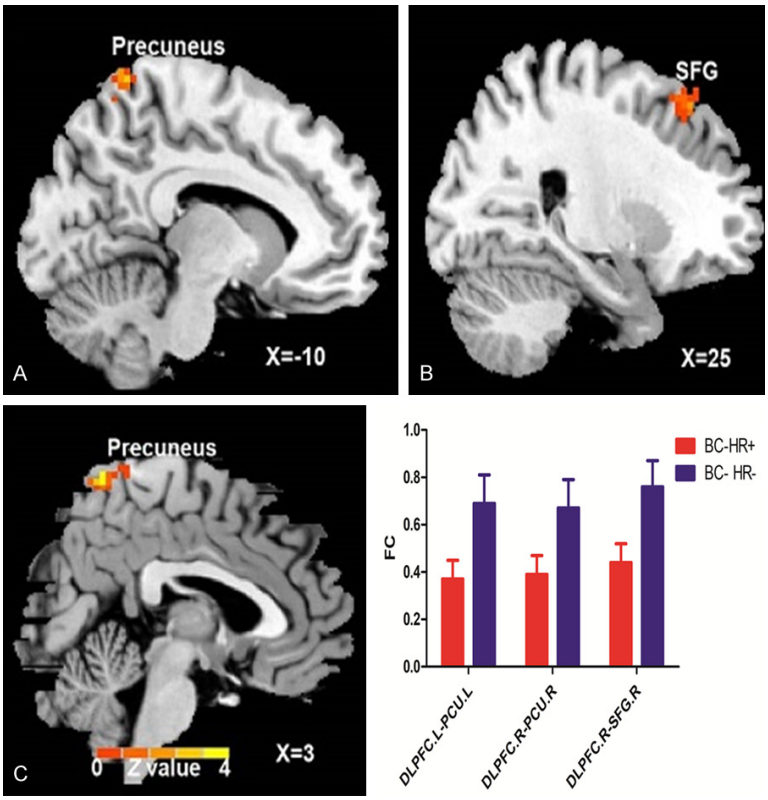

Figure 2. Brain regions showing significant differences in the bilateral DLPFC functional connectivity networks between the HR+ group and the HR- group breast cancer after chemotherapy are illustrated in (A) (Left Precuneus), (B) (Right SFG) and (C) (Right Precuneus). The numerical representation of significant differences in the bilateral DLPFC networks is described in the histograms. The color bar presents Z scores. Abbreviations: L.DLPFC, left dorsolateral prefrontal cortex; L.PCU, left precuneus; R.DLPFC, right dorsolateral prefrontal cortex; R.SFG, right superior frontal gyrus; R.PCU, right precuneus. BC-HR+, breast cancer patients with ER+/PR+ status; BC-HR-, breast cancer patients with ER-/PR- status.

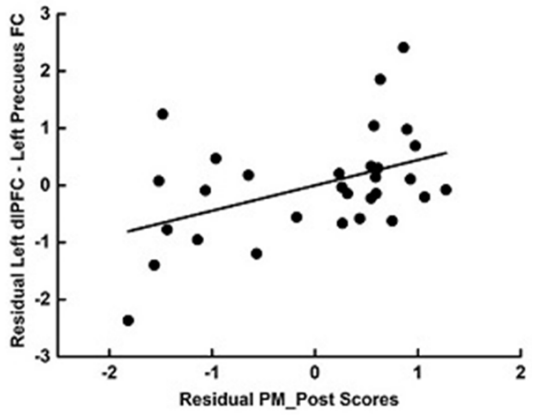

Figure 3. Scatter plot of the DLPFC functional connectivity and the PM Test. A significant positive correlation was found between the PM scores and the functional connectivity of the left DLPFC with the left precuneus in the HR- group (r=0.444, P=0.02). The x-axis represents the PM test of the breast cancer patients in the HR- group after chemotherapy (scores), and the y-axis represents the functional connectivity strength. The threshold was set to P<0.05 (corrected using the Monte Carlo method). DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; PM, prospective memory.

cognitive decline [30]. Estrogen works by binding to estrogen receptors and plays a key role in cognitive function, especially in memory. Progesterone is involved in regulating the expression of nerve nutrients and promoting cell survival. When progesterone binds to its receptor, it can activate signal transduction pathways and trigger relevant cellular events, which is the key to neural protection [31]. It can be seen that PRs can mediate the neuroprotective effect of progesterone in the central nervous system, especially the release of brain-derived neurotrophic factor, which is widely and richly expressed in the brain [32]. Brain-derived neurotrophic factors play an important role in neuronal homeostasis, plasticity, and memory consolidation and recovery [33]. The study also found that estrogen not only has nutritional and neuroprotective effects, but also can enhance memory and language ability [34, 35]. Our results suggest that cognitive impairment is more significant in breast cancer patients with negative hormone receptor expression than in breast cancer patients with positive receptor expression after chemotherapy, which may be related to the role of estrogen and progesterone in regulating cognitive function.

The DLPFC is believed to play a key role in the working memory, prospective memory and executive function, and damage to this region will cause executive dysfunction syndrome [36]. A significant positive correlation was observed between the functional connectivity strength of the left DLPFC and the left PCU and the pro-

spective memory (PM) in the HR- group. The increased functional connectivity between the left DLPFC and the left PCU might account for the prospective memory impairment. The PCU is an area located in the posterior portion of the parietal lobe, which is reported to be involved with attentional tracking and visual-spatial imagery [37]. Memory impairment is the most prominent aspect of CRCI, which has attracted increasing recognition as an identifiable cognitive change [38, 39]. Prospective memory is the recall of plans or intentions that need to be made or carried out in the future and is most closely related to daily activities [40]. Neuropsychological studies have reported that the PM is associated with the prefrontal cortex [41]. It has been demonstrated that breast cancer survivors exhibited increased functional connectivity between the left DLPFC and left PCU, which had significant relevance to the prospective memory, reflecting a certain level of memory impairment. This study showed the functional connectivity between the left DLPFC and left precuneus, as well as the right DLPFC with the right precuneus and right superior frontal gyrus were increased. Most of researches suggest that the influence of chemotherapy on brain structure and function involves the frontal lobe [42, 43]. The function of the frontal lobe is related to attention, executive function and learning ability. The frontal lobe is also a significant brain region in our findings that the functional connectivity of SFG increased after chemotherapy. Typically, increased connectivity of a neural network is associated with improved performance and efficiency of that network. Sometimes over-connectivity can be a problem, but that is typically because the increased efficiency of that network is interfering with a more important component of the network or the function of a more important competing network.

The current study strongly suggested that BC patients with different hormone receptor expression have altered functional connectivity of DLPFC as well as different levels of CRCI after chemotherapy. However, one limitation of our study should be considered. The number of BC patients was limited. Future investigations could include a larger sample of breast cancer patients to verify the reliability and validity of the tests.

Conclusion

The present research combined neuropsychological tests with fMRI examination and suggests that BC patients with different hormone receptor expression may present with differences in CRCI, and the DLPFC may be selectively involved in the heterogeneity of CRCI in BC patients with different hormone receptor expression, especially in the prospective memory.

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Disclosure of conflict of interest

None.

Address correspondence to: Huaidong Cheng, Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui, China. E-mail: chd1975ay@126.com

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