Neuroradiology (2016) 58:921–928
DOI 10.1007/s00234-016-1708-8

FUNCTIONAL NEURORADIOLOGY

Functional connectivity change of brain default mode network in breast cancer patients after chemotherapy

Hui Miao[1] · Xingui Chen[2] · Yunwen Yan[3] · Xiaoxuan He[1] · Sheng Hu[1] · Jian Kong[4] · Meiqi Wu[1] · Yarui Wei[1] · Yawen Zhou[1] · Lu Wang[1] · Kai Wang[2] · Bensheng Qiu[1,5]

Received: 19 February 2016 / Accepted: 12 May 2016 / Published online: 9 June 2016

Abstract
Introduction Complaint about attention disorders is common among breast cancer patients who have undergone chemotherapy, which may be associated with the default mode network (DMN). To validate this hypothesis, we investigated the DMN functional connectivity (FC) change and its relationship with the attention function in breast cancer patients (BC) using resting-state functional magnetic resonance imaging (rs-fMRI).
Methods Twenty-two BC treated with chemotherapy and 22 healthy controls (HC) were recruited into this study. The FC between the DMN's hubs and regions of the dorsal medial prefrontal cortex (dMPFC) and medial temporal lobe (MTL) subsystems was respectively calculated for each participant.
Results The statistical result showed significantly lower connectivity in dMPFC and MTL subsystems in the BC group. In addition, the partial correlation analysis result indicated that the low connectivity of some brain regions in MTL subsystem was correlated with attention dysfunction following BC chemotherapy.
Conclusion These results suggest that the functional disconnection in MTL subsystem of the DMN may have association with attention function of BC after chemotherapy.

Keywords Default mode network · Breast cancer · Cognitive impairment · Chemotherapy · Attention deficit

Introduction

Breast cancer patients (BC) after chemotherapy exhibit widespread cognitive dysfunctions, such as attention deficit [1–3], working memory deterioration [4], thought processes confusion [5], and executive impairment [6]. Such attention deficit compromises learning efficiency and life quality severely. However, the exact mechanisms are still cryptic and remain to be dissected. Therefore, the study seeks to explore attention function decline following BC chemotherapy and the possible neural mechanisms related to these changes.

The resting-state functional magnetic resonance imaging (rs-fMRI) estimates the resting state connectivity in the neural activity across brain regions by measuring synchronous patterns of fluctuations in the blood oxygenation level-dependent (BOLD) signal. This non-invasive imaging technique has been widely used to study complex cognitive processes and synchronous brain activity. By using rs-fMRI, many research observed functional connectivity (FC) disconnection in patients with cognition-related disorders such as Alzheimer's disease (AD), mild cognitive impairment (MCI), and schizophrenia [7–9]. A previous study also reported that FC alterations in the default mode network (DMN) could be used for discriminating BC from healthy women [10]. The DMN

HM and XC contributed equally to this work.

✉ Kai Wang
wangkai1964@126.com

✉ Bensheng Qiu
bqiu@ustc.edu.cn

[1] Center for Biomedical Engineering, University of Science and Technology of China, Hefei, Anhui, China

[2] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, China

[3] Department of Breast Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

[4] Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA, USA

[5] Anhui Computer Application Institute of Traditional Chinese Medicine, Hefei, Anhui 230038, China

included highly interconnected neocortical regions, which were active during wakeful self-reflection and introspection, and inactive during task-specific processing [11]. It has gained extensive attention in the neuroscience and neurology communities since first introduced [12]. The DMN was reported to be associated with cognitive function [13, 14]. The structural alterations of DMN were also found in BC after chemotherapy as follows. Some MRI studies showed that BC exhibited a significant atrophy in gray matter regions associated with the DMN, particularly the precuneus, cingulate, lateral parietal cortex, medial frontal gyrus, and hippocampus [15–17]. The disruption of white matter, including cingulum and bilateral superior frontal occipital fasciculus, was also found in BC [15]. And these regions were connected with the DMN region. These structural alterations might reduce functional specialization in brain network, given that previous DMN studies indicated that attention might be specifically modulated by the DMN [13, 18, 19]. The spontaneous intrinsic activity was attenuated and suppressed in the DMN during performing attention-demanding tasks [20]. More specifically, by using graph-analytic and hierarchical clustering methods, the DMN can be parsed into a core set of hubs (posterior cingulate cortex [PCC], anterior medial prefrontal cortex [aMPFC]), and two subsystems: the dMPFC subsystem (dMPFC, temporo-parietal junction [TPJ], lateral parietal cortex [LTC], temporal pole [TempP]) and MTL subsystem (ventral dorsal medial prefrontal cortex [vMPFC], posterior inferior parietal lobule [pIPL], retrosplenial cortex [Rsp], parahippocampal cortex [PHC], hippocampal formation [HF]) [14]. However, few studies have investigated the links between DMN's three systems and attention deficit following BC chemotherapy. While some studies indicated that regions of the MTL subsystem might be associated with attention function. For example, insufficient deactivation of vMPFC was found in children with attention-deficit/hyperactivity disorder (ADHD) [21]. The posterior parietal cortex was also reported to be associated with attention [22]. In addition, pathological damage in the Rsp was discovered in patients with attention-deficit disorders, like schizophrenia and bipolar disorder [23–25]. A fMRI study revealed that the PHC was modulated by attention, whereas HF was insensitive to the attentional manipulation [26], and so HF was not considered in this study. Taken together, we hypothesized that attention function might be associated with MTL subsystem of the DMN.

In the study, we analyzed ROI-ROI connectivity between the DMN's hubs and regions of the dMPFC and MTL subsystems. Then, in order to investigate whether FC within the DMN is associated with aspects of attention function, we examined the relationship between DMN connectivity and attention function using a widely used measure of attention performance. Given the relevance of the MTL subsystem for attention function, we predicted that chemotherapy-treated BC might exhibit abnormal connectivity within MTL subsystem compared to HC. Furthermore, we hypothesized that changed FC within the MTL subsystem would be associated with attention deficit.

Materials and methods

Participants

Twenty-two female patients with breast cancer and 22 healthy female controls participated in the study. All subjects had given their informed consent before the experiment. The BC (stages II–III) were diagnosed with primary breast carcinoma with no evidence of metastatic disease. They were treated with the standard-dose chemotherapy regimen (taxotere/adriamycin/cyclophosphamide (TAC)) and assessed within 1 month after their chemotherapy-treatment. No patients suffered from any acute side effects of the chemotherapy, such as anemia or weakness. Furthermore, previously or currently, no patients had suffered from psychological disorders nor had they reported the usage of psychotropic medication. The detailed information gathered from each participant is described in Table 1. The healthy controls were recruited from the patients' relatives and local universities. All participants with subtle or severe affective disorder (HAMA > 7 and/or HAMD > 7) were excluded from the study in order to decrease the interference with neuropsychological assessment.

Neuropsychological background tests

Under the administration of skilled psychologists and psychiatrists, each participant was required to complete the neuropsychological background tests within approximately 1 h. The MoCA test was conducted to assess general cognitive function. The Chinese version of the Cancer-Related Fatigue (CRF) test was performed to evaluate fatigue symptoms [27], and the HAMD and HAMA tests were respectively performed to assess the participants' potential depression and anxiety symptoms [28].

The Stroop test [29], including Stroop Color test, Stroop Word test, and Stroop Interference test, was assessed as a profitable and trustworthy tool in clinical investigations of psychological cognitive neuroscience [30, 31]. More specially, the Stroop Color test and Stroop Word test were regarded as measures of attention function in general [32]. Given additional requirement to the "ignore-the-word" goal for accurate responding, the Stroop Interference test was generally considered as a measure of selective attention [33–35]. Therefore, in the current study, the Stroop test was used to assess the attention of BC after chemotherapy.

In the Stroop Color test, all participants were required to name the exact color of solid circles which would be displayed in four possible colors (i.e., yellow, red, blue and green). In the

Table 1 Demographic and clinical characteristics of the patients received chemotherapy and healthy controls

Variable	BC group ($n = 22$)	HC group ($n = 22$)	Two-sample t test	
	Mean (SD)	Mean (SD)	T value	P value
Age (years)	43.68 (6.81)	44.5 (7.44)	−.372	.712
Education (years)	10.82 (2.35)	10.55 (1.75)	.427	.672
Fatigue	23.00 (3.64)	21.64 (3.75)	1.195	.239
HAMA	4.59 (1.19)	4.36 (1.23)	.609	.546
HAMD	4.91 (1.24)	4.36 (1.30)	1.433	.159
MoCA	25.36 (1.37)	25.45 (1.23)	−.226	.822
Stroop Color test(sec)	16.90 (3.20)	14.49 (2.93)	2.544	.015
Stroop Word test(sec)	22.64 (3.57)	17.99 (2.75)	4.723	<.001
Stroop Interference test(sec)	36.12 (8.01)	32.48 (5.55)	2.654	.012

SD standard deviation, *HAMA* Hamilton Anxiety Rating Scale, *HAMD* Hamilton Depression Rating Scale, *MoCA* Montreal Cognitive Assessment Test

Stroop Word test, all participants were required to name the color of different words which did not relate to the colors they were displayed in. In Stroop Interference test, all participants were asked to figure out the right color of the words while the name of a color was printed in a color not denoted by the name (e.g., the word "red" printed in green ink). The response time of Stroop test for participants was recorded to assess attention and selective attention functions in our study.

Image acquisition

All MRI images were collected by using a GE 3 T MRI scanner (GE Medical Systems, Milwaukee, WI) equipped with a standard head coil. The resting-state functional images were recorded with the following parameters: repetition time (TR)/echo time (TE) = 2000 ms/22.5 ms, flip angle = 30 degrees, 33 slices, thickness/gap ratio = 4.0/0.6 mm, voxel size = 3.4 × 3.4 × 4.6 mm^3, matrix size = 64 × 64, and field of view = 220 × 220 mm^2. During the resting-state fMRI scans, all participants were instructed to close their eyes and maintain motionless.

T1-weighted anatomic images were acquired in sagittal orientation with three-dimensional inversion recovery prepared fast spoiled gradient recalled sequence with the following parameters: TR/TE = 8.676 ms/3.184 ms, inversion time = 800 ms, flip angle = 8 degrees, field of view = 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3 and the number of slices = 188.

Image preprocessing

The fMRI data were preprocessed by using Analysis of Functional NeuroImages (AFNI) software tools (Medical College of Wisconsin, Milwaukee, WI, USA) and FSL (the FMRIB Software Library, Oxford, UK). First, the anatomical and functional images were reconstructed and realigned using a unified matrix. Then, skull stripping and motion correction were performed, followed by coregistration between functional and anatomical images and normalized to the Montreal Neurological Institute (MNI) 152 standard brain atlas. The motion was also calculated and data with head motion over 2 mm or 2° were excluded. To remove low-frequency drift and high-frequency noises, all fMRI signals were filtered by band-pass filtering (0.01–0.08Hz) and then spatially smoothed using a 6-mm full width at half maximum Gaussian kernel. After being preprocessed, the individual data were used for further correlation analyses.

Definition of the regions of interest

We defined regions of interests (ROIs, 8-mm spheres) comprising the DMN's hubs (PCC, aMPFC), dMPFC subsystem (dMPFC, TPJ, LTC, TempP), and MTL subsystem (vMPFC, pIPL, Rsp, PHC) (see Fig. 1 for a depiction of these regions and coordinates) based on the previous study [36].

Network connectivity analysis

For each subject, FC was estimated between all pairs of ROIs in the DMN, based on the Pearson correlation between BOLD residual time series averaged across all voxels in each region. Fisher's r-to-z transformation was applied to correlation coefficients in order to increase normality of the distribution. A two-sample two-tailed t test was conducted in order to determine the statistical differences in FC between the BC group and the HC group. To reduce the probability of type I error, we controlled the false-discovery rate (FDR, $q < .05$) for comparisons within each subsystem.

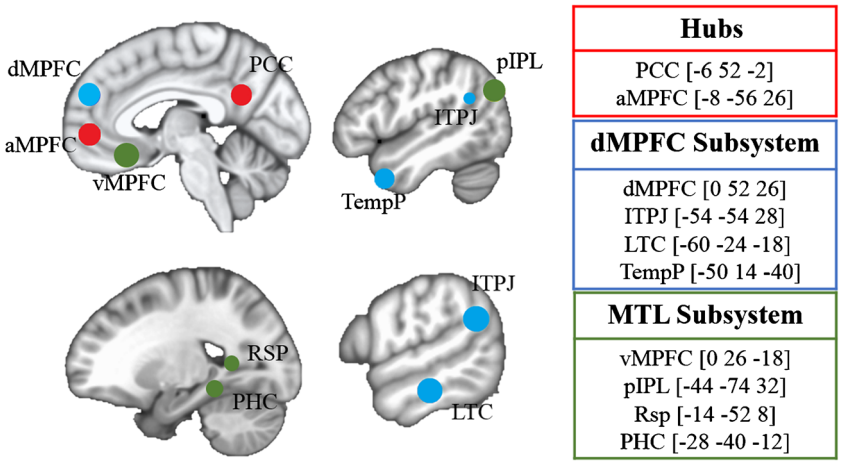

Fig. 1 Depiction of the DMN's hubs (*red*), dMPFC subsystem (*blue*) and MTL subsystem (*green*), and accompanying MNI coordinates. *PCC* posterior cingulate cortex, *aMPFC* anterior medial prefrontal cortex, *dMPFC* dorsal medial prefrontal cortex, *lTPJ* left temporo-parietal junction, *LTC* lateral temporal cortex, *TempP* temporal pole, *MTL* medial temporal lobe, *vMPFC* ventral medial prefrontal cortex, *pIPL* posterior inferior parietal lobule, *Rsp* retrosplenial cortex, *PHC* parahippocampal cortex

Results

Demographic and behavioral results

Table 1 shows the clinical characteristics of the BC group and those of the HC group. The education background, general cognitive function, and fatigue scores were not significantly different between the two groups ($p > 0.1$), indicating that there were no global cognitive impairments in the BC group. However, the BC group demonstrated significantly worse performance than the HC group in attention tests (i.e., the Stroop Color test and Stroop Word test) and executive function test (i.e., Stroop Interference test).

Functional connectivity analysis

In order to investigate intergroup differences in FC between the DMN's hubs, and the regions of the dMPFC subsystem and MTL subsystem, pairwise FC of all ROIs was calculated per subject. The pairwise FC strength of the BC and HC groups was shown in Table 2 and Fig. 2. Compared with the HC group, the BC group exhibited significantly lower connectivity in the following pairwise connectivity: vMPFC–Rsp, pIPL–vMPFC, pIPL-Rsp and pIPL-PHC in the MTL subsystem (Fig. 3) and dMPFC-TempP in the dMPFC subsystem (Fig. 3). No group differences were observed in FC between the DMN's hubs.

Relationship between FC and the Stroop test

Partial correlation analysis within the BC group indicated that FC of the vMPFC-Rsp in MTL subsystem significantly correlated with their response time in the attention tests (i.e., the Stroop Color test $p = .007$, $r = -.188$; the Stroop Color test $p = .044$, $r = -.391$). Additionally, the connectivity of pIPL-Rsp was negatively correlated with the response time of the Stroop Color test ($p = .040$, $r = -.400$). No significant correlations were found in the DMN's hubs and the dMPFC subsystem (p's $> .10$).

Discussion

In the study, we found significantly lower connectivity within the dMPFC subsystem and MTL subsystem in BC group, which indicated inefficient functional integration of the DMN in patients. The results of correlation analysis demonstrated that attention function was associated with the FC of the following pairwise connectivity: vMPFC-Rsp and pIPL-Rsp. These results were consistent with previous studies which demonstrated that the fronto-parietal structures were engaged in attentional modulation [37, 38]. The results provide novel evidence that lower strength of the FC among certain regions of the DMN may be associated with the attention deficit in BC after chemotherapy.

Relationship between attention and FC of the DMN

The medial prefrontal cortex (MPFC) was reported to be associated with cognitive functions such as working memory, spatial learning, and attention and emotional response [39–41]. In attention-demanding cognitive task performance, the reductions in activity of vMPFC could be often observed [42, 43]. The Rsp, a part of the PCC, was associated with a series of tasks including memory, guide, and creative thinking [44]. Furthermore, the Rsp had a close relationship with the hippocampus, parahippocampal gyrus, and other brain structures [45], as reflected in our connectivity analysis results that the Rsp had a strong FC with the PHC. A study in rat revealed that the damage of retrosplenial granular cortex was associated with the impaired working memory [46]. A fMRI study revealed that the top-down mechanisms in human selective

Table 2 Group-wise comparison of pairwise FC in the DMN

	Region 1	Region 2	BC group Mean (SEM)	HC group Mean (SEM)	*T* value	*p* value	*q* value
Hubs	aMPFC	PCC	0.3853 (0.0481)	0.429 6(0.0475)	−0.6551	0.5160	–
dMPFC	dMPFC	LTC	0.4673 (0.0429)	0.6066 (0.0358)	−2.444	0.0190	0.0570
	dMPFC	TempP	0.4083 (0.0442)	0.6105 (0.0450)	−3.1632	0.0029	0.0174[a]
	dMPFC	ITPJ	0.5772 (0.0657)	0.5559 (0.0738)	0.2156	0.8304	0.8304
	ITPJ	TLC	0.5226 (0.0635)	0.6871 (0.0686)	−1.7138	0.0945	0.1387
	ITPJ	TempP	0.3934 (0.0435)	0.5164 (0.0612)	−1.6124	0.1156	0.1387
	LTC	TempP	0.3035 (0.0591)	0.4671 (0.0539)	−1.9761	0.0552	0.1104
MTL	vMPFC	pIPL	0.0922 (0.0089)	0.2295 (0.0371)	−2.5543	0.0144	0.0432[a]
	vMPFC	PHC	0.1274 (0.0572)	0.1916 (0.0447)	−0.8860	0.3809	0.3809
	vMPFC	Rsp	0.0413 (0.0348)	0.2232 (0.0594)	−2.6426	0.0124	0.0432[a]
	pIPL	PHC	0.4069 (0.0656)	0.5931 (0.0527)	−2.2138	0.0326	0.0489[a]
	Rsp	pIPL	0.4199 (0.0601)	0.6080 (0.0519)	−2.3676	0.0227	0.0454[a]
	Rsp	PHC	0.5081 (0.0660)	0.6453 (0.0501)	−1.6545	0.1061	0.1273

SEM standard error of the mean

[a] Significant difference in connectivity of pair ROIs within the DMN dMPFC subsystem and MTL subsystem corrected by the false-discovery rate ($q < .05$)

attention might have the same neural circuits for working memory [47]. Together, the Rsp might play a very important role in attention function. The parietal cortex, situated at the intersection of visual, auditory, and tactile cortices, was associated with attention function [48, 49]. The inferior parietal lobule (IPL), an important component of the temporal-parietal-limbic neural network, played a key role in various cognitive function including attention [50]. The previous research about AD patients accompanied by sustained attention and selective attention deficits also found white matter and gray matter atrophy in IPL. In our study, the BC group showed that the lower FC strength within MTL subsystem significantly correlated to attention dysfunction. A lower value for pairwise FC meant lower local functional coupling in patients. The MTL subsystem overlapped with the dorsal attention network including fronto-parietal regions and

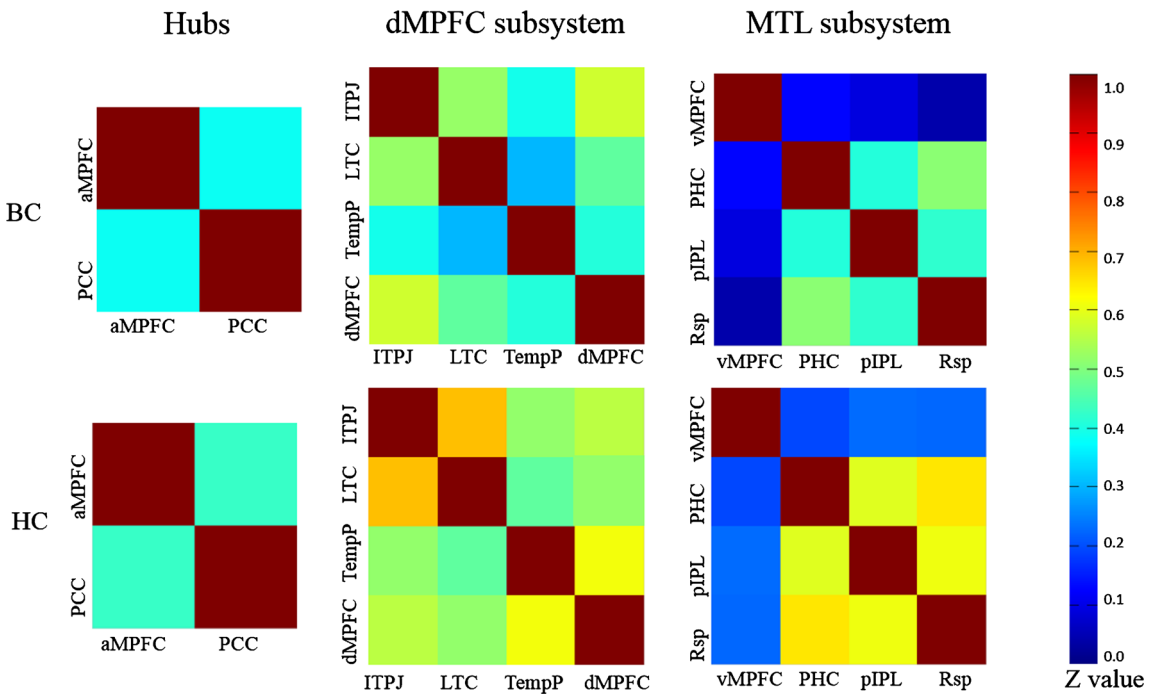

Fig. 2 Average FC matrices across all ROIs between the DMN's hubs and regions of the dMPFC subsystem and MTL subsystem for the HC group (*below*) and BC group (*above*). *Colors* of the grid represent the strength of pairwise FC

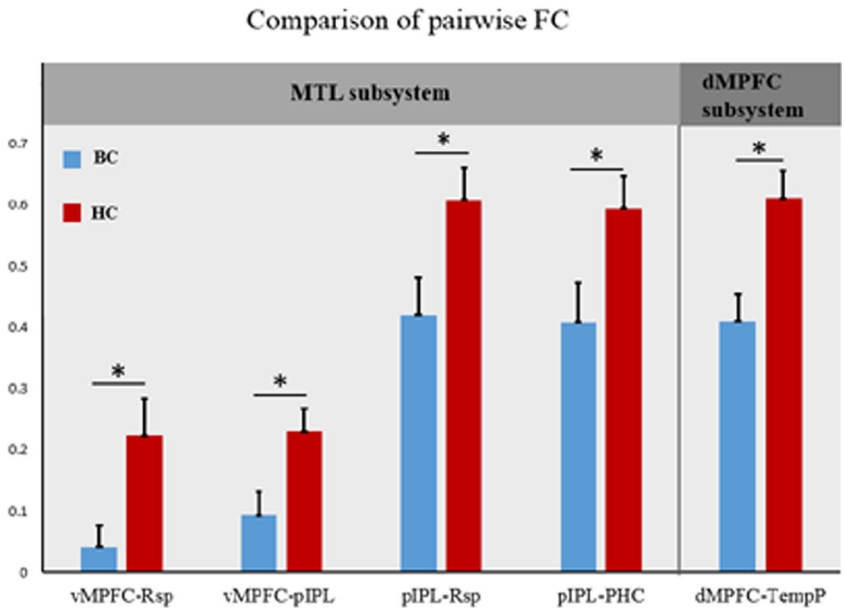

Fig. 3 Statistical differences of FC between the HC group and the BC group (FDR corrected at $q < 0.05$). The horizontal axis is pair ROIs with significantly different connectivity coefficient, the vertical axis is mean FC in HC group and BC group, respectively. *Error bars* depict standard error of the mean. *Stars* indicate a significant difference

temporal lobes [51]. While the previous functional MRI study revealed that the dMPFC subsystem was preferentially engaged when participants were directed to think about their present mental states [14]. In our study, no significant correlations were found between the dMPFC subsystem and attention. Therefore, one possible explanation for our findings is that lower connectivity of the MTL subsystem might cause negative outcomes of attention function.

The underlying neural mechanism of FC alterations within dMPFC subsystem and MTL subsystem

The study about amnestic MCI and mild AD revealed by amplitude of low-frequency fluctuation (ALFF) using rs-fMRI: mild AD patients showed significantly decreased ALFF in the vMPFC and dMPFC; and amnestic MCI showed significantly changed ALFF in the vMPFC, IPL, and PHC [52]. Our results of this study are consistent with these above discoveries. So the lower connectivity in the DMN could be regarded as an indicator of attention deficit in the BC group. However, it is difficult to interpret the decrease in FC from the perspective of neurobiology. We speculate that the changes of connectivity within the DMN may be related to the effects of chemotherapy. Possible mechanisms include direct neurotoxic damage (e.g., injury to neurons or surrounding cells, altered neurotransmitter levels) [53]; oxidative damage [54]; indirect effects such as induced hormonal changes [55]; immune response deregulation with release of cytokines [56], blood coagulating in small vessels of the central nervous system [57]; anemia and genetic predisposition [58]. The discovery of current study may supply further evidence for exploring the neural mechanisms of attention deficit following BC chemotherapy. Moreover, previous study reported that both cognitive and physical exercise could increase DMN functional connectivity in healthy adults [59]. So further study of the DMN effects on chemotherapy-related cognitive deficit may aid making early intervention to prevent progressive decline and making a reasonable training plan to increase functional connectivity and improve cognitive function.

Limitations of this study

The current study strongly suggests that attention dysfunction of BC could be characterized by the disrupted FC within the MTL subsystem. However, several limitations in our study should be considered. First, the study was limited to small sample size. Future study should increase the number of BC and controls to examine whether the BC truly have the aberrant FC in the DMN and the relationship with attention. Second, the design of this study was a cross-sectional study. Cognitive function and rs-fMRI were not assessed in the patients before their breast cancer diagnoses but after their chemotherapies. Several studies indicated that there was no significant difference between the non-chemotherapy breast cancer patients and the healthy controls [3, 10]. A future longitudinal study should assess the baseline cognitive function of the patients prior to chemotherapy to identify the attention deficit and DMN FC changes that result from post-chemotherapy cognitive dysfunction rather than pre-chemotherapy cognitive dysfunction. Third, we did not evaluate causal or directional relationships instead we only evaluated interregional temporal correlations. Future study should explore the exact mechanisms of attention deficit following BC chemotherapy combined with physiology and pathology.

Conclusion

In this study, we investigated FC alteration in the DMN and its relationship with attention function. Our findings showed the significantly lower connectivity within the dMPFC subsystem and MTL subsystem. The results of correlation analysis also indicated that FC within the MTL subsystem was significantly related to attention function of patients. This study provides further evidence that the functional disconnection of the MTL subsystem may be a contributing factor related to cognitive dysfunction, especially the attention impairment in BC after chemotherapy.

Acknowledgments This work was supported by National Science Foundation of China (Grant numbers: 81371537, 91432301), Major State Basic Research Development Program of China (973 Program) (Grant number: 2013CB733803) and the Fundamental Research Funds for the Central Universities of China (WK2070000033).

Compliance with ethical standards We declare that all human and animal studies have been approved by the research ethics committee of the First Affiliated Hospital of Anhui Medical University and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

References

1. Jim HS, Phillips KM, Chait S, Faul LA, Popa MA, Lee YH, Hussin MG, Jacobsen PB, Small BJ (2012) Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol 30(29):3578–3587. doi:10.1200/JCO.2011.39.5640
2. Kaemingk K, Lundy S, Patton T, Remninger S, Kervick R (2006) Attention is frequently weaker than would be expected based on intelligence in breast cancer survivors treated with chemotherapy. In: Psycho-oncology. vol 1. John Wiley & Sons Ltd The Atrium, Southern Gate, Chichester PO19 8SQ, W Sussex, England, pp S3–S4
3. Chen X, Li J, Ren J, Hu X, Zhu C, Tian Y, Hu P, Ma H, Yu F, Wang K (2014) Selective impairment of attention networks in breast cancer patients receiving chemotherapy treatment. Psychooncology 23(10):1165–1171. doi:10.1002/pon.3539
4. Bender CM, Sereika SM, Berga SL, Vogel VG, Brufsky AM, Paraska KK, Ryan CM (2006) Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 15(5):422–430. doi:10.1002/pon.964
5. Deprez S, Amant F, Smeets A, Peeters R, Leemans A, Van Hecke W, Verhoeven JS, Christiaens MR, Vandenberghe J, Vandenbulcke M, Sunaert S (2012) Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J Clin Oncol 30(3):274–281. doi:10.1200/JCO.2011.36.8571
6. Chan RC, Shum D, Toulopoulou T, Chen EY (2008) Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol : Off J Natl Acad Neuropsychol 23(2):201–216. doi:10.1016/j.acn.2007.08.010
7. Damoiseaux JS, Prater KE, Miller BL, Greicius MD (2012) Functional connectivity tracks clinical deterioration in Alzheimer's disease. Neurobiol Aging 33(4):828. doi:10.1016/j.neurobiolaging.2011.06.024, e819-830
8. Friston KJ, Frith CD (1995) Schizophrenia: a disconnection syndrome? Clin Neurosci 3(2):89–97
9. Binnewijzend MA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, Adriaanse SM, Damoiseaux JS, Scheltens P, van Berckel BN, Barkhof F (2012) Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 33(9):2018–2028. doi:10.1016/j.neurobiolaging.2011.07.003
10. Kesler SR, Wefel JS, Hosseini SM, Cheung M, Watson CL, Hoeft F (2013) Default mode network connectivity distinguishes chemotherapy-treated breast cancer survivors from controls. Proc Natl Acad Sci U S A 110(28):11600–11605. doi:10.1073/pnas.1214551110
11. Uddin LQ, Kelly AM, Biswal BB, Castellanos FX, Milham MP (2009) Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Hum Brain Mapp 30(2):625–637. doi:10.1002/hbm.20531
12. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98(2):676–682. doi:10.1073/pnas.98.2.676
13. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH (2012) The role of default network deactivation in cognition and disease. Trends Cogn Sci 16(12):584–592. doi:10.1016/j.tics.2012.10.008
14. Andrews-Hanna JR (2009) The brain's default network: anatomy, function, and consequence of disruption. Harvard University
15. Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T, Wada N, Imoto S, Murakami K, Uchitomi Y (2007) Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. Cancer 109(1):146–156. doi:10.1002/cncr.22368
16. McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ (2010) Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res Treat 123(3):819–828. doi:10.1007/s10549-010-1088-4
17. Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, Dhabhar FS (2013) Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun 30(Suppl):S109–S116. doi:10.1016/j.bbi.2012.05.017
18. Uddin LQ, Kelly AC, Biswal BB, Margulies DS, Shehzad Z, Shaw D, Ghaffari M, Rotrosen J, Adler LA, Castellanos FX (2008) Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169(1):249–254
19. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ (2009) Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 33(3):279–296. doi:10.1016/j.neubiorev.2008.09.002
20. Fransson P (2006) How default is the default mode of brain function?: further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 44(14):2836–2845
21. Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, Schweitzer JB (2009) A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res 1273:114–128
22. Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12(1):1–47
23. Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, Zarate CA, Pine DS, Price JL, Drevets WC (2006) Cortical

abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. NeuroImage 30(2):485–497. doi:10.1016/j.neuroimage.2005.09.029
24. Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS (2005) Volume of the cingulate and outcome in schizophrenia. Schizophr Res 72(2–3):91–108. doi:10.1016/j.schres.2004.02.011
25. Bluhm RL, Miller J, Lanius RA, Osuch EA, Boksman K, Neufeld RW, Theberge J, Schaefer B, Williamson PC (2009) Retrosplenial cortex connectivity in schizophrenia. Psychiatry Res 174(1):17–23. doi:10.1016/j.pscychresns.2009.03.010
26. Dudukovic NM, Preston AR, Archie JJ, Glover GH, Wagner AD (2011) High-resolution fMRI reveals match enhancement and attentional modulation in the human medial temporal lobe. J Cogn Neurosci 23(3):670–682. doi:10.1162/jocn.2010.21509
27. So WK, Dodgson J, Tai JW (2003) Fatigue and quality of life among Chinese patients with hematologic malignancy after bone marrow transplantation. Cancer Nurs 26(3):211–219
28. Lezak MD (1984) Neuropsychological assessment in behavioral toxicology—developing techniques and interpretative issues. Scand J Work Environ Health :25–29
29. Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18(6):643
30. MacLeod CM (1991) Half a century of research on the Stroop effect: an integrative review. Psychol Bull 109(2):163–203
31. MacLeod CM, MacDonald PA (2000) Interdimensional interference in the Stroop effect: uncovering the cognitive and neural anatomy of attention. Trends Cogn Sci 4(10):383–391
32. Kane MJ, Conway AR, Hambrick DZ, Engle RW (2007) Variation in working memory capacity as variation in executive attention and control. Var Work Mem 1:21–48
33. Lamers MJ, Roelofs A, Rabeling-Keus IM (2010) Selective attention and response set in the Stroop task. Mem Cogn 38(7):893–904. doi:10.3758/MC.38.7.893
34. Zarghi A, Zali A, Tehranidost M, Ashrafi F, Zarindast M, Moazezi M, Khodadadi S (2012) Assessment of selective attention with cscwt (computerized stroop color-word test) among children and adults. US-China Educ Rev A 1:121–127
35. Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121(1):65
36. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010) Functional-anatomic fractionation of the brain's default network. Neuron 65(4):550–562
37. Naghavi HR, Nyberg L (2005) Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? Conscious Cogn 14(2):390–425. doi:10.1016/j.concog.2004.10.003
38. Coull JT, Frith CD, Frackowiak RS, Grasby PM (1996) A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34(11):1085–1095
39. Dalley JW, Cardinal RN, Robbins TW (2004) Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev 28(7):771–784. doi:10.1016/j.neubiorev.2004.09.006
40. Arnsten AF, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 57(11):1377–1384. doi:10.1016/j.biopsych.2004.08.019
41. Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10(3):211–223. doi:10.1038/nrn2573
42. Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 98(7):4259–4264. doi:10.1073/pnas.071043098
43. Elliott R, Dolan RJ, Frith CD (2000) Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex 10(3):308–317
44. Vann SD, Aggleton JP, Maguire EA (2009) What does the retrosplenial cortex do? Nat Rev Neurosci 10(11):792–802
45. Sugar J, Witter MP, van Strien NM, Cappaert NL (2011) The retrosplenial cortex: intrinsic connectivity and connections with the (para)hippocampal region in the rat. An interactive connectome. Front Neuroinformatics 5:7. doi:10.3389/fninf.2011.00007
46. Vann SD, Wilton LK, Muir JL, Aggleton JP (2003) Testing the importance of the caudal retrosplenial cortex for spatial memory in rats. Behav Brain Res 140(1):107–118
47. Gazzaley A, Nobre AC (2012) Top-down modulation: bridging selective attention and working memory. Trends Cogn Sci 16(2):129–135. doi:10.1016/j.tics.2011.11.014
48. Critchleey M (1953) Parietal lobes. Giornale di Psichiatria e di Neuropatologia 81(4):872–873
49. Perry RJ, Hodges JR (1999) Attention and executive deficits in Alzheimer's disease. A critical review. Brain 122(Pt 3):383–404
50. Caspers S, Schleicher A, Bacha-Trams M, Palomero-Gallagher N, Amunts K, Zilles K (2013) Organization of the human inferior parietal lobule based on receptor architectonics. Cereb Cortex 23(3):615–628. doi:10.1093/cercor/bhs048
51. Visintin E, De Panfilis C, Antonucci C, Capecci C, Marchesi C, Sambataro F (2015) Parsing the intrinsic networks underlying attention: a resting state study. Behav Brain Res 278:315–322
52. Xi Q, Zhao XH, Wang PJ, Guo QH, He Y (2013) Abnormal intrinsic brain activity in amnestic mild cognitive impairment revealed by amplitude of low-frequency fluctuation: a resting-state functional magnetic resonance imaging study. Chin Med J 126(15):2912–2917
53. Tuxen MK, Hansen SW (1994) Neurotoxicity secondary to anti-neoplastic drugs. Cancer Treat Rev 20(2):191–214
54. Joseph JA, Denisova N, Fisher D, Shukitt-Hale B, Bickford P, Prior R, Cao G (1998) Age-related neurodegeneration and oxidative stress: putative nutritional intervention. Neurol Clin 16(3):747–755
55. Ahles TA (2004) Do systemic cancer treatments affect cognitive function? Lancet Oncol 5(5):270–271. doi:10.1016/s1470-2045(04)01463-9
56. Barton D, Loprinzi C (2002) Novel approaches to preventing chemotherapy-induced cognitive dysfunction in breast cancer: the art of the possible. Clin Breast Cancer 3:S121–S127
57. Costa SD, von Minckwitz G, Raab G, Blohmer JU, Dresel V, Eidtmann H, Hilfrich J, Jackisch C, Merkle E, Gademann G, Kaufmann M (1999) The role of docetaxel (Taxotere) in neoadjuvant chemotherapy of breast cancer. Semin Oncol 26(3 Suppl 9):24–31
58. Saykin A, Ahles T, McDonald B (2003) Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry 4:201–216
59. Langer N, von Bastian CC, Wirz H, Oberauer K, Jancke L (2013) The effects of working memory training on functional brain network efficiency. Cortex; J Devoted Study Nervous Syst Behav 49(9):2424–2438. doi:10.1016/j.cortex.2013.01.008