Executive function alternations of breast cancer patients after chemotherapy: evidences from resting-state functional MRI

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Ethical approval

We declare that this study has been approved by the Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in this study.

Abstract:

Rationale and Objectives: Chemotherapy has many side-effects on breast cancer patients, including cognition and other brain functions impairment, which can be studied using functional MRI. Our study aimed at investigating the executive function alternations of breast cancer patients after chemotherapy using resting-state functional MRI.

Materials and Methods: This study included 32 breast cancer patients (BC group) and 24 control subjects (HC group). The functional connectivity of dorsolateral prefrontal cortex (DLPFC) of the two groups was calculated from the rs-fMRI data, and the correlation between the strength of right DLPFC's connectivity and the behavior performance was analyzed with two-tailed Pearson correlative analysis.

Results: Evaluation of the capability of processing various complex cognition events showed that the executive function of the BC group was impaired after chemotherapy in comparison with the HC group. The functional connectivity of right DLPFC with right inferior frontal gyrus (right IFG), right medial frontal gyrus (right MFG), and left superior temporal gyrus (left STG) in the BC group were significantly decreased in comparison with those in the HC group, respectively. The executive deficits were found correlated with the functional connectivity between right DLPFC and right IFG. Meantime, functional connectivity from right DLPFC to right middle temporal gyrus (right MTG) and the precuneus was compensatorily increased in the BC group, respectively.

Conclusion: These findings suggest that breast cancer patients after chemotherapy demonstrates executive control impairment and provide an evidence that the observed defects are correlated with alternations in the executive network of the brain.

Keywords: breast cancer; chemotherapy treatment; functional connectivity; executive function; resting-state functional MRI.

1. Introduction

Breast cancer is the most common cancer in women (1). Most of patients diagnosed of breast cancer are treated with surgery and combined with chemotherapy or endocrine therapy. However, with the increase of survival probability, the side-effects of chemotherapy and endocrine therapy are reported frequently (2). Chemotherapy is commonly applied in cancer treatment, nevertheless, its central nervous system toxicity affects long-term quality of life (3).

Chemotherapy influences the central nervous system possibly through triggering cell death, increasing oxidative stress and microglia activity, suppressing hippocampal neurogenesis, and decreasing the neurotrophic factors and hippocampal catecholamines (4). Previous studies indicate that breast cancer patients show cognitive impairments after chemotherapy, particularly in the capability of memory, attention, executive controlling and information processing (5). The executive function mainly includes information processing, problem solving, planning and execution (6). Central executive network, which is responsible for the executive function, mainly involves the frontal lobe and part of the parietal and temporal lobes (7, 8). The prefrontal cortex (PFC) comprises of the frontal part of the frontal lobe, and connects several neocortical areas that send and receive projections from almost all of the cortical sensory systems, motor systems and numerous subcortical structures (9). Clinical neuropsychological trials indicate that the prefrontal cortex plays a central role in the cognitive control behavior. Correspondingly, patients with prefrontal cortex damage show impaired judgement, organization, and decision-making capability, as well as the neuropsychological disinhibition and intellectual difficulties (10, 11).

Several cross-sectional fMRI studies demonstrate that the cognitive impairments are mainly related to the frontal lobe of the brain (12, 13). Another research reports that chemotherapy could reduce white matter integrity and induce microstructural damage to the white matter tracts (14). There are significant correlations found between the structural abnormality in the frontal white matter tracts of the brain and the neuropsychological performance (15). Meanwhile, gray matter alterations in the frontal lobes are also found in breast cancer patients after chemotherapy (16). Chemotherapy-induced neurotoxicity have effects on both structure and function of the brain, especially the frontal lobe and the cognition processes (17). The dorsolateral prefrontal cortex (DLPFC), which in the middle frontal gyrus plays roles in the executive function. The ventral part of DLPFC is involved in detecting visuospatial signals, as the primary interface for sensory signals. The dorsal part of DLPFC is involved in integrating multiple forms of information for planning action and representing processed motor information, such as arm use or target location (18). According to the previous study, the activation of DLPFC is notably decreased in patients after chemotherapy (19). The acquired brain damage, not only leads to decreased activation of the brain, but also the brain plastic compensation of the brain cortex during the cognitive impairment process (20), as suggested by previously report increased compensation activity of several brain areas to maintain the fundamental function of the brain after cognition impairments (21-23). Thus, considering the complexity of brain function, it is important to analyze the functional alternation within brain network.

The altered structure and activation pattern of the executive network in breast cancer patients might imply relevant abnormal brain function, but few evidences in neuroimaging have been found between altered functional connectivity of central executive network and cognitive performance. Whether the evidences from functional and neuropsychological studies are correlated in the central executive network is still inexplicit. Therefore, the aim of this study was to explore whether the functional

connectivity of DLPFC has been changed among the breast cancer patients undergoing chemotherapy treatment using neuroimaging methods and neuropsychological tests, and the conceivable underlying mechanism of the cognition alternations of breast cancer patients.

2. Materials and methods

2.1 Participants

All participants were recruited from the First Affiliated Hospital of Anhui Medical University, Hefei, China. Participants were divided into two groups in this study. The chemotherapy treatment group (BC group) was composed of 32 female patients, who were diagnosed Stage II or III breast cancer and treated with the common standard-dose chemotherapy regimen (Docetaxel/ Adriamycin / Cyclophosphamide (TAC)), and eight of them were postmenopausal. All of the patients did not receive any other treatments and were assessed 1 month after the end of the chemotherapy treatment. The healthy control group (HC group) included 24 females matched with BC group for age and education level, and seven of them were postmenopausal. The detailed information gathered from each participant was described in Table A. All participants were examined to exclude neurological, psychiatric or medical conditions known to affect cognitive function and any magnetic resonance imaging (MRI) contraindications. All participants provided informed consent.

2.2 Neuropsychological background tests

General cognitive function was measured using the Beijing Version of the Montreal Cognitive Assessment Test (MoCA Test) (24). The Chinese version of the Cancer Related Fatigue (CRF) test was performed to rule out fatigue symptoms (25). The Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Rating Scale (HAMA) were used to assess the participants' potential depression and anxiety symptoms, respectively

(26). The CRF, MoCA, HAMA, HAMD were used to screen current psychiatric symptoms that could confound between-group comparisons (Hamilton Depression Rating Scale scores >7 and/or Hamilton Anxiety Rating Scale scores >7 were excluded from the study). Results of neuropsychological background tests were showed in Table A.

2.3 Stroop Color-Word Test

The Stroop Color-Word Test (SCWT) is highly reliable in measuring the ability of attention and executive control of the subjects. In the Stroop Color Test, participants were asked to name the color of a solid circle. In the Stroop Word Test, participants were required to name the color of the word. In the Stroop Interference Test, participants were asked to figure out the right color of the word while the name of the color was printed in a color not denoted by the name. Naming the color of the word took longer time and it's more prone to make errors than when the color of the ink matches the name of the color. It took each participant approximately 1 h to complete the neuropsychological tests. All of the assessments were performed by the skilled psychologists and psychiatrists and the detailed information was described in Table A. Neuropsychological tests were administered the same day as the MRI scan.

2.4 Image acquisition

Functional MRI (fMRI) data were obtained using a GE 3.0T MRI scanner (GE Healthcare, Milwaukee, Wisconsin, USA) equipped with a standard head coil. During the resting-state fMRI scans, all participants were instructed to keep their eyes closed, and avoid falling asleep or getting distracted during the scanning. The resting-state functional images were recorded with the following parameters: repetition time/echo time = 2000/22.5 ms, flip angle = 30 degrees, 33 slices, thickness/gap ratio = 4.0/0.6 mm, voxel size = $3.4 \times 3.4 \times 4.6 \text{ mm}^3$, matrix size = 64×64 , and field of view = $220 \times 220 \text{ mm}^2$. The T1-weighted 3D-SPGR images were obtained with the following parameter settings:

repetition time (TR) = 7.2 ms, echo time (TE) = 3.1 ms, flip angle = 12 degrees, slice thickness = 1 mm, image resolution = 1mm×1mm×1mm, field of view (FOV)=24 cm×24 cm, matrix size = 256 × 256, acquisition time approximately 9 minutes, and 172 sagittal slices.

2.5 Image preprocessing

The fMRI data were preprocessed by using a combination of FSL (Analysis Group, FMRIB, Oxford, UK), AFNI (Medical College of Wisconsin, Milwaukee, Wisconsin, USA), and Freesurfer (Martinos Center for Biomedical Imaging, Laboratory for Computational Neuroimaging, USA). Firstly, the anatomical and functional images were reconstructed and realigned by using a unified matrix. Then, skull stripping and motion correction were performed, followed by co-registration between functional and anatomical images and normalization to the Montreal Neurological Institute (MNI152) standard brain. The head motion was also assessed by estimating the motion magnitude and its differential, and the data with magnitude over 2 mm or 2° were excluded. Volumes with differential motion over 0.2 mm were censored out. To remove low-frequency drift and high-frequency noises, all fMRI signals were filtered by band-pass filtering (0.01 – 0.08 Hz) and then spatially smoothed by using a 6 mm full width at half maximum Gaussian kernel. After preprocessing, the individual data was used for further connectivity analyses.

2.6 Functional connectivity analysis

The region of interest (ROI) was extracted from the right DLPFC (MNI coordinate: 42, 33, 33) according to a previous study (27). Then, the functional connectivity of right DLPFC was computed. The temporal signal series of cerebrospinal fluid, cerebral white matter and the MRI signal of seed point of right DLPFC was extracted. Thereafter, several sources of variances were removed from the data by linear regression as follows:

(a) 6 parameters obtained by rigid body correction of head motion, (b) the signal from cerebrospinal fluid, and (c) the signal from the region centered in the white matter.

2.7 Group and correlative analysis

Intergroup analysis was carried out by using the two sample t-test between BC group and HC group. The results were corrected with Monte Carlo method, in which whole brain mask of MNI template was used and Full Width Half Maximum was set to Gaussian filter width (6 mm). The threshold of statistical significance was set to $P = 0.05$, $\alpha = 0.05$ and a minimum cluster size of 157 voxels. In order to clearly demonstrate the relationship between the alternations in functional connectivity and the response time, the scatter plots of functional connectivity in all brain areas above the threshold were provided using two-tailed Pearson correlation analysis.

3. Results

3.1 Neuropsychological evaluation

Table A showed the characteristics and neuropsychological background tests of patients and healthy controls recruited in this study. The years of education and general cognitive function had no significant difference between the BC group and the HC group ($p > 0.05$), indicating that there was no global cognitive impairment in both groups. The BC group had significantly worse performance in all Stroop test blocks than the HC group. Stroop Color Test ($t = 2.731$, $p < 0.01$), Stroop Word Test ($t = 4.238$, $p < 0.01$), and Stroop Interference Test ($t = 2.586$, $p < 0.05$).

3.2 Alternation of the central executive network connectivity

There was significant lower functional connectivity in BC group compared with HC group in the following areas: left superior temporal gyrus (left STG), right inferior frontal gyrus (right IFG) and right medial frontal gyrus (right MFG). Meanwhile, increased

functional connectivity had also been found in both right middle temporal gyrus (right MTG) and right precuneus (Fig. 1 and Table 2).

3.3 Correlation analysis

A negative correlation between the response time in Stroop Interference Test and the functional connectivity strength of right DLPFC within signal lower areas including right IFG ($r = -0.376$, $p = 0.0339$) in BC group is presented in Fig. 2. No significant correlations were observed between the response times in Stroop tests and the strength of functional connectivity of right DLPFC with other significantly changed areas. In addition, no significant correlation was observed between fatigue and functional connectivity of right DLPFC (all P 's > 0.10).

4. Discussion

In this study, we found that breast cancer patients receiving chemotherapy displayed abnormal functional connectivity in right DLPFC compared to that of the healthy controls. In the meantime, the altered functional connectivity between right DLPFC and right IFG was correlated to the worse neuropsychological performance of the BC group. Chemotherapy-induced cognitive impairments are widely associated with the frontal lobe and corresponding brain change (28). Cancer survivors who had previously received chemotherapy for several years showed hypo-responsiveness in prefrontal cortex during executive function and episodic memory tasks (19). DLPFC is assumed to play a key role in working memory and executive function, and damage to this part provokes dysexecutive syndrome (29). In this part, we would firstly discuss which areas are altered and then focus on what these changes might imply in breast cancer survivors.

4.1 Functional connectivity reduction of areas related to the executive network

4.1.1 The decreased functional connectivity was correlated to the worse

neuropsychological performance.

A significant negative correlation was observed between the response times in Stroop Interference Test and the functional connectivity strength of right DLPFC and right IFG in BC group. The decreased functional connectivity between right DLPFC and right IFG might account for the dysfunction of response control. The IFG is a gyrus of the frontal lobe and strongly connects to PFC. According to several neuroimaging studies, IFG is consistently and specially activated during the processing of response inhibition (30), which refers to the ability to withhold a response to an event, stop an ongoing response and resist or control interference (31). The right IFG and inhibitory control have been typically implicated in Stroop tests, which produce two competing kinds of information. Participants are required to inhibit processing of one to select and respond to the other one (32). Response inhibition is the cognitive process required to inhibit pre-planned or on-going motor action, which constitutes a critical function of executive control. Functional MRI studies revealed that a right-frontal deficit impaired response inhibition in IFC lesioned group. Problems with response inhibition have been widely documented in children and adults with a diagnosis of attention-deficit hyperactivity disorder (33). It has been demonstrated that breast cancer survivors exhibited decreased connectivity strength between the right DLPFC and the right IFG that had significant relevance with the Stroop Interference Test, reflecting a certain level of impairment of response inhibit capacity. The study demonstrated the connectivity between right IFG and right DLPFC could significantly influence the ability to control and manage cognitive processes in breast cancer patients.

4.1.2 The decreased functional connectivity was related to the executive network.

Significant decreases in functional connectivity were also observed in left STG and right MFG to right DLPFC. Both of areas are essential in executive control and are reported to be significantly less activated during verbal memory retrieval tasks in breast

cancer patients receiving chemotherapy (34). The STG is one of three gyri in the temporal lobe. Situated laterally to the head and above ear (35), it is involved in auditory processing and has been implicated as a critical structure in social cognition (36). Processing of syntactic violations specifically involved STG according to an event-related functional MRI study (37). The MFG is located in the frontal lobe of the mammalian brain. This gyrus is one of the ridges on the outer part of the cortex. An fMRI study based on the test Perceptual Go/No-Go Decisions differentiates the organization and function of the MFG and suggests that the executive mechanisms operative within the MFG preserve fundamental aspects of input processing streams (38). Cancer survivors often complain about the social issues and difficulties in decision making after the completion of chemotherapy (4). The effects of abnormal functional connectivity in these areas on the brain function were complicated in an interactive way through segregation and integration (39). In this study, we only found that the functional connectivity in left STG and right MFG with right DLPFC was decreased, which had no correlation with the neuropsychological tests. This result might demonstrate, on the other hand, the importance of the right IFG in descended executive function of breast cancer patients.

4.2 Compensatory increase of connectivity between right middle temporal gyrus, right precuneus and right DLPFC

Increased functional connectivity was observed between right DLPFC and right MTG, as well as the functional connectivity between right DLPFC and right precuneus. The MTG is located between the superior temporal gyrus and inferior temporal gyrus. Its function has been implicated in maintenance during phonological working memory (40). Persons with MTG lesions show disrupted comprehension ability of language (41), suggesting its mediating role in verbal working memory. The right MTG is extensively activated for a more rapid response to the task in schizophrenia patients according to an

fMRI study (21). Research also shows that temporal areas are hyperactivated as a compensatory reaction under increasing demand to accomplish comparable performances in memory tasks (22). The precuneus is an area located in the posteromedial portion of the parietal lobe, which has been reported to be involved in attentive tracking, visuospatial imagery and spatially guided behaviors (42, 43). That the precuneus may be possibly involved in successful compensation for the cognitive difficulties in older adults, is suggested by a positive correlation between recollection and precuneus activity (23). Compensation is a type of defense mechanism in which people overachieve in some brain areas to compensate for failures in others. As mentioned above, though there were significant worse performances of executive functions in BC group, the attention ability and general cognitive abilities were reserved. The hyper-activation of right MTG and right precuneus may indicate a compensation mechanism in cognition ability among breast cancer patients, which should be further investigated in combination with other cognitive tests.

4.3 Limitations of this study

Although consistent and interesting results were found, there were several limitations in this study. One was that the cognition performance of the patients had not been measured before chemotherapy. The short interval after chemotherapy was another limitation. Long-term effects of chemotherapy on executive function should be taken into consideration. In this study, the abnormal connectivity in left STG and right MFG with the right DLPFC was found but had no significant correlation to the neuropsychological tests. Therefore, a follow-up and targeted study should be involved to explore the underlying mechanism.

5. Conclusion

The present functional MRI research combined with neuropsychological tests in this

study suggests that breast cancer survivors treated with chemotherapy demonstrates a significant executive control alteration, which is correlated with altered functional connectivity in areas related to executive network of the brain in comparison with healthy controls. Such discrepancies between breast cancer survivors and healthy people in cognitive functions prompt attention on auxiliary cognitive therapy in combination with chemotherapy. This study also shows the important role of the connectivity between right DLPFC and right IFG in executive control. Overall, the study improves our understanding regarding the brain changes and neurological dysfunction that occur during chemotherapy for breast cancer.

Conflicts of interest

There are no conflicts of interest.

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Caption for figures

Fig. A Connectivity-altered areas with right DLPFC

The right DLPFC used for this analysis was determined by the seed-based method. The threshold was set to $P \leq 0.05$, $\alpha \leq 0.05$ (corrected using the Monte Carlo method), and cluster size = 157. The colors represent the degree of correlation (Z-value) between functional connectivity strength. The connectivity altered areas included left STG, right IFG, right MFG, right MTG, precuneus, and declive.

Abbreviations: DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; IFG, inferior frontal gyrus; MFG, medial frontal gyrus; MTG, middle temporal gyrus. L, left hemisphere; R, right hemisphere.

Fig. B Scatter plot of right DLPFC functional connectivity and the response times for Stroop Interference Test

A negative correlation was found between the response times and the strength of functional connectivity between right DLPFC and right IFG ($r = -0.376$, $P = 0.0339$). The x-axis represents the response times for the Stroop Interference Test (sec) and the y-axis represents the functional connectivity strength. The threshold was set to $P \leq 0.05$ (corrected using the Monte Carlo method).

Abbreviations: DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus.

L

R

Table A: Summary of characteristics and neuropsychological tests of patients and healthy controls recruited for this study.

Variable	BC group(n=32)	HC group(n=24)	T value	P value
	Mean(SD)	Mean(SD)		
Age(years)	44.19(6.61)	43.25(8.45)	0.450	.655
Education(years)	10.56(2.63)	10.63(2.26)	-0.095	.924
Fatigue	23.03(3.80)	21.71(4.13)	1.227	.226
HAMA	4.47(1.24)	4.42(1.25)	0.155	.878
HAMD	4.91(1.20)	4.54(1.38)	0.329	.744
MoCA	25.28(1.42)	25.50(1.29)	-0.603	.549
Stroop Word Test(sec)	16.38(3.69)	14.07(2.65)	2.731	.009
Stroop Color Test(sec)	21.73(3.90)	17.99(2.69)	4.238	<0.001
Stroop Interference Test(sec)	34.28(7.90)	29.72(5.29)	2.586	.012

Abbreviations: BC, breast cancer; HC, health controls; SD, standard deviation; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; MoCA, Montreal Cognitive Assessment Test.

Table B: Group analysis results of functional connectivity of right DLPFC

Region (BA)	MNI coordinates				Peak (Z value)
	Side	X(mm)	Y(mm)	Z(mm)	
Superior temporal gyrus(22)	L	-56	0	0	-2.94
Inferior frontal gyrus(47)	R	54	18	2	-3.71
Medial frontal gyrus(6)	R	10	2	56	-2.98
Middle temporal gyrus(39)	R	52	-70	14	3.08
Precuneus(31)	R	6	-52	30	2.51
Declive	R	4	-82	-18	2..81

Abbreviations: DLPFC, dorsolateral prefrontal cortex; BA, Brodmann area; L, left; R, right; MNI, Montreal Neurological Institute.

The threshold was set to $P \leq 0.05$, $\alpha \leq 0.05$ (corrected using the Monte Carlo method).