Original Investigation

Executive Function Alternations of Breast Cancer Patients After Chemotherapy: Evidence From Resting-state Functional MRI

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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 magnetic resonance imaging (fMRI). Our study aimed at investigating the executive function alternations of breast cancer patients after chemotherapy using resting-state fMRI.

Materials and Methods: This study included 32 breast cancer patients (BC group) and 24 control subjects (HC group). The functional connectivity of the dorsolateral prefrontal cortex (DLPFC) of the two groups was calculated from the resting-state fMRI data, and the correlation between the strength of the 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 connectivities of the right DLPFC with the right inferior frontal gyrus, right medial frontal gyrus, and left superior temporal gyrus 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 the right DLPFC and the right inferior frontal gyrus. Meantime, the functional connectivity from the right DLPFC to the right middle temporal gyrus and the precuneus was compensatorily increased in the BC group, respectively.

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

Key Words: Breast cancer; chemotherapy treatment; functional connectivity; executive function; resting-state functional MRI.

INTRODUCTION

Breast cancer is the most common cancer in women (1). Most of the 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 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

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(9). Clinical neuropsychologic trials indicate that the PFC plays a central role in the cognitive control behavior. Correspondingly, patients with PFC damage show impaired judgment, organization, and decision-making capability, as well as neuropsychologic disinhibition and intellectual difficulties (10,11).

Several cross-sectional functional magnetic resonance imaging (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 neuropsychologic performance (15). Meanwhile, gray matter alterations in the frontal lobes are also found in breast cancer patients after chemotherapy (16). Chemotherapy-induced neurotoxicity has effects on both structure and function of the brain, especially the frontal lobe and the cognition processes (17). The dorsolateral prefrontal cortex (DLPFC), which is 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 leads not only to decreased activation of the brain, but also brain plastic compensation of the brain cortex during the cognitive impairment process (20), as suggested by previously reported 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 the brain network.

The altered structure and activation pattern of the executive network in breast cancer patients might imply relevant abnormal brain function, but few evidence in neuroimaging has been found between the altered functional connectivity of the central executive network and cognitive performance. Whether the evidence from functional and neuropsychologic studies is 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 breast cancer patients undergoing chemotherapy treatment using neuroimaging methods and neuropsychologic tests, and the conceivable underlying mechanism of the cognition alternations of breast cancer patients.

MATERIALS AND METHODS

Participants

All participants were recruited from The First Affiliated Hospital of Anhui Medical University, Hefei, China. Participants were divided into two groups. 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 female patients matched with BC group for age and education level, and seven of them were postmenopausal. The detailed information gathered from each participant is described in Table 1. All participants were examined to exclude neurologic, psychiatric, or medical conditions known to affect cognitive function and any MRI contraindications. All participants provided informed consent.

Neuropsychologic Background Tests

General cognitive function was measured using the Beijing version of the Montreal Cognitive Assessment test (24). The Chinese version of the Cancer Related Fatigue test was performed to rule out fatigue symptoms (25). The Hamilton

TABLE 1. Summary of Characteristics and Neuropsychologic 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 (y)	44.19 (6.61)	43.25 (8.45)	0.450	0.655
Education (y)	10.56 (2.63)	10.63 (2.26)	−0.095	0.924
Fatigue	23.03 (3.80)	21.71 (4.13)	1.227	0.226
HAMA	4.47 (1.24)	4.42 (1.25)	0.155	0.878
HAMD	4.91 (1.20)	4.54 (1.38)	0.329	0.744
MoCA	25.28 (1.42)	25.50 (1.29)	−0.603	0.549
Stroop Word Test (s)	16.38 (3.69)	14.07 (2.65)	2.731	0.009
Stroop Color Test (s)	21.73 (3.90)	17.99 (2.69)	4.238	<0.001
Stroop Interference Test (s)	34.28 (7.90)	29.72 (5.29)	2.586	0.012

BC, breast cancer; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HC, healthy controls; MoCA, Montreal Cognitive Assessment test; SD, standard deviation.