

Default mode network connectivity distinguishes chemotherapy-treated breast cancer survivors from controls

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Breast cancer (BC) chemotherapy is associated with cognitive changes including persistent deficits in some individuals. We tested the accuracy of default mode network (DMN) resting state functional connectivity patterns in discriminating chemotherapy treated (C+) from non-chemotherapy (C-) treated BC survivors and healthy controls (HC). We also examined the relationship between DMN connectivity patterns and cognitive function. Multivariate pattern analysis was used to classify 30 C+, 27 C-, and 24 HC, which showed significant accuracy for discriminating C+ from C- (91.23%, $P < 0.0001$) and C+ from HC (90.74%, $P < 0.0001$). The C- group did not differ significantly from HC (47.06%, $P = 0.60$). Lower subjective memory function was correlated ($P < 0.002$) with greater hyperplane distance (distance from the linear decision function that optimally separates the groups). Disrupted DMN connectivity may help explain long-term cognitive difficulties following BC chemotherapy.

fMRI | machine learning

Breast cancer (BC) chemotherapy is associated with cognitive dysfunction based on both human and animal research (1, 2). The exact mechanisms of this dysfunction remain unclear, although there is emerging evidence that chemotherapy may accelerate cognitive and brain aging. For example, one study noted that gray matter atrophy in chemotherapy-treated (C+) BC survivors was comparable to the effect of 4 y of additional aging (3). Additionally, a previous epidemiological study demonstrated that C+ BC survivors were at higher risk for dementia than non-chemotherapy-treated survivors (C-) (4).

One of the most promising biomarkers of pathological age-related cognitive decline is reduction of default mode network (DMN) connectivity (5). The DMN, one of the most commonly observed resting state networks, includes precuneus, posterior cingulate, medial frontal, middle temporal, and lateral parietal regions as well as hippocampus (6). The DMN is believed to support important core processes such as implicit learning, autobiographical memory retrieval, prospection, monitoring, and other internally focused thought processes (7). DMN connectivity tends to decrease with age and is markedly decreased in individuals with amnesic mild cognitive impairment and Alzheimer's disease (8, 9).

There are several lines of evidence that suggest DMN impairment following BC chemotherapy. These include reduced gray matter volumes of brain regions associated with the DMN, particularly the precuneus, cingulate, lateral parietal cortex, medial frontal gyrus, and hippocampus (10–12). Gray matter atrophy can significantly alter DMN connectivity (8). Functional neuroimaging studies suggest reduced task-related deactivation of medial frontal and lateral parietal regions following BC chemotherapy (13).

White matter tracts, including cingulum, bilateral superior frontal occipital fasciculus, and the genu of the corpus callosum connect the regions of the DMN (14). BC chemotherapy is

associated with widespread reductions in white matter pathway integrity in similar regions, including cingulum and superior frontal occipital fasciculus (15, 16). A previous study from our laboratory demonstrated disorganization of large-scale structural brain networks following BC chemotherapy, including reduced participation of precuneus in the network (17). These neuroimaging findings are supported by animal studies that demonstrate chronic suppression of hippocampal neurogenesis as well as white matter myelin damage following administration of systemic chemotherapeutic agents (1, 18).

Our previous study indicated disruption of the global resting state network in C+ BC survivors, including reduced capacity for functional specialization (19). However, this analysis did not allow for direct assessment of specific resting state networks such as the DMN. To our knowledge, explicit investigation of DMN connectivity following BC chemotherapy has not been conducted to date. The present study aimed to determine if reduced functional connectivity of the DMN could accurately discriminate between C+ and C- BC survivors and healthy female controls (HC). We used resting state functional MRI (fMRI) to measure connectivity among DMN regions and multivariate pattern analysis (MVPA) to classify groups based on profiles of functional connectivity.

MVPA is a type of supervised machine learning that strives to create algorithms to automatically characterize complex data (20). MVPA methods can demonstrate patterns of neurobiology that discriminate between groups and tend to have greater power to make these differentiations compared with traditional, univariate methods (21). This increased power stems from MVPA's ability to use subtle signals across voxels that are undetectable by univariate analyses (22). This increased sensitivity is especially important for the study of BC-related cognitive dysfunction, which tends to be subtle or difficult to detect (23). We hypothesized that patterns of functional connectivity in the DMN would show significant accuracy in distinguishing C+ from C- as well as HC.

Results

C+ vs. C- MVPA. Support vector machine (SVM) classifiers achieved significant accuracy (91.23%, $P < 0.0001$), sensitivity (93.33%, $P < 0.0001$), and specificity (88.89%, $P < 0.0001$) as well as positive (89.36%, $P < 0.0001$) and negative (93.02%, $P < 0.0001$) predictive values (Fig. 1, Table S1, and Fig. S1). The

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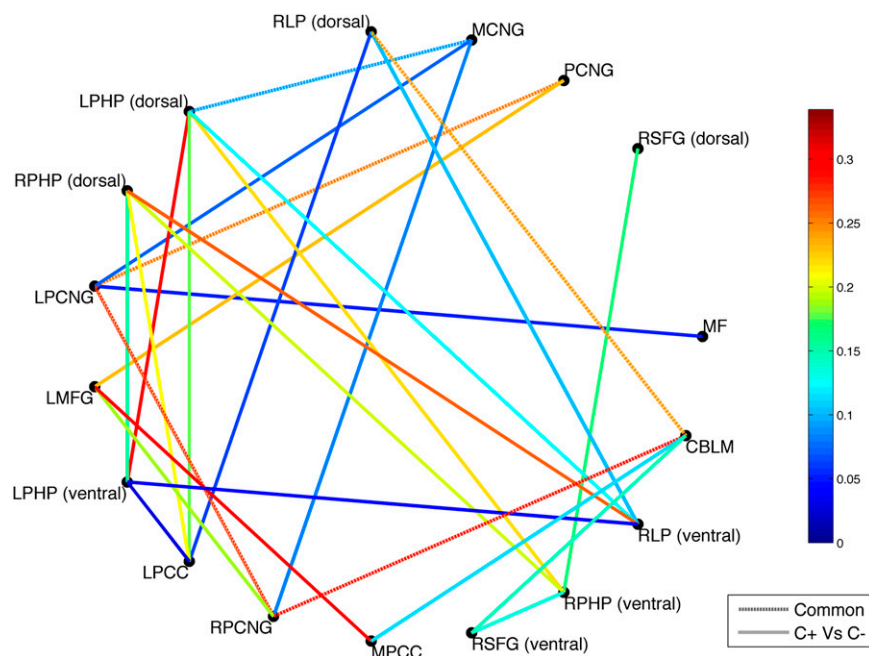


Fig. 1. Multivariate pattern classification of DMN intrinsic connectivity in C+ compared with C-. The graph shows connections specific to the C+ vs. C- classifier (solid lines) as well as those that were common between the C+ vs. C- and C+ vs. HC classifiers (dashed lines). Warmer colors correspond to higher absolute weights in the discrimination between C+ and C-. CBLM, cerebellum; LMFG, left middle frontal gyrus; LPCC, left precuneus; LPCNG, left precuneus/posterior cingulate; LPHP, left parahippocampus; MCNG, medial cingulate; MF, medial frontal; MPCC, medial precuneus; PCNG, posterior cingulate; RLP, right lateral parietal; RPCNG, right posterior cingulate; RPHP, right parahippocampus; RSFG, right superior frontal gyrus.

area under the receiver operator curve (ROC) for this analysis was 0.97.

C+ vs. HC MVPA. SVM classifiers achieved significant accuracy (90.74%, $P < 0.0001$), sensitivity (90.00%, $P = 0.003$), and specificity (91.67%, $P < 0.0001$) as well as positive (91.53%, $P <$

0.0001) and negative (90.16%, $P = 0.0005$) predictive values (Fig. 2, Table S2, and Fig. S2). The ROC for this analysis was 0.98.

C- vs. HC MVPA. SVM classifiers were not significantly better than chance in terms of accuracy (47.06%, $P = 0.60$), sensitivity (51.85%, $P = 0.69$), specificity (41.67%, $P = 0.52$), and positive

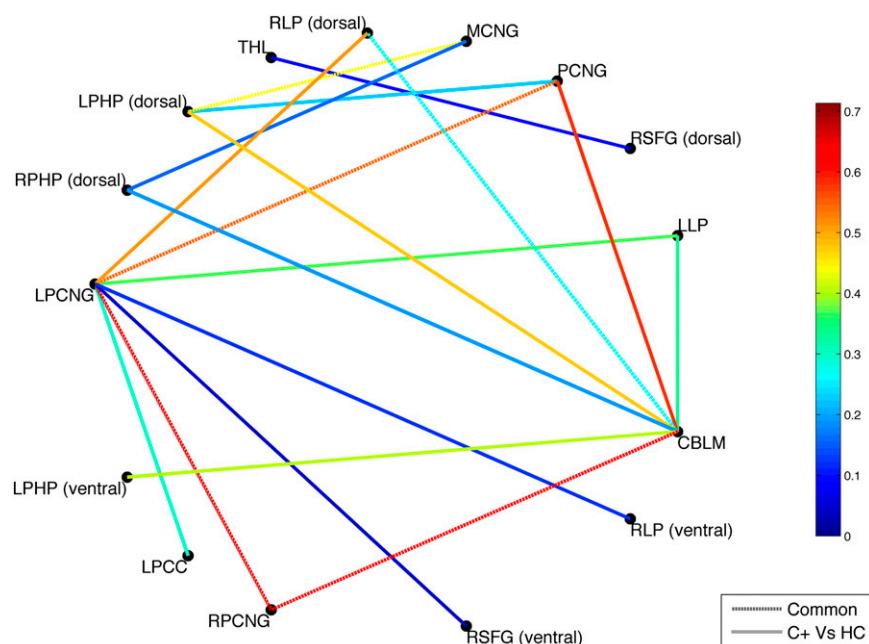


Fig. 2. Multivariate pattern classification of DMN intrinsic connectivity in C+ compared with HC. The graph shows connections specific to the C+ vs. HC classifier (solid lines) as well as those that were common between the C+ vs. HC and C+ vs. C- classifiers (dashed lines). Warmer colors correspond to higher absolute weights in the discrimination between C+ and HC. LLP, left lateral parietal; THL, thalamus.

(47.06%, $P = 0.60$) or negative (46.39%, $P = 0.55$) predictive values. The ROC for this analysis was 0.48.

Disease-Stage MVPA. SVM classifiers were not significantly better than chance for stage 1 vs. 2 (accuracy = 48.94%, $P > 0.50$) and stage 1 vs. 3 (accuracy = 34.21% $P > 0.50$) as well as stage 1 vs. 2+3 (accuracy = 31.58%, $P > 0.50$). ROCs were less than 0.50 for these analyses.

Cognitive Status. There were no significant group differences on cognitive tests. On self-report measures, the C+ group demonstrated significantly elevated Behavioral Rating Inventory of Executive Function (BRIEF) scores and reduced Multifactorial Memory Questionnaire (MMQ) scores compared with both the HC and C− groups. The C− group did not differ from the HC group on any measures (Table 1).

Correlations. Lower MMQ score was significantly associated with greater hyperplane distance using either the HC ($r = -0.68$, $P < 0.0001$) or the C− ($r = -0.40$, $P = 0.002$) classifier (Fig. 3). There were no significant correlations between hyperplane distance, BRIEF, or Clinical Assessment of Depression (CAD) scores. Radiation, tamoxifen, time since treatment, menopausal status, and disease stage were not correlated with hyperplane distance.

Discussion

Our results indicate abnormal DMN connectivity associated with BC chemotherapy. Patterns of DMN connectivity distinguished C+ from both C− survivors and HC with 90–91% accuracy. Classification performance resulted in areas of 0.97–0.98 under the ROC, indicating excellent categorization power. Results were controlled for age, education, psychiatric status, and gray matter volume. The C+ group also reported significantly greater executive function and memory difficulties on self-report measures compared with the C− and HC groups. The hyperplane distance significantly correlated with subjective memory ability providing further support for the validity of the classifier. Additionally, abnormal DMN connectivity was not associated with disease stage in SVM classification or correlational analyses.

Together, these findings suggest that altered DMN connectivity may represent a promising biomarker of cognitive dysfunction following BC chemotherapy. For example, in prospective studies, MVPA classifiers could predict individuals who will have persistent cognitive impairment using baseline neuroimaging data. This method has been used successfully in other conditions, such as the prediction of conversion from mild cognitive impairment to dementia (24). SVM of neuroimaging data often outperforms

other outcome prediction methods including those that rely on cognitive-behavioral data (21).

The DMN connections that carried the highest weights across both classifiers (C+ vs. C− and C+ vs. HC) included left parahippocampus, medial and posterior cingulate, left precuneus, and right lateral parietal lobe. These regions support memory retrieval, self-referential processes, and awareness (9). Cerebellar connections also were common across both classifiers. The cerebellum has been shown to contribute to several distributed networks including executive control, salience, and DMN (25). Cerebellar abnormalities including reduced gray matter volume (16) and hyperactivation during memory recall (13) have been associated with BC chemotherapy.

Consistent with the role of DMN regions in memory function, we demonstrated significantly reduced self-rated memory ability in the C+ group. Distance from the hyperplane for each subject was significantly negatively correlated with self-rated memory ability within both classifiers. By definition, hyperplane distances were negative for comparison groups and positive for the C+ group, indicating that subjects with higher positive hyperplane distances are more distinguished from comparison subjects in terms of DMN connectivity. Thus, the observed negative correlation suggests that the greater the separation between a C+ subject and the comparison group in terms of DMN connectivity, the lower the memory function (Fig. 3). Correspondingly, the closer a comparison group subject to the C+ group in terms of DMN connectivity, the lower the memory function. Hyperplane distance was not associated with executive dysfunction despite the fact that several prefrontal regions were included in the classifiers. However, executive function may rely more on task-positive (executive control) rather than task-negative (DMN) networks (26). Therefore, this dissociation between memory and executive function correlations with DMN connectivity seems to provide further validation of our results.

Our findings indicate that the overall multivariate profile of DMN connectivity is highly discriminating between C+ subjects and controls, suggesting that the DMN is significantly affected by chemotherapy. The SVM analysis does not provide information about the direction of connectivity. The association of increased versus decreased DMN connectivity with specific disease states is very complex. For example, altered DMN connectivity has been associated with normal as well as pathological aging. However, DMN regions tend to show increased connectivity during early phases of mild cognitive impairment followed by decreased connectivity later on (27, 28). Both increased and decreased DMN connectivity have also been associated with mood disorder (29, 30). Longitudinal examination of DMN connectivity in BC is

Table 1. Cognitive and self-report data shown as mean (SD)

Measure	C+	N	C−	N	HC	N	P (omnibus)
Global Intelligence	58 (7)	30	59 (7)	27	60 (8)	24	0.63
WCST	46 (9)	30	48 (7)	27	52 (12)	20	0.11
DKEFS Letter Fluency	57 (10)	30	57 (10)	27	60 (13)	24	0.51
HVLT-R TR	53 (8)	29	53 (9)	27	56 (10)	20	0.45
HVLT-R DR	53 (6)	29	53 (9)	27	54 (9)	20	0.49
NAB categories	50 (7)	29	54 (5)	27	56 (9)	20	0.03
BRIEF GEC	61 (11) ^{HC(1.5), C−(1.4)}	30	48 (8)	27	47 (8)	24	<0.0001*
MMQ	42 (11) ^{HC(2.1), C−(1.5)}	29	58 (8)	27	61 (7)	22	<0.0001*
CAD	51 (10) ^{HC(0.93), C−(0.80)}	30	43 (10)	27	43 (7)	24	0.002*

For CAD and BRIEF, higher scores equal increased impairment; for all other tests, lower scores equal increased impairment. Effect size is shown in the superscript parenthesis for pairwise comparisons. ^{C−}, significantly different from C− group; DKEFS, Delis-Kaplan Executive Function System; GEC, Global Executive Composite; ^{HC}, significantly different from HC group; HVLT-R DR, Hopkins Verbal Learning Test-Revised Delayed Recall; HVLT-R TR; HVLT-R Total Recall; MMQ, Multifactorial Memory Questionnaire Ability Scale; NAB, Neuropsychological Assessment Battery.

*Significant at $P < 0.00556$ level indicated by Bonferroni correction for multiple comparisons.

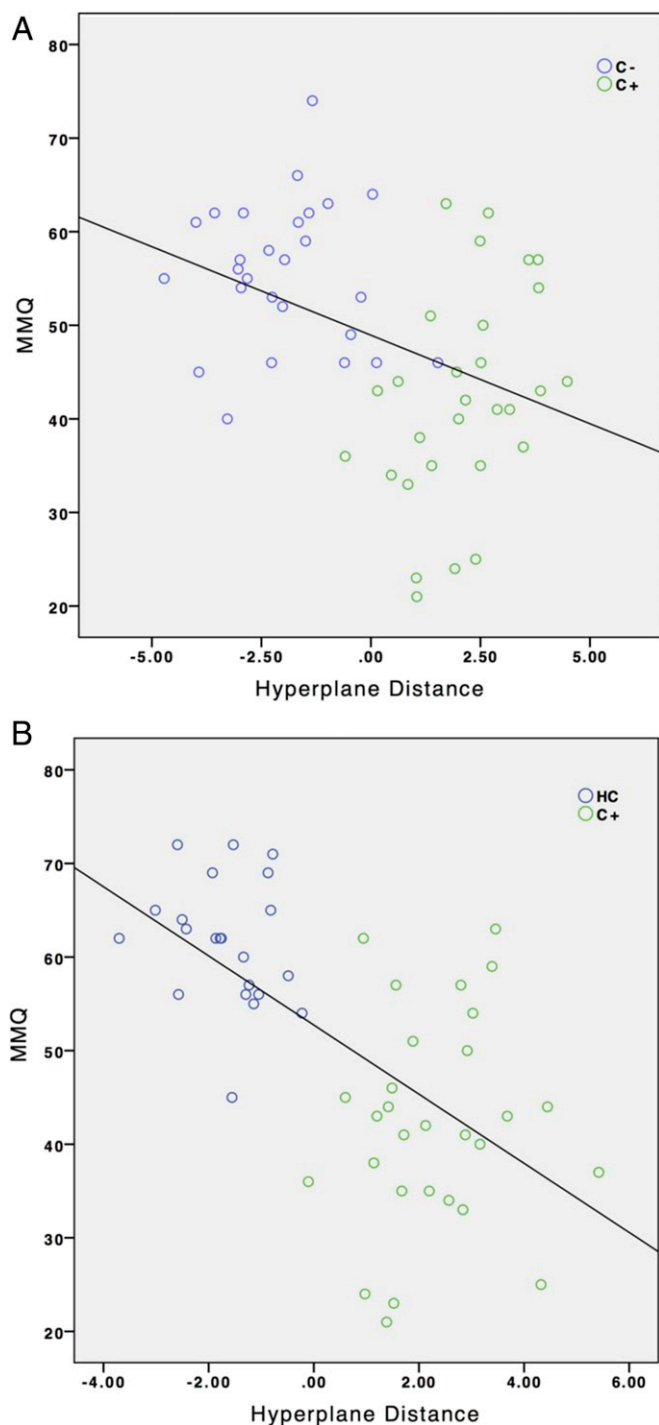


Fig. 3. Correlation between hyperplane distance and self-rated memory ability. A significant negative correlation was observed within the (A) C+ vs. C- as well as the (B) C+ vs. HC classifiers.

required to investigate potential changes in connectivity direction over time.

Prefrontal cortex connections also contributed highly to the classifiers. The superior frontal gyrus has been shown to have abnormal resting state connectivity with DMN regions in Alzheimer's disease (8). The strength of the negative correlation between default mode and cognitive control networks (which rely critically on prefrontal cortex) is predictive of cognitive performance in healthy individuals (31). Previous studies, including

our own, have demonstrated reduced prefrontal cortex activation during cognitive control following BC chemotherapy (32, 33). These tasks were very challenging, likely representing high cognitive load.

One possible explanation for these previous findings is that chemotherapy disrupts the interaction between DMN and the cognitive control network. This disruption reduces adaptation of neural resources in response to increased cognitive challenge. Individuals with amnesic mild cognitive impairment show difficulty switching between DMN and task-positive networks such that DMN resources are used in response to a task rather than the appropriate task network, compromising performance (31). However, the interaction between DMN and cognitive control network has not been previously evaluated in BC. The inclusion of parametric fMRI and cognitive tasks in future studies of BC chemotherapy will be essential for investigating this hypothesis.

The BC groups did not differ in terms of hormonal therapy, radiation, or menopausal status; these variables also were not associated with the SVM hyperplane. However, previous studies have demonstrated cognitive abnormalities in participants treated with radiation and/or hormonal therapy only (34). These previous results in combination with our present findings suggest that there are likely region- and/or network-specific effects of cancer and its treatments. For example, C- may be more associated with prefrontal network disruption compared with DMN (11, 32, 35). However, it is also possible that our sample sizes were too small and/or the cross-sectional nature of the present study prevented us from detecting differences in DMN in the C- group. Further study is required to determine the factors that result in differential vulnerabilities within the brain to cancer and its treatments.

There were no significant differences between C+ and C- survivors on objective cognitive tests. Previous research has shown that decline on cognitive tests occurs in a subset of patients such that mean group performance may not adequately represent this effect (36). This relative decline is most clearly demonstrated through the use of longitudinal designs. Determining the optimal definition of cognitive decline remains a challenge. However, some progress has been made toward unifying the field in terms of the cognitive domains and tests deemed most important in such studies (37). Incorporating resting state imaging studies into longitudinal investigations of treatment-related cognitive change will allow development of diagnostic and prognostic biomarkers.

More importantly, prospective designs are required to determine individual differences in DMN connectivity that may contribute to individual cognitive outcome. For example, it is not possible with the present results to examine how DMN connectivity differs between participants who had acute versus persistent or late onset cognitive difficulty (36). Our small sample sizes may have reduced statistical power for detecting certain correlational effects. There are a variety of methods available to examine DMN connectivity. Although DMN is highly consistent across studies (6), it is possible that different results would be observed using different methods. Our subject recruitment materials specifically mentioned cognitive dysfunction and therefore the sample may have been biased toward survivors who were concerned about their cognitive status. Our sample of BC survivors was heterogeneous in terms of treatment histories. However, this is common among studies of this population, partially reflecting the high degree of individualized treatment associated with this disease.

Despite these limitations, the present study demonstrates abnormalities in DMN connectivity that are highly specific to C+ BC survivors and associated with memory difficulties reported by patients. Disrupted DMN connectivity may help explain long-term cognitive difficulties following BC chemotherapy. Continued research in this area using prospective study designs could potentially yield novel neuroimaging biomarkers and diagnostic/

prognostic tools for chemotherapy-related cognitive dysfunction. Neuroimaging-based SVM classification could improve the precision of prognostic indicators. The identification of patients who are at increased risk for these difficulties could aid in treatment decision-making and help prioritize patients for neuropsychological surveillance as well as early intervention to prevent progressive decline.

Materials and Methods

Participants. This study included 58 women ages 41–73 y with a history of primary BC (stage I–IIIA) who were at least 6 mo off-therapy (chemotherapy/radiation; mean = 4.9 ± 3.4 y; range = 0.5–12 y). Of these, 31 received adjuvant chemotherapy (C+) and 27 did not receive chemotherapy (C–). We also enrolled 27 HC females in this study. This sample was included in a previous study that focused on global resting-state brain network topology (19). There were no between group differences in age, minority status, or education level (Table 2). There were significantly more women in the BC group who were postmenopausal compared with the HC group, which was expected given that chemotherapy can induce early menopause (38). There were no differences between the C+ and C– groups in menopausal status, time off-therapy, radiation, or tamoxifen, although the C+ group had significantly higher disease stage at diagnosis, as expected (Table 2). Five participants in the C+ group and six in the C– group were still taking tamoxifen at the time of assessment.

Individual chemotherapy treatment protocols included Adriamycin/Cytoxan/Taxol or Taxotere = 27, Cytosin/methotrexate/5-fluorouracil = 5 and Adriamycin/Cytosin + Cytosin/methotrexate/5-fluorouracil = 2. Participants were recruited from community support groups, local advertisements, and the Army of Women (www.armyofwomen.org). BC survivors were excluded for history of relapse or prior chemotherapy treatment. All participants were excluded for diagnosed psychiatric, neurologic, or comorbid medical conditions that are known to affect cognitive function as well as pregnancy, MRI contraindications, or major sensory deficits (e.g., blindness). Participants were also excluded for significant ($T > 69$) CAD score (39). The Stanford University Institutional Review Board approved the present study. All participants provided written informed consent.

fMRI Data Analysis. Resting-state fMRI and volumetric MRI were obtained for each participant (*SI Materials and Methods*). To define DMN connectivity, we used 19 independent regions of interest (ROIs) including 9 dorsal and 10 ventral DMN seed regions encompassing 13,278 voxels (Fig. S3) (40). Functional connectivity analysis was performed using the CONN Toolbox (41). Functional volumes were band-pass-filtered to 0.008–0.09 Hz and CompCor correction method was used to reduce physiological and other noise artifacts (41). ROI-to-ROI temporal correlations based on corrected BOLD signal were computed resulting in a 19×19 correlation matrix, containing normalized z-scores for each individual. Volumetric MRI data were used to measure gray matter volumes (*SI Materials and Methods*). These data were used only to control fMRI data for potential differences in gray matter volume.

MVPA. Using our MVPA Toolbox (21), we performed a multivariate, linear SVM analysis (20) separately for each pair of groups (C+ and C–, C+ and HC, C– and HC). We constructed a class vector comprising either “+1” (C+) or “–1” (C– or HC). Connectivity matrices for each individual were converted to a feature vector containing 171 unique ROI-to-ROI connections

($19 \times 18/2$). A linear regression analysis was performed at every feature to remove the effects of age, education, CAD score, and gray matter volume. The residuals of this regression were then substituted for the feature values.

During the training phase, the SVM uses data that have been previously categorized into groups to determine the hyperplane/classifier that optimally separates the groups (20). This process involves searching for a weight vector that maximizes the margin of separation between the groups by using the data points that are closest to the hyperplane (and therefore the most difficult to classify) as the defining points. These minimally distant data points are known as “support vectors” and the classifier is thus fully specified by this subset of training samples (20) (Fig. S4). The weight of a connection represents how important that connection is for discriminating between groups. It should be noted that these weights do not provide information regarding “increased” or “decreased” connectivity.

The validity of the classifier was tested using leave-one-out cross-validation to avoid overfitting and allow generalization of the models (21). Dimensionality reduction was performed using principal component analysis within the cross-validation loop, resulting in 11 principal components. In each repetition, one subject’s data were left out as a test case and the remaining subjects’ data were used to train the classifier. This procedure was repeated such that each subject was left out once and the accuracy of the model was then estimated as the proportion of correct predictions. This process ensures that the training and test cases are independent and gives an estimate of how the model will generalize to an independent data set. Permutation analysis was then performed for each classifier 2,000 times to empirically determine whether classification accuracies were significantly greater than chance (21). We adjusted the alpha level for the permutation analysis to $P < 0.017$ based on three separate group comparisons. Effect size of the classifier was calculated using area under the ROC.

We also performed control MVPAs using disease stage in the combined BC group. We examined SVM classification accuracy for stage 1 ($n = 28$) vs. 2 ($n = 19$), stage 2 vs. 3 ($n = 10$) and stage 1 ($n = 28$) vs. 2+3 ($n = 29$). These analyses were covaried for age, education, gray matter volume, CAD score, and chemotherapy (1 = chemotherapy, 0 = no chemotherapy).

For visualization purposes and to show the connections that had the highest discriminative contribution, we averaged the weights of each feature (connection) across participants and only showed the connections with an absolute value of average weight greater than 1 SD from the mean weights (across participants and features). Brain maps were created using BrainNet Viewer software (www.nitrc.org/projects/bnv) and circular maps were created using in-house code (<http://nnl.stanford.edu/tools.html>).

Cognitive Status. We administered several standardized cognitive tests including Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale, fourth edition (42), used to derive an estimate of global intelligence, Delis–Kaplan Executive Function System Letter Fluency subtest (43), Neuropsychological Assessment Battery Categories test (44), Hopkins Verbal Learning Test-Revised (45), and Wisconsin Card Sorting test (WCST) (46). We used the perseverative errors outcome of the WCST given that our previous research showing that this score discriminates between C+ and HC (32). All scores were converted to T scores (mean = 50 ± 10) based on each test’s published normative data.

We also administered domain-specific self-report measures including the Behavioral Rating Inventory of Executive Function (47) and the Multifactorial Memory Questionnaire Ability Scale (48). Certain scores were missing for some participants (Table 1). Between-group differences in cognitive testing were evaluated using ANOVA. Fisher’s least significant difference post hoc test was used to conduct pairwise comparisons for analyses with significant, Bonferroni-corrected omnibus F statistics ($P < 0.006$).

Correlations. We computed exploratory, two-tailed Pearson correlations between cognitive test scores and the distance of each subject from the hyperplane that maximally distinguished between the C+ and the respective comparison group. Only the test scores that differed significantly between groups using ANOVA were included in this analysis. We also conducted two-tailed Pearson or Spearman correlations, as appropriate, between the hyperplane distance and time off-therapy, radiation (1 = yes, 0 = no), tamoxifen (1 = yes, 0 = no), menopausal status (1 = postmenopause, 0 = premenopause), and disease stage within each BC group. Only the C+ vs. C– hyperplane was used for these analyses.

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Table 2. Demographic and medical/treatment data shown as mean (SD) unless otherwise specified

Measures	C+ ($n = 30$)	C– ($n = 27$)	HC ($n = 24$)
Age, y	55 (7)	58 (7)	56 (9)
Education, y	17 (3)	17 (2)	17 (3)
Minority status, %	10	11	12
Postmenopausal, %	89 ^{HC}	79	54
Tamoxifen, %	53	56	
Radiation, %	67	63	
Disease stages 1, 2, 3; %	13, 53, 33 ^{C–}	89, 11, 0	
Time off-therapy, y*	4.5 (3.3)	5.5 (3.5)	

^{C–}, significantly different from C– group ($P < 0.0001$); ^{HC}, significantly different from HC group ($P = 0.01$).

*Time off-therapy refers to chemotherapy and/or radiation.

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