

Aberrant Within- and Between-Network Connectivity in Chemotherapy Treated Breast Cancer Patients: A Longitudinal Resting State Functional MRI Study

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Abstract

Background Previous studies have found abnormal structural and functional brain alterations in breast cancer survivors undergoing chemotherapy. However, the network-level brain changes following chemotherapy remains unknown. The purpose of this study was to investigate the dynamic changes of large-scale intra- and inter- network functional connectivity in chemotherapy-treated breast cancer patients. **Methods** Eighteen breast cancer patients were evaluated with resting state functional MRI (rs-fMRI), neuropsychological tests and blood examination before postoperative chemotherapy (t0), one week after completing chemotherapy (t1) and six months after completing chemotherapy (t2). Nineteen age- and education level-matched healthy controls (HC) were also recruited. Independent component analysis (ICA) was performed to assess network component using rs-fMRI data. The functional network changes were then correlated with cognitive assessment scores and blood biochemical indexes. **Results** One-way repeated measures ANOVA revealed significantly changed within-network functional connectivity, which mainly located in the default mode network (DMN), frontoparietal network, visual network and self-referential network. Post-hoc test showed that most within-network functional connectivity decreased one week after chemotherapy and increased six months after chemotherapy. As for the between-network functional connectivity, the posterior DMN-SMN connectivity showed the same tendency. These within- and between-network functional connectivity changes were associated with blood biochemical indexes and cognitive assessment scores. **Conclusions** These results indicated that network-level connectivity alterations may serve as a potential biomarker of chemotherapy related cognitive impairment, providing insights for further functional recovery treatment.

Background

Chemotherapy-related cognitive impairments (CRCI) are common in non-central nervous system cancers which show multiple-domain cognitive deficits such as attention, executive function, learning ability, memory and information processing speed during or after chemotherapy[1, 2]. Although accumulating researches had focused on these cognitive problems, the neural mechanism remains largely unclear. Cross-sectional[3, 4, 5] and longitudinal neuroimaging studies[6, 7, 8, 9] have shown structural and functional alterations during or after chemotherapy, which provide neural substrates of CRCI. Brain activation and connectivity studies also showed that breast cancer survivors had abnormal brain activity and decreased neural network transfer efficiency from large-scale perspectives[10, 11, 12]. These damaged brain structural and functional areas partially overlapped, mostly located in the frontal and temporal lobes. This indicates that chemotherapy induced common cognitive deficits may be related to the large-scale abnormal brain activity/connectivity.

Human cognitive activity is the result of the synergetic action of multiple functional neural networks in the brain, not only from the activities within the network, but also from the synergetic activities between the networks[13, 14]. Resting-state functional MRI (rs-fMRI) evaluates the resting state brain functional connectivity and makes it possible to describe the interaction of sub-networks which are spatially distinct regions[15], which can help understand the cooperative relationship of different brain regions at a large

scale. Studies have found about 7 common resting state networks (RSNs) in healthy adults[16]. Alterations in RSNs have been observed in many neuropsychiatric diseases such as Parkinson's disease, mild cognitive impairment and dementia[17, 18, 19]. Default mode network (DMN) is the most commonly investigated RSN in breast cancer survivors for its preferential vulnerability and sensitivity to tumor chemotherapeutics. Decreased functional connectivity of DMN was reported particularly in the medial prefrontal cortex, posterior cingulate cortex and the medial temporal cortex[20, 15]. Our previous study found abnormal hippocampal connectivity in superior/middle temporal gyrus/insula and frontal gyrus, most are parts of the RSNs[21]. These altered functional connectivities were involved in the regulation of executive, memory and emotion, supporting chemotherapy induced widespread cognitive networks disruption.

Most of the previous CRCI related rs-fMRI researches focused on a specific RSN alterations in breast cancer patients[22, 23]. To the best of our knowledge, no studies have reported the dynamic changes of RSN functional connectivity in breast cancer survivors from a large-scale network perspective. Therefore, the purpose of this study was to investigate the dynamic changes of large scale intra- and inter- network functional connectivity in chemotherapy-treated breast cancer survivors. We hypothesize that chemotherapeutic agents not only induced extensive RSNs abnormality, but also disrupted the connections between these RSNs. Hence, we designed this prospective, longitudinal study aiming to investigate the temporal course of the resting state intra- and inter- network functional connectivity changes in breast cancer patients before and after chemotherapy. The correlation between RSNs changes and potential risk factors such as anxiety, depression, hemoglobin and blood lipids, as well as cognitive assessment scores were also analyzed.

Materials And Methods

Participants

The study was approved by the Medical Ethics Committee of Jinling Hospital. All participants signed the written informed consent prior to the study. Women newly diagnosed with primary non-metastatic breast cancer (stages I-III) were recruited from March 2017 to December 2018. Brain MRI scans, cognitive assessment and blood biochemical examinations were performed at baseline (before postoperative or neoadjuvant chemotherapy, t0), one week after completing chemotherapy (t1, mean 6 days), and six months after completing chemotherapy (t2, mean 171 days). Healthy control (HC) recruited from local community were evaluated at the baseline. The inclusion criteria were: right handedness; with no history of psychiatric or neurological diseases; with 9 years or higher educational level; no chronic illness, no intracranial radiotherapy and other diseases that might affect brain function or cognitive assessment. Study flowchart with included and excluded patient numbers is shown in Fig. 1. Seventeen female breast cancer patients (mean age: 45.6 ± 10 years old) completing four to six courses of chemotherapy and 19 age (mean age: 45.8 ± 9.4 years old) and education level matched HCs were finally included in this study (Fig. 1). There was no radiotherapy or endocrine therapy during chemotherapy for the 17 breast cancer patients .

Neuropsychological Assessment

All subjects completed the following neuropsychological assessments before each MR examination: 1) Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), which were used to assess the subjects' common cognitive function; 2) Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS), which were used to evaluate anxiety and depression state; 3) Number connection test type A (NCT-A) and digital symbol test (DST) for the assessment of attention and executive ability; 4) Auditory verbal learning memory (WDT) for intelligence and memory assessment; 5) Line tracing test (LTT) for the visual ability; 6) Serial dotting test (SDT) for assessing the fine motor skills; 7) The Chinese version of the Stroop color- word test for measuring reaction and conversion. All subjects were scored according to the standard of each scale. The specific operation and instructions were completed by the same skilled researcher.

Blood Biochemical Examinations

The fasting venous bloods of all subjects were obtained (the same day of MRI examination) to assess basic metabolism of endocrine, immune and digestive systems function. Blood tests included Estradiol (E2), prolactin (PRL), follicle growth hormone (FSH), luteinizing hormone (LH), total cholesterol, triglyceride, high sensitivity C-reactive protein, and hemoglobin (Hb) concentration. For HCs with normal menstrual cycles, blood samples were collected 3–10 days after menstruation. All blood samples were collected, stored and tested in the same way.

MRI Data Acquisition

Breast cancer patients underwent brain MRI scans at three time points on the same GE 3.0-T MRI scanner (Discovery MR 750, GE Healthcare, Milwaukee, USA) equipped with a standard 32-channel head coil. Our structural and functional MRI scan paradigms had been described in our previous study in detail (Feng et al. 2019). The sagittal three-dimensional T1-weighted (3D-T1) images for anatomic reference were collected by using 3D inversion recovery prepared fast spoiled gradient recalled sequence. Rs-fMRI data were acquired with a gradient echo EPI sequence during the motionless and unintentional thinking condition. Routine T2- fluid attenuated inversion recovery (FLAIR) sequence was used to exclude primary brain lesion. The HC group completed the MRI examinations at the baseline, follow-up examinations were not performed.

Image Preprocessing

The fMRI data analysis was done by using Data Processing Assistant for Resting-State fMRI (DPARSF) (<http://rfmri.org/DPASF>). After removing the first 10 time points for the signal stabilization, a total of 240 time points were left for the following processing: slice timing correction was used to eliminate time errors between slices; motion correction (subjects with head motion > 1.5 mm translation or rotation > 1.5° would be removed); T1 structural images were segmented into gray matter, white matter, and cerebrospinal fluid. The realigned functional images were spatially normalized to the Montreal Neurological Institute (MNI) space with a voxel size of $3 \times 3 \times 3 \text{ mm}^3$ by using unified segmentation

algorithm; the final images were smoothed using a $6 \times 6 \times 6$ mm Gaussian kernel at full-width at half-maximum.

Independent Component Analysis (ICA)

Analyses were conducted using ICA with GIFT software (<http://icatb.sourceforge.net/>). ICA is a data-driven, multivariable approach without priori assumptions which can separate unknown mixed fMRI signal sources into maximum spatial activation maps or independent temporal components. Independent components were estimated by GIFT software from pre-processed data of t0, t1 and t2 time points in breast cancer patients and HC group at baseline. Principal component analysis (PCA) was used to reduce the data dimension. Using the minimum description length criteria, 39 independent components were separated from four groups of smooth data dimensions. We selected the ICASSO algorithm as stability analysis type by running ICA estimation 100 times. Subsequently, the Z value of each independent component was obtained by back-reconstruction using spatial-temporal regress. The z-value measures the correlation between the time series of each voxel and each independent component, which was used for further statistical analyses. Finally, the time series of 39 independent components reflecting the spontaneous activity of brain and the spatial activation distribution map reflecting the intensity of brain activity were obtained. According to the maximum spatial correlation, the normalized average spatial activation map and the interested spatial template were calculated using automatic template matching process in the GIFT software. The component with the best “goodness of fit” of standard RSNs template was taken as the final resting state sub-network map. In this study, 9 sub-network templates of RSN were used: default mode network (DMN), frontoparietal network (FPN), dorsal attention network, (DAN), sensorimotor network (SMN), central executive network (CEN), self-referential network (SRN), visual network (VN), auditory network (AN), and central network (CN).

Statistical Analyses

Demographic and Clinical Data

SPSS17.0 software (SPSS Inc. Chicago, IL) was used for the evaluation of the demographic and clinical data of all subjects. At baseline, the two-sample t-test was used to examine the differences between the breast cancer group and HC group. Non-normal distribution data were analyzed using two independent sample nonparametric tests. One-way repeated measures ANOVA was used to test the within subjects' effects in breast cancer group, time as repeated effect, the level of clinical data as the dependent variable. Bonferroni post hoc test was used to conduct pairwise comparisons between groups (t0, t1, t2).

Within–Network Functional Connectivity

SPM8 software was used to obtain the group-level spatial distribution map of each RSN subnetwork by using the one sample t-test (family-wise error (FWE) corrected $P < 0.05$). In order to restrict the within–network functional connectivity differences, a group mask was also generated. (1) Two-sample t-test was used to compare between the patients and controls at baseline, the Gaussian Random Field theory correction (GRF) (voxel P value < 0.001 , cluster P value < 0.05) was used for multiple comparisons.

Parameters such as SAS, SDS, age, education level and gray matter volume that may affect functional connections were used as covariates. (2) One-way repeated measures ANOVA was used to assess the dynamic changes of within-network functional connectivity in breast cancer patients at three time points (GRF correction, voxel P value < 0.001, cluster P value < 0.05). In the ANOVA model, we used REST software (<http://www.fil.ion.ucl.ac.uk/spm>) to extract the average time series of significantly different brain regions within the subject, and evaluated the changes at t0, t1, and t2. Pairwise comparisons based on three time points were performed in the breast cancer group (post hoc test, P < 0.05).

Between-Network Functional Connectivity

ICA time series was used to analyze between-network connectivity and the functional connectivity coefficients between the RSNs were obtained using the GIFT toolkit. The functional connection coefficients of all pairs of sub-networks were analyzed and the correlation coefficients results were converted to z values. In the breast cancer group, one-way repeated measures ANOVA was used to test the between-network functional connectivity coefficients differences at three time points (Bonferroni multiple comparison correction, P < 0.05). Post hoc test was used to conduct pairwise comparisons between groups (t0, t1, t2), and P < 0.05 was considered to be statistically significant.

Correlation Analysis

According to the formula (Δ value = t2-t1), the z value changes of significantly different within-network connectivity and between-network connectivity of each subject were calculated. Pearson correlation analysis was used to analyze the correlation between brain function connection parameter changes and clinical index changes. P < 0.05 was considered to be statistically significant.

Results

Demographic and Clinical Data

A total of 17 breast cancer patients receiving chemotherapy completed follow-up at three time points (t0, t1 and t2). Nineteen HCs with matched age and education level only completed baseline assessments (t0). In breast cancer group, 11 women had normal menstrual status at baseline, 10 of the 11 premenopausal women had amenorrhea (90.9%, 10/11) at t1, and one had menstrual disorders (9.1%, 1/11). In the breast cancer group, 6 patients received endocrine therapy after the end of chemotherapy and 6 patients recovered their menstruation at t2.

At baseline, there was no significant difference in menstrual status, E2, LH, and FSH levels between the breast cancer patients group and HC group (all P > 0.05). The baseline anxiety and depression scores in the breast cancer group were significantly higher than those in HC group, however, these scores were in the normal range (P = 0.012, P = 0.002; respectively). The total cholesterol, triglyceride, fasting blood glucose and hemoglobin levels in the breast cancer group were higher than those in HC group (all P < 0.05), and the cognitive assessments scores of SDT, WDR and Stroop test were higher than those of HC group (all P < 0.05). Demographic data and clinical data at baseline are shown in Table 1.

Demographic and Clinical Data Changes

One-way repeated measures ANOVA showed that E2 values were significantly different between three time points ($F = 5.089$; $P = 0.012$). Post-hoc tests showed significant decreases from t1 to t2 ($P = 0.041$), and a rising trend 6 months after chemotherapy. Pairwise comparisons showed significantly increased triglycerides from t0 to t1 ($P = 0.041$) and decreased triglycerides levels at t2 without statistical significance. The Hb level decreased slightly from t0 to t1, and significantly increased from t1 to t2 ($P = 0.003$) (Table 2).

Repeated measures ANOVA showed significantly different WDT and LTT scores ($P = 0.008$, $P = 0.013$, respectively), the breast cancer patients showed slightly decreased WDT scores from t0 to t1, and significantly decreased scores from t0 to t2 ($P = 0.002$); LTT score decreased significantly at t1 ($P = 0.010$) and slightly lower from t1 to t2, while the difference was statistically significant from t0 to t2 ($p = 0.012$) (Table 2). The NST, SDT and Stroop-test scores fluctuated after chemotherapy, but the differences were not statistically significant. Anxiety and depression scores were higher from t0 to t1 and alleviated from t1 to t2, but the difference was not statistically significant (Table 2).

Spatial Distribution of RSNs

Thirty nine independent components were separated from the temporally concatenated 4D population data. After automatic template matching and visual discrimination confirmation, networks with the best matching were selected as the interest network. They were anterior and posterior DMN (aDMN, pDMN), DAN, left and right FPN (LFPN, RFPN), SMN, CEN, SRN, VN, AN and CN. One sample t-test showed that both breast cancer group and HC group demonstrated a typical spatial distribution pattern of RSNs.

Within-Network Functional Connectivity

Independent sample t-test showed no significant difference in within-network functional connectivity between the breast cancer group and HC group at baseline (GRF corrected).

The component of aDMN, pDMN, LFPN, RFPN, CN, SRN and VN revealed significantly different between time points in breast cancer group (GRF corrected) (Tables 3, 4). The locations of the peak value cluster are shown in Table 3. Post-hoc tests showed significantly increased within-network functional connectivity from t0 to t1 in aDMN, pDMN, LFPN, RFPN, SRN and CN ($P = 0.015$, 0.001 , 0.037 , 0.006 , 0.001 and 0.011 , respectively) and significantly decreased connectivity in these above-mentioned networks from t1 to t2. Only the VN functional connectivity decreased slightly from t0 to t1 and significantly increased from t1 to t2 ($P = 0.002$) (Fig. 2).

Between-Network Functional Connectivity

The between-network connectivity did not show significant difference between the patient and HC group at baseline. One-way repeated measure ANOVA analysis showed that the connectivity between aDMN and CN, pDMN and SMN, SMN and VN were different at three time points. Post-hoc test showed the functional connectivity between pDMN and SMN decreased from t0 to t1 ($P = 0.051$), while increased

from t1 to t2 ($P = 0.023$). The functional connectivity between aDMN and CN, SMN and VN showed continuous decrease (all $P < 0.05$) (Fig. 3).

Correlation Analysis

The between-network functional connectivity changes of aDMN and CN negatively correlated with the fasting glucose and DST score changes ($r = -0.497$, $P = 0.043$; $r = -0.547$, $P = 0.035$ respectively). The between-network functional connectivity changes of SMN and VN negatively correlated with changes in blood estrogen levels and SDS scores ($r = -0.655$, $P = 0.039$; $r = -0.498$, $P = 0.041$; respectively) (Fig. 4). The within-network connectivity changes in the supplementary motor area for CN positively correlated with fasting blood glucose changes ($r = 0.561$, $P = 0.019$) and negatively correlated with total cholesterol changes ($r = -0.484$, $P = 0.049$). The within-network connectivity changes in the right calcarine sulcus cortex for VN negatively correlated with the change of Stroop-W ($r = -0.563$, $P = 0.019$).

Discussion

In this study, we found increased within-network connectivity in most RSNs in breast cancer patients one week after chemotherapy, and all the within-network connectivity of RSNs tended to recover towards the baseline level six months after chemotherapy. Chemotherapeutics showed selective damage to the between-network connectivity. The connectivity between pDMN and SMN showed a recovery trend six months after chemotherapy, while the connectivity between aDMN and CN, SMN and VN continued to decline. Furthermore, both within- and between-network connectivity changes significantly correlated with blood indicators and cognitive function alterations. This prospective longitudinal study provided the evidence that chemotherapy may induce widespread connectivity abnormalities in RSNs, which might serve as potential biomarkers of chemotherapy related cognitive deficits in breast cancer patients.

Our results suggested that chemotherapeutics can damage the large-scale resting state brain networks, including aDMN, pDMN, LFPN, RFPN, SRN, CN and VN. These findings provided the evidence that chemotherapy induced widespread cognitive deficits across various domains. DMN is one of the most common RSNs, which is considered to support process such as active episodic memory and introspection, and would be deactivated during specific goal-directed task[24]. In our study, abnormal within-network functional connectivity in DMN were mainly located in the superior frontal gyrus and posterior cingulate cortex (PCC), which were consistent with the most previous studies[25, 20, 12], indicating that DMN is more vulnerable to chemotherapeutic agent attack. The CN, FPN, SRN and VN also showed abnormal within-network functional connectivity changes after chemotherapy. The LFPN is associated with language-related cognition, while the RFPN is associated with working memory, abstract reasoning, planning and somatosensory processing[26]. SRN is involved in self-understanding and self-reference processing, which is considered to be the hub network regulating primary perception, self-reference processing and advanced cognitive processing[27, 28]. CN is related to activity inhibition, emotion and participates in multiple advanced cognitive tasks, playing an important role in adaptive cognitive control. Abnormalities in multiple within-network functional connectivity provided the evidence

that chemotherapy induced widespread cognitive deficits in attention, executive function, memory, learning ability and processing speed.

In addition, chemotherapy induced abnormal RSNs functional connectives were mainly located in the superior frontal gyrus, PCC, supplementary motor area, orbital inferior frontal gyrus and calcarine sulcus. Neuroimaging studies have shown that some intrinsic network regions exhibit task-induced activation or deactivation during goal-directed tasks, which also namely the “task-positive network” or “task-negative network”. It was considered to support the process of target activity by regulating the allocation of neural resources[29, 30]. PCC and superior frontal gyrus mainly located in the task-negative network and deactivated for self-referential processing tasks, while the supplementary motor area and orbital inferior frontal gyrus located primarily within or near the task-positive network and activated for demanding cognitive tasks. These different task-evoked neuronal responses reflected the integrative role of the brain functional organization across several spatial and temporal ranges[31]. The increased within-network functional connectivity after chemotherapy may represent a compensation for dysfunction which needed to recruit more neural regions and increase the strength of functional connectivity in order to maintain normal neural activity. The functional connectives strength of RSNs also predicted chemotherapy induced higher or lower neural activity during task[30]. Previous multitask-based fMRI of CRCI showed increased[32, 33, 34] and decreased activity[35, 36, 37] located mainly in several frontal and parietal regions, anterior cingulate cortex and supplementary motor area. The altered RSNs functional connectivity regions in our study were matched well with previous task-related studies.

Chemotherapeutics also showed selective damage to the between-network connectivity in this study. The DMN can integrate primary perception and advanced cognitive functions. It accepts more information from other RSNs than it outputs. Liao et al. showed that SRN, CEN, CN and AN had significant effect on connections to the DMN[38]. Sridharan et al. found that CN may regulate DMN, CEN and dorsal attention network[39]. The collaborative work among these RSNs completes the integration and transformation of information. In this study, the decreased functional connectivity between networks after chemotherapy suggested that chemotherapeutic drugs did not alter central brain regions and hemodynamics through a single resting brain network, but the multiple between-networks dysfunction. The chemotherapy related cognitive impairments were the result of reduced coordination between multiple networks. The RSNs compete more processing resources from the “central cognitive operator” to compensate for their impaired cognition[29]. This may explain that functional impairment in multiple cognitive domains after chemotherapy but without significant difference from the baseline period.

Interestingly, most of the within-network connectives tended to recover to the baseline levels six months after chemotherapy, while the between-network connectives showed partial recovery. Recovery of some brain regions to baseline levels has also been reported in other CRCI-related functional and structural MRI studies[40, 41, 42, 8], and the acute damage mostly appeared 1 month after chemotherapy and (partially) recovered one year later. These studies suggested that chemotherapy-induced brain structural and functional damage may be temporary, the frontal regions (such as frontal and temporal gyrus) may recover over time, and the brain abnormalities in the posterior region may persist for a long time[43]. Brain

function and structural recovery may be attributed to neuroplasticity mechanisms. In this study, most of the subjects were young women, cognitive challenges in daily work and social activities promoted early rehabilitation through neuroplasticity mechanisms. Additionally, the frontal regions began to show signs of recovery six months after chemotherapy. We hypothesized that the frontal lobe might be one of the first sensitive brain regions to experience functional recovery. However, our finding was inconsistent with some previous studies as for recovery time, which may be related to the age, chemotherapy dose, chemotherapeutic drug, treatment stage, cognitive function type and the different control groups. The recovery to the baseline level may reflect compensation ability improvements over time to some extent, it does not mean a return to normal level, and some brain dysfunction may persist for a long time. Sustained networks alterations may further affect patient's cognitive function, such as sustained memory deterioration and executive ability impairment, which showed poor WDT and NST scores in this study. We are not sure whether the brain abnormality in the posterior brain region (such as visual function areas) alteration was a sustained change in acute effects after chemotherapy or a delayed brain injury occurring at a certain time after chemotherapy. Further long-term follow-up studies are thus needed.

Breast cancer patients also showed decreased visual ability and memory at baseline compared to HC group. This pre-treatment mild cognitive decline may be associated with tumor-related physical and psychological stress[44, 37]. Additionally, the improved test scores in LTT, SDT and Stroop test after chemotherapy may be related to the compensatory effect of the functional network. Furthermore, partial networks alterations were associated with estrogen, fasting blood glucose and blood lipids changes, though the improved blood indicator was still in the abnormal range compared to HC group. We speculated that the increased blood estrogen levels, decreased blood sugar and lipid levels six months later may play a positive role in the cognition improvement. Estrogen can alter the metabolic level of the frontotemporal lobe, affecting the structure and function of specific brain regions[45]. Animal experiments and clinical practice have shown that estrogen can be used to treat attention and memory loss. Abnormalities in blood lipids, fasting blood glucose, and hemoglobin have also been found in neuropsychiatric diseases such as Alzheimer disease and diabetic encephalopathy[46, 47]. The improved cholesterol metabolism would reduce the risk of vascular related cognitive impairment. However, the use of chemotherapeutic agents and endocrine therapy confuses the assessment of underlying metabolic changes. Although there was no direct evidence that baseline metabolism changes were significantly associated with cognitive improvement six months after chemotherapy, we speculate that the improvement of baseline metabolism in patients can play an irreplaceable role in the recovery mechanism of CRCI.

Anxiety and depression scores were significantly higher in the breast cancer group than HC group at baseline, and continued to increase one week after chemotherapy, but decreased over time after the end of chemotherapy. The dynamic changes of depression and anxiety scores were similar as that of some cognitive functions. Studies have suggested that there were competitive interactions between emotion and cognition[7, 30], we speculate that the decreased negative emotion may benefit cognitive function recovery in this study.

The study had some limitations. Although HC was included in this study, the control group had no serial follow-up, making it impossible to evaluate the interaction between the groups and time. However, all breast cancer patients performed a series of neuropsychological tests, blood examination and MRI scans at three times points, which enabled the longitudinal analysis of RSNs in these patients. Secondly, the breast cancer patients were heterogeneous, some confounding factors such as the different severities of the disease, the different treatment strategies may induce some impacts on the results of our study. Thirdly, the basic metabolism and hormone level may fluctuate greatly in a relatively short time, and untangling these effects was difficult. Fourthly, the sample size is relatively small due to some patients refusing follow-up. Finally, the definition and selection of the RSN may affect the results, and the source of abnormal nodes is not fully understood.

Conclusion

This prospective longitudinal study found that the breast cancer survivors showed a large-scale functional connectivity damage after chemotherapy, and these impaired RSNs partly tended to return to the baseline level 6 months after chemotherapy. The altered functional connectivities were related to the patient's cognitive function and hematology changes. Therefore, RSNs could be promising markers for potential chemotherapy-related brain damage, which provide an important basis for the observation of brain function impairment process and the subsequent cognitive rehabilitation interventions.

Abbreviations

CRCI: chemotherapy related cognitive impairment; fMRI: functional magnetic resonance imaging; HC: healthy controls; RSNs: resting state networks; E2: Estradiol; DMN: default mode network; FPN: frontoparietal network; DAN: dorsal attention network; SMN: sensorimotor network; CEN: central executive network ; SRN: self-referential network; VN: visual network; AN: auditory network; CN: central network; PCC: posterior cingulate cortex.

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Authors' contributions

YF conducted the subject's MRI examination, participated in the interpretation and analysis of data and drafted the manuscript. YFW participated in the interpretation of the data and the revision of the manuscript. ZS participated in the MRI examination and the collection of clinical data. LJZ recruited chemotherapy patients and normal control population. WH contributed to the statistical analysis. LJZ conceived of the study, participated in its design, and was responsible for the preparation of the manuscript. The authors read and approved the final manuscript.

Ethics approval and consent to participate

All the procedures involving human subjects were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained

from all subjects.

Consent for publication

All authors have read the manuscript and agreed with the submission.

Competing Interests

All authors declare that they have no competing interests.

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Tables

Table 1 Demographic, Clinical, and Neuropsychological Data at Baseline

Variables	BC group (n=17)	HC group(n=19)	P value
Age, years	45.6 ± 9.3	45.8 ± 9.4	0.505 ^c
Education levels, years	11.6 ± 3.6	13.1 ± 3.3	0.070 ^c
Premenopause, n (%)	11 (58.8)	11 (57.9)	0.896 ^b
Menopause, n (%)	6 (35.2)	8 (42.1)	0.734 ^b
Breast cancer stage, n (%)			
0	1 (5.9)	NA	NA
I	4 (23.5)	NA	NA
II	6 (32.3)	NA	NA
III	6 (32.3)	NA	NA
Chemotherapy regimen, n (%)			
AC-T (four cycles)	11 (64.7)	NA	NA
TEC (six cycles)	6 (35.3)	NA	NA
Endocrinotherapy	6 (35.3)	NA	NA
Clinical data			
SAS, score	29.6 ± 3.4	24.7 ± 3.2	0.012 ^{ca*}
SDS, score	28.5 ± 4.4	23.9 ± 3.2	0.002 ^{ca*}
E2, pmol/L	342.5 ± 80.4	161.7 ± 180.1	0.220 ^{ca*}
FSH, IU/L	27.3 ± 45.0	48.0 ± 30.7	0.021 ^{aa*}
LH, IU/L	26.8 ± 19.1	35.3 ± 28.0	0.234 ^c
Hemoglobin, g/L	121.4 ± 5.4	130.7 ± 0.03	0.334 ^c
Total cholesterol, mmol/L	5.30 ± 1.4	5.05 ± 0.9	0.037 ^{ca*}
Triglycerides, mmol/L	2.2 ± 1.5	1.22 ± 0.8	0.030 ^c
Fasting glucose, mmol/L	5.8 ± 1.3	5.0 ± 0.4	0.005 ^{aa*}
Cognitive performance			
MMSE, score	28.3 ± 1.5	28.0 ± 1.5	0.061 ^c
DST, score	54.1 ± 33.2	55.7 ± 18.1	0.408 ^c
LTT, sec	67.1 ± 27.6	38.4 ± 12.1	0.429 ^c
SDT, sec	41.0 ± 10.0	32.1 ± 5.6	0.050 ^{aa*}
WDR, score	24.24 ± 3.4	26.4 ± 3.1	0.010 ^{aa*}
Stroop-C, sec	17.7 ± 7.7	14.2 ± 3.0	0.005 ^{aa*}
Stroop-W, sec	22.8 ± 5.6	16.7 ± 3.4	<0.001 ^{ca*}
Stroop-I, sec	30.5 ± 7.4	25.6 ± 7.1	0.003 ^{ca*}

* P < 0.05, ** P < 0.01; a: k-independent samples nonparametric tests; b: chi square test; c: two-sample t test.

Abbreviations: A, Doxorubicin; C, Cyclophosphamide; T, Docetaxel; E, Epirubicin; SD, standard deviation; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; DST, digit symbol test; MMSE, Mini-mental state examination; LTT, line tracing test; NCT-A, number connection test A; SDT, serial dotting test; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale; Stroop-C, Stroop colour test; Stroop-D, Stroop word test; Stroop-I, Stroop interference test; WDR, Auditory verbal learning memory.

Table 2 Blood Examination and Cognitive Assessment Results in Breast Cancer Group at Three Time Points

	Mean ± SD			P value			F value	P value
	t0	t1	t2	t0 vs t1	t0 vs t2	t1 vs t2		
E2 (pmol/L)	301.7 ±255.1	120.1 ±119.2	195.0 ±179.6	0.041	0.188	0.506	5.089	0.012^{c*}
FSH (IU/L)	27.3 ± 45.0	63.8 ± 43.0	62.8 ± 49.8	0.031*	0.385	0.965	2.958	0.075 ^c
LH (IU/L)	26.8 ± 19.1	41.2 ± 12.7	40.2 ± 12.7	0.662	0.926	0.156	3.344	0.106 ^c
Hemoglobin (g/L)	121.4 ± 5.4	120.9 ± 3.3	134.4 ± 3.5	0.989	0.325	0.003*	3.876	0.075 ^c
Fasting glucose (mmol/L)	5.8 ± 1.3	5.6 ± 1.0	5.5 ± 0.7	0.677	0.523	0.832	0.215	0.808 ^a
Total cholesterol (mmol/L)	5.3 ± 1.4	5.1 ± 0.9	5.2 ± 1.3	0.745	0.732	0.990	0.076	0.927 ^c
Triglycerides (mmol/L)	2.1 ± 1.5	2.8 ± 1.8	2.1 ± 0.8	0.041	1.000	0.194	3.281	0.052 ^a
SAS (score)	29.6 ± 3.4	32.6 ± 4.8	28.7 ± 6.9	0.186	0.659	0.098	1.548	0.228 ^a
SDS (score)	28.5 ± 4.4	33.3 ± 5.9	31.9 ± 9.5	0.133	0.221	0.677	1.418	0.257 ^c
Stroop-C (sec)	17.7 ± 7.67	15.8 ± 6.1	15.9 ± 4.8	0.480	0.493	0.985	0.340	0.714 ^c
Stroop-W (sec)	22.8 ± 5.6	19.7 ± 5.8	19.4 ± 6.9	0.235	0.179	0.876	1.156	0.327 ^c
Stroop-I (sec)	30.5 ± 7.4	30.4 ± 8.1	30.5 ± 10.1	0.999	0.992	0.991	0.001	0.999 ^c
NST (sec)	50.8 ± 20.0	51.2 ± 28.4	67.2 ± 41.0	0.973	0.187	0.224	1.101	0.345 ^c
DST (score)	54.1 ± 33.2	51.5 ± 18.6	56.0 ± 15.6	0.798	0.855	0.672	0.093	0.912 ^c
LTT (sec)	67.1 ± 27.6	42.8 ± 18.8	42.6 ± 13.5	0.010**	0.012	0.978	5.013	0.013^{c*}
MMSE (score)	28.1 ± 1.7	28.8 ± 0.97	28.9 ± 2.7	0.431	0.301	0.879	0.619	0.545 ^c
SDT (sec)	41.0 ± 1.0	37.7 ± 11.8	35.7 ± 10.6	0.451	0.247	0.659	0.728	0.491 ^c
WDT (score)	24.2 ± 3.7	21.6 ± 6.0	17.4 ± 1.6	0.278	0.002**	0.082	5.595	0.008^{c**}

Mean ± standard deviation; * P < 0.05, ** P < 0.01; a: k-independent samples nonparametric tests; c: two-sample t test.

Abbreviations: t0, baseline assessment; t1, one week after chemotherapy; t2, six month after chemotherapy; SD, standard deviation; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; DST, digit symbol test; MMSE, Mini-mental state examination; LTT, line tracing test; NCT, number connection test; SDT, Serial dotting test; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale; Stroop-C, Stroop colour test; Stroop-W, Stroop word test; Stroop-I, Stroop interference test; WDR, Auditory verbal learning memory.

Table 3 Statistically Significant Differences of Within-network Functional Connectivity for Breast Cancer Group

Anatomic region (RSN)	Cluster voxel	MNI Coordinates			F-score (peak value)
		x	y	z	
Right superior frontal gyrus (aDMN)	17	15	36	48	22.892
Posterior cingulate (pDMN)	13	-12	-51	18	16.763
Left supplementary motor area (CN)	50	16	1	70	16.752
Right supplementary motor area (CN)	30	-9	-3	69	16.047
Left superior frontal gyrus (LFPN)	27	-15	30	48	19.190
Right triangle inferior frontal gyrus (RFPN)	14	45	31	26	18.939
Left orbital inferior frontal gyrus (SRN)	8	-24	27	-9	15.689
Right calcarine sulcus cortex (VN)	14	18	-72	15	12.241

Gaussian Random Field theory correction, voxel P value < 0.001, cluster P value < 0.05

Table 4 Summary of Within-network Functional Connectivity for Breast Cancer Group at three times

	Mean ± SD			P value			F value	P value
	t0	t1	t2	t0 vs t1	t0 vs t2	t1 vs t2		
aDMN	1.32±0.59	1.79±0.56	1.23±0.48	0.015*	0.658	0.005**	5.110	0.010*
pDMN	0.86±0.40	1.35±0.38	1.01±0.34	0.001**	0.270	0.012*	7.321	0.002**
LFPN	1.66±0.59	2.10±0.74	1.51±0.44	0.037*	0.464	0.006**	4.469	0.017*
RFPN	1.92±0.71	2.69±0.90	2.11±0.74	0.006**	0.489	0.034*	4.518	0.016*
CN	2.20±0.79	3.79±1.49	2.29±0.72	0.000**	0.812	0.001**	12.163	0.001**
SRN	1.27±0.47	1.79±0.68	1.19±0.56	0.011*	0.722	0.004**	5.381	0.008**
VN	2.09±0.69	1.65±0.57	2.58±1.10	0.123	0.087	0.002**	5.503	0.007**

NOTE: **, P<0.01; *, P<0.05; t0, baseline assessment; t1, one week after chemotherapy; t2, six month after chemotherapy

Figures

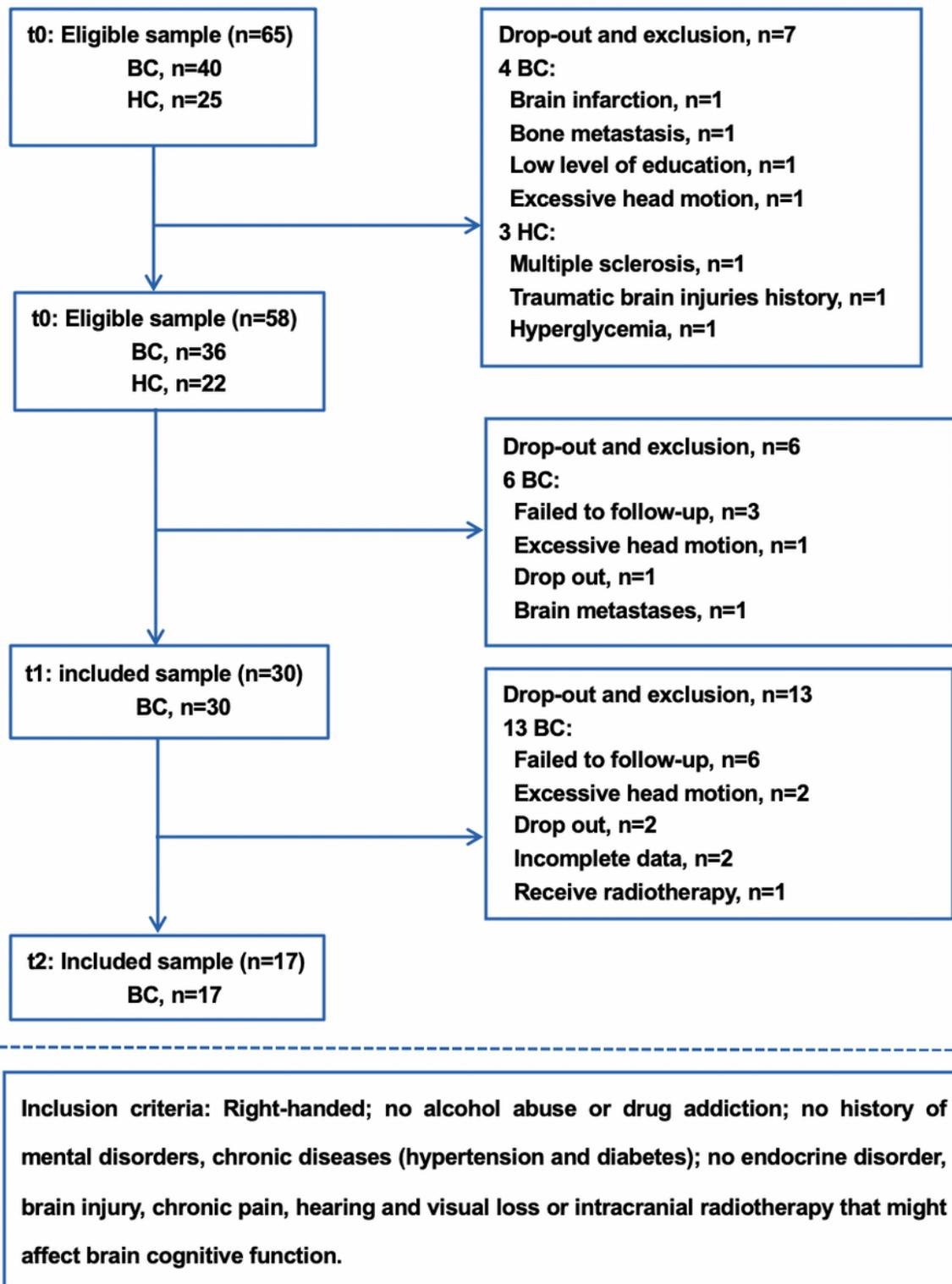


Figure 1

Flowchart of this study. BC = breast cancer; HC = healthy controls

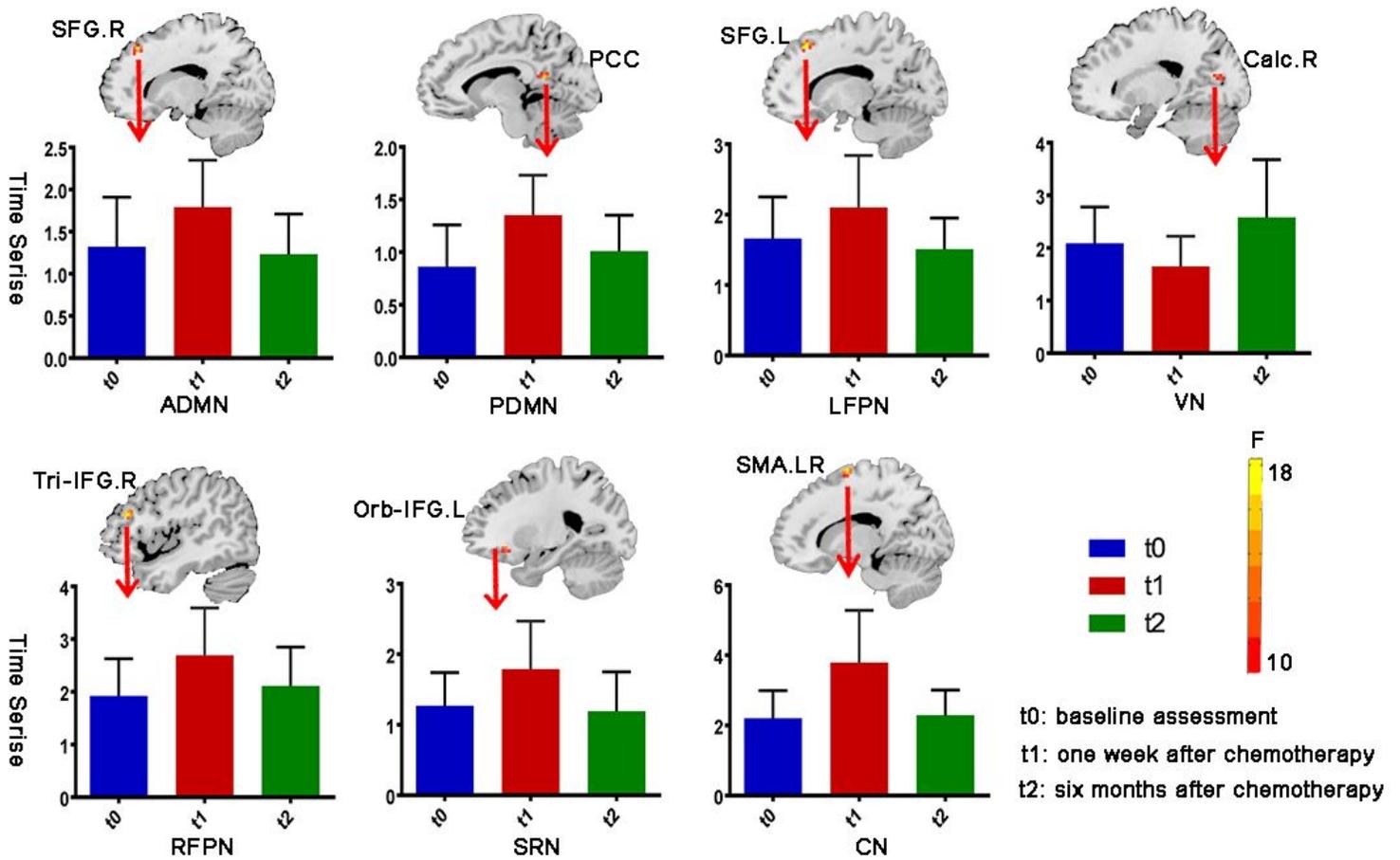


Figure 2

Seven RSNs show significant within-network connectivity changes in breast cancer patients among three time points. The histograms display the longitudinal evaluation of the within-network functional connectivity changes in the peak cluster regions for each RSN at three time points. t0, baseline assessment; t1, one week after chemotherapy; t2, six months after chemotherapy. SFG.R: right superior frontal gyrus, PCC: posterior cingulate gyrus, SFG.L: left superior frontal gyrus, Tri-IFG.R: right triangle inferior frontal gyrus, SMA.R: right supplementary motor area, Orb-IFG.L: Left orbital inferior frontal gyrus, Calc. R: right calcarine sulcus cortex.

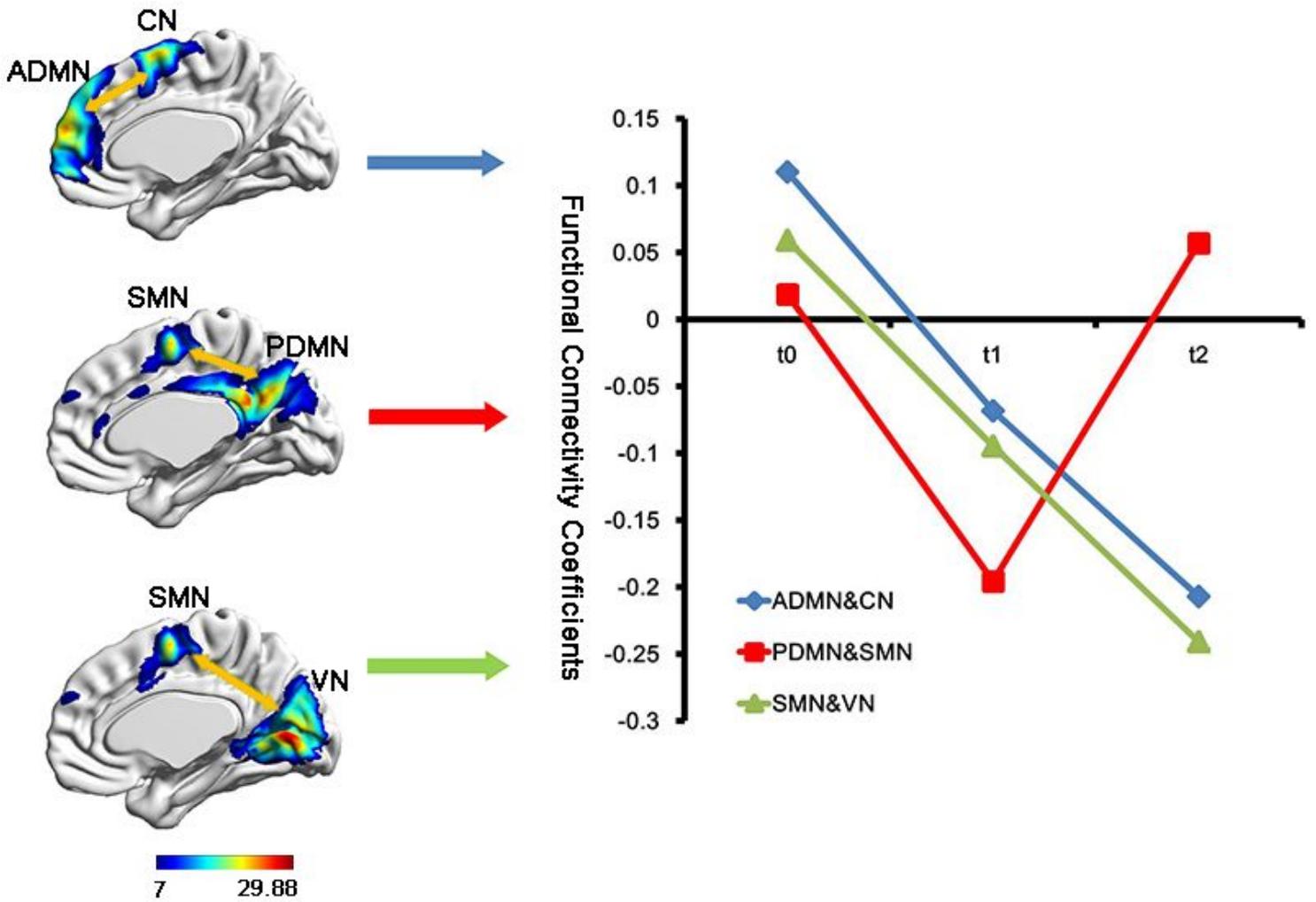


Figure 3

The between-network connectivity changes in breast cancer patients among three time points. t0, baseline assessment; t1, one week after chemotherapy; t2, six months after chemotherapy. ADMN, anterior default mode network; PDMN, posterior default mode network; SMN, sensorimotor network; VN, visual network; CN, central network.

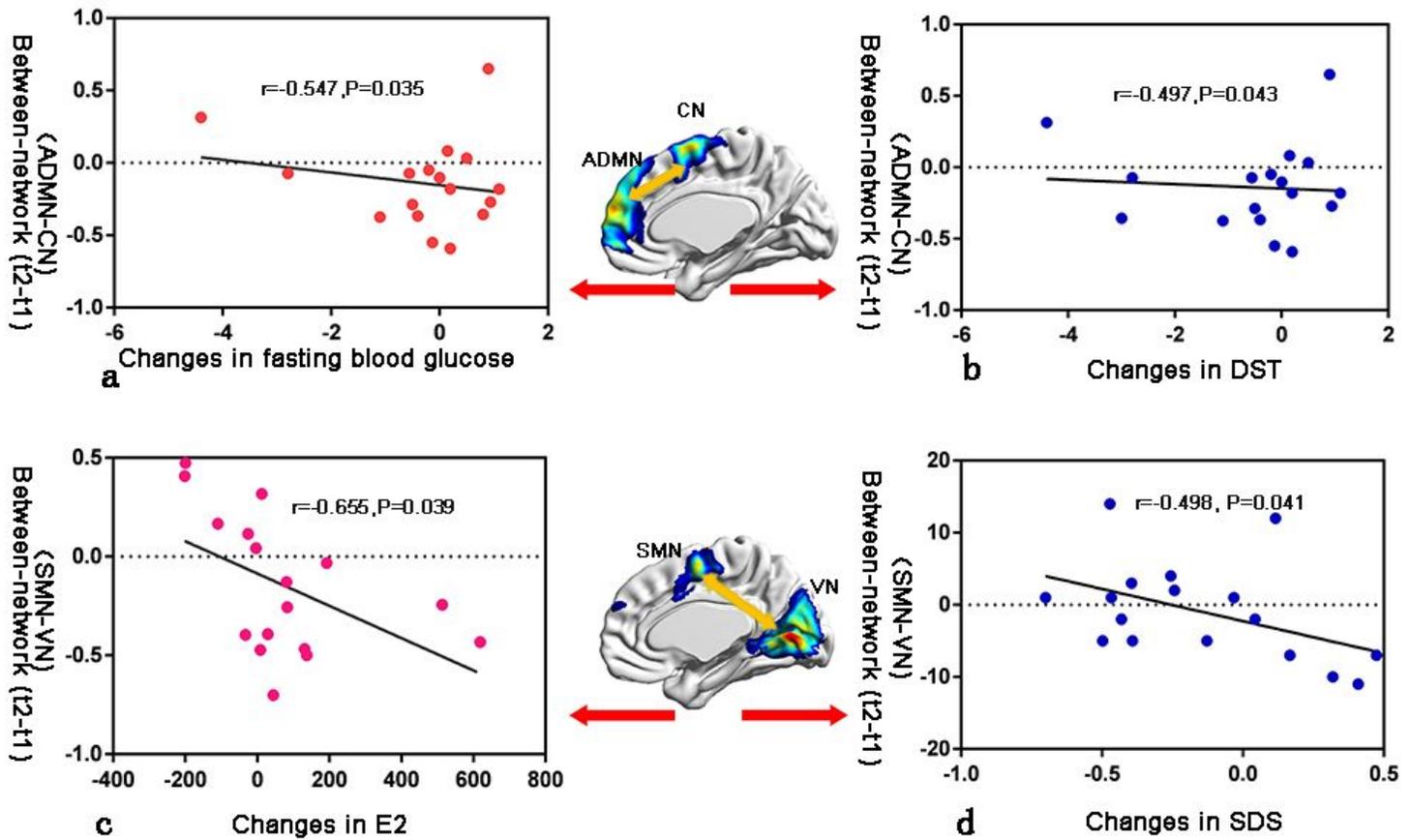


Figure 4

The correlation between the inter-network connectivity changes and clinical variables changes in breast cancer survivors from t1 to t2. a-b: Changes of the functional connectivity between ADMN and CN correlated with the fasting glucose and DST score changes. c-d: Changes of the functional connectivity between SMN and VN correlated with blood estrogen levels and SDS scores changes. t1, one week after chemotherapy; t2, six months after chemotherapy. ADMN, anterior default mode network; SMN, sensorimotor network; VN, visual network; CN, central network; SDS, Self-Rating Depression Scale; DST, digit symbol test.