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ORIGINAL RESEARCH

Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis

Mi Sook Jung[1] · **Min Zhang**[2] · **Mary K. Askren**[3] · **Marc G. Berman**[4] · **Scott Peltier**[2] · **Daniel F. Hayes**[2] · **Barbara Therrien**[2] · **Patricia A. Reuter-Lorenz**[2] · **Bernadine Cimprich**[2]

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Abstract Neural dysfunction and cognitive complaints are associated with chemotherapy for breast cancer although trajectory and contributory factors remain unclear. We prospectively examined neurocognition using fMRI and self-reported cognitive, physical and psychological symptoms in women treated with adjuvant chemotherapy over one year. Patients treated with (n = 28) or without (n = 34) chemotherapy for localized breast cancer and healthy controls (n = 30) performed a Verbal Working Memory Task (VWMT) during fMRI and provided self-reports at baseline (pre-adjuvant treatment), five- (M5) and 12-months (M12). Repeated measures ANOVA and multivariable regression determined change over time and possible predictors (e.g., hemoglobin, physical symptoms, worry) of VWMT performance, fMRI activity in the frontoparietal executive network, and cognitive complaints at M12. Trajectories of change in VWMT performance for chemotherapy and healthy control groups differed significantly with the chemotherapy group performing worse at M12. Chemotherapy patients had persistently higher spatial variance (neural inefficiency) in executive network fMRI-activation than both other groups from baseline to M12. Cognitive complaints were similar among groups over time. At M12, VWMT performance and executive network spatial variance were each independently predicted by chemotherapy treatment and their respective baseline values, while cognitive complaints were predicted by baseline level, physical symptoms and worry. Executive network inefficiency and neurocognitive performance deficits pre-adjuvant treatment predict cognitive dysfunction one-year post-baseline, particularly in chemotherapy-treated patients. Persistent cognitive complaints are linked with physical symptom severity and worry regardless of treatment. Pre-chemotherapy interventions should target both neurocognitive deficits and symptom burden to improve cognitive outcomes for breast cancer survivors.

Keywords Cognitive disorders · Attention · Short-term memory · Functional magnetic resonance imaging · Symptom assessment

Introduction

Adjuvant chemotherapy reduces breast cancer-related mortality by approximately one-third (Early Breast Cancer Trialists' Collaborative Group et al. 2012). However, adjuvant chemotherapy is associated with considerable toxicities including nausea, alopecia, peripheral neuropathy, and bone marrow suppression. Several studies have suggested that cognitive dysfunction following chemotherapy, referred to in the lay press as "chemobrain," is a serious complication, but the exact mechanism remains unclear (Wefel et al. 2011).

Recent prospective studies using brain imaging techniques and neuropsychological testing have suggested that factors beyond a direct organic effect of chemotherapy contribute to cognitive problems (Ahles et al. 2010; Hermelink et al. 2010;

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✉ Mi Sook Jung
msjung@cnu.ac.kr

[1] College of Nursing Chungnam National University, 266 Munhwa-ro Jung-gu, Daejeon 35015, South Korea

[2] University of Michigan, 500 S State St, Ann Arbor, MI 48109, USA

[3] University of Washington, Seattle, WA, USA

[4] University of Chicago, 5801 S Ellis Ave, Chicago, IL 60637, USA

Janelsins et al. 2014; Reuter-Lorenz and Cimprich 2013). We (Askren et al. 2014; Berman et al. 2014; Cimprich et al. 2010) and others (Ahles et al. 2010; Wefel et al. 2010; Menning et al. 2015) have shown that cognitive problems may be present before adjuvant treatment for newly diagnosed breast cancer patients. In addition, breast cancer treatment factors do not consistently predict test performance *and* cognitive complaints suggesting the possibility of distinct trajectories and differing contributory factors (Hermelink et al. 2010; Janelsins et al. 2014). Pre-treatment cognitive problems may be exacerbated by psychological distress (Berman et al. 2014) and physical symptoms that could potentially compound any cognitive effects of chemotherapy (Askren et al. 2014; Ganz et al. 2011; Menning et al. 2015). While symptoms may be implicated in cognitive dysfunction (Cimprich and Ronis 2001), the contribution of overall symptom burden to chemotherapy-associated cognitive problems is unknown. Increasing understanding of the possible modifiable sources of "chemobrain" is an essential step in determining interventions to achieve optimal cognitive functioning in cancer survivors.

We used blood oxygen level dependent (BOLD) fMRI to examine the brain executive network which underlies performance of tasks requiring attention and working memory. We prospectively assessed self-reported cognitive complaints, and neurocognitive task performance and executive network function during fMRI over a one-year period in breast cancer patients treated with and without adjuvant chemotherapy and healthy controls without breast cancer. Using these measures, we tracked the trajectory of changes in neurocognitive function and self-reported complaints, and examined possible contributory factors including overall symptom burden over time.

Methods

Participants

We recruited 116 right-handed women from the University of Michigan Comprehensive Cancer Center, including two groups of women surgically treated for breast cancer (stage 0 – IIIa) awaiting adjuvant chemotherapy (CT, n = 36) or radiotherapy without chemotherapy (non-CT, n = 41) and age-matched healthy controls (HC, n = 39) with negative mammograms (Fig. 1). Screening criteria included: absence of MRI contraindications, cognitive disorder (Mini-Mental Status Examination) (Folstein et al. 1975), clinical depression (Patient Health Questionnaire, PHQ-8) (Kroenke et al. 2009), and secondary diagnosis of neurological or psychiatric disorders. At baseline, nine were excluded due to inability to tolerate scanning. Another 10 women (CT, n = 2; non-CT, n = 5; HC, n = 3) did not return for post-baseline assessments due to unstable medical conditions or new MRI contraindication. Also five were excluded for the following reasons: two erratic performance 3.5 standard deviations worse than their respective group means (CT, n = 1; HC, n = 1); one technical issue in the imaging session (HC, n = 1); and two extraordinary life stressors (HC, n = 2). Attrition proportions did not differ significantly across the three groups. Ninety-two women (CT, n = 28; non-CT, n = 34; HC, n = 30) were included in the final sample. A subset of data from this sample was previously reported (Askren et al. 2014; Berman et al. 2014; Churchill et al. 2014; Mišić et al. 2014). There were no demographic differences between 24 women who did not complete all assessments and the final sample (all Ps > .10). Participants provided informed written consent approved by the University of Michigan Institutional Review Board Medicine.

Procedures and materials

Design

Participants were prospectively evaluated with neurocognitive measures during fMRI scanning followed by self-report questionnaires at three time points. Baseline (M0) assessment occurred about one month (24–36 days) post-surgery before any planned adjuvant chemotherapy, radiotherapy, or endocrine therapy. The second assessment occurred about five months (M5) following baseline, at least a month post-chemotherapy, and the third approximately one year (M12) post-baseline (Fig. 1).

Self-reported measures

Subjective assessments included cognitive complaints (Attentional Function Index, AFI) (Cimprich et al. 2011), physical symptom severity (Breast Cancer Prevention Trial Symptom Scales, BCPTSS) (Cella et al. 2008) and psychological distress (Three-Item Worry Index, TIWI) (Kelly 2004). Perceived cognitive function (cognitive complaints) was assessed with the Attentional Function Index (AFI). The AFI evaluates cognitive functioning in daily activities that require working memory and executive function like planning, performing tasks and clarity of thinking (Cimprich et al. 2011). This measure was composed of 16 items, each a 10-point Likert scale, with higher scores indicating better cognitive functioning. Cronbach's alpha coefficients for the three assessments were .94 to .95, indicating satisfactory reliability, consistent with estimates from previous studies. The Breast Cancer Prevention Trial Symptoms Scale, a 16-item instrument, assessed physical symptoms associated with cancer treatment, menopause and normal aging (e.g., hot flashes, bladder control, musculoskeletal pain, and vaginal, cognitive and weight problems) on a 0 to 4 scale of symptom severity. Validity and reliability have been established for women with

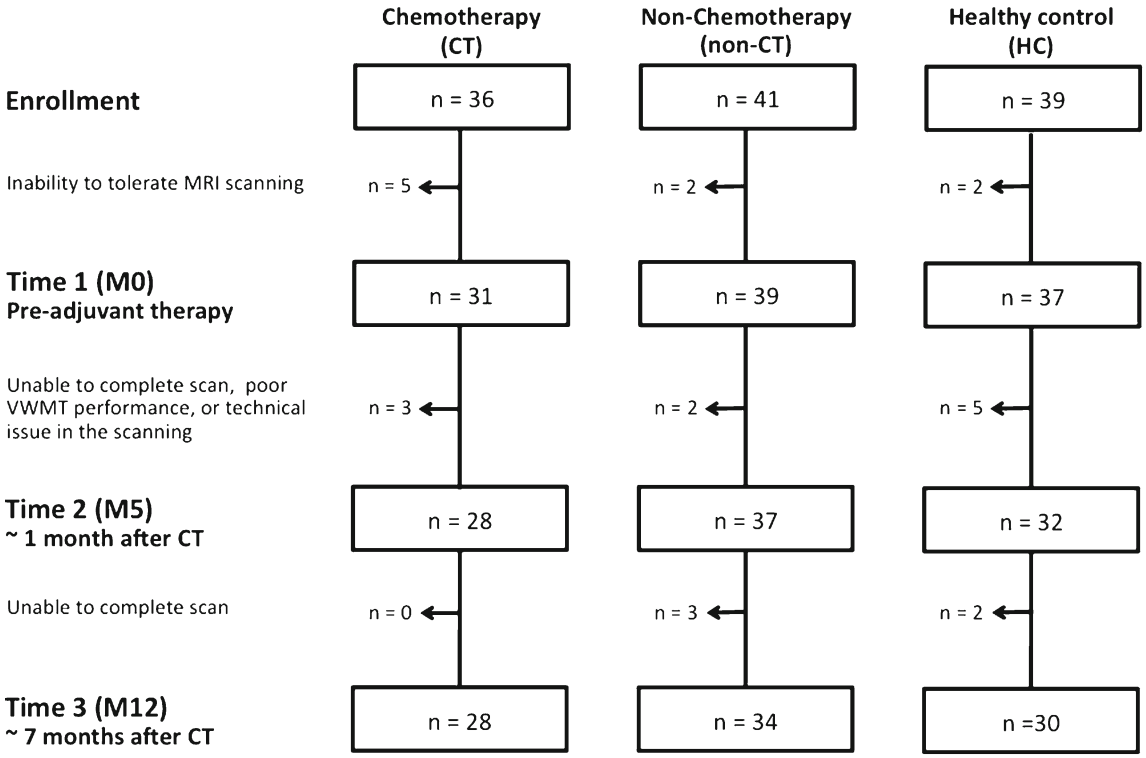

Fig. 1 CONSORT diagram

and without breast cancer with Cronbach's alpha ranging from .75 to .82 across time points in this study (Cella et al. 2008). The Three-Item Worry Index (Kelly 2004) measured trait worry (psychological distress) in women treated for breast cancer and those without history of cancer (Askren et al. 2014; Berman et al. 2014; Lehto and Cimprich 2009). Cronbach's alpha coefficients in this sample were satisfactory (.89–.92).

fMRI task: Verbal working memory task

A previously described Verbal Working Memory Task (VWMT) (Fig. 2) was used to assess objective task performance and neurocognitive indices during fMRI scanning (Askren et al. 2014; Berman et al. 2014; Nelson et al. 2003). During fMRI scanning, participants completed a verbal working memory task, to activate the executive network that supports working memory function. Over 192 trials, participants responded "yes" or "no" by pressing a key to indicate whether a probe letter had appeared in the current four-letter memory set. To avoid response bias, half of the trials required a "yes" response. We analyzed test scores obtained from the "no" response trials that were classified as low, medium, and high working memory demand based on how recently the probe letter had been presented in a previous memory set. An overall VWMT performance deficit score was derived from summed z-scores for error rates and reaction times based on means and standard deviations across groups. Higher scores indicated greater performance deficit.

MRI acquisition parameters

A 3 Tesla GE Signa scanner equipped with a standard quadrature head coil was used to acquire images. T2* weighted timeseries (25 slices, voxel size =3.75 × 3.75 × 5 mm, repetition time (TR) = 1500 ms; echo time (TE) = 30 ms; flip angle =70°; field of view (FOV) = 24 cm) were acquired using a spiral sequence. A T1-weighted gradient-echo anatomical overlay with the same geometry (TR = 225 ms, TE = 5.7 ms, flip angle =90°) and a high-resolution T1-weighted spoiled-gradient-recalled acquisition (SPGR; TR = 9 ms, TE = 1.8 ms, flip angle =15°, FOV = 25–26 cm, slice thickness = 1.2 mm) were also collected for registration.

MRI post-processing

Timeseries were slice-time corrected with SPM8, motion corrected with MCFLIRT (Jenkinson et al. 2002), temporally de-spiked by reducing values that were greater than 3 standard deviations from the mean (Lazar et al. 2001), normalized to MNI space using the overlay and skull-stripped (Smith 2002; Smith et al. 2004), inhomogeneity-corrected SPGR as intermediates, and spatially smoothed with a Gaussian kernel of FWHM = 8 mm. The first principal component of the linear, squared, derivative, and squared derivative of the rigid-body motion parameters generated by MCFLIRT was calculated for use as a nuisance regressor (Lund et al. 2005).

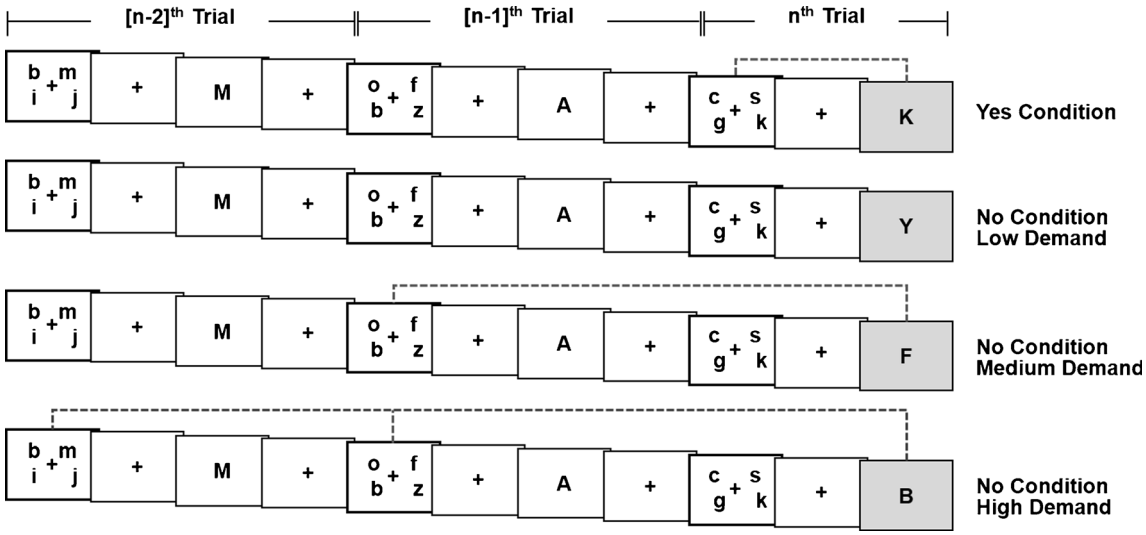

Fig. 2 Diagram of Verbal Working Memory Task by level of demand. In the low demand trial, the final probe letter Y did not appear in the current memory (n^{th}) set as well as two previous ($[n-1]^{th}$, $[n-2]^{th}$) sets. In the medium demand trial, the probe letter F appeared in the preceding ($[n-1]^{th}$) but not in the current set. In the high demand set, the probe B appeared in two previous memory sets but not in the current set. Familiarity with the letter in recent sets generates interference and more difficulty in responding correctly to whether or not it appeared in the current set

Generation of network masks

Functional images were entered into a general linear model in SPM5 in which high, medium, and low-demand probes were modeled as zero-duration events convolved with the hemodynamic response function. Error trials and positive probes were also modeled separately, but not analyzed here. The first principal component of the motion regressors was included as a covariate of no interest. To generate a voxelwise map of the frontoparietal "executive network" of brain regions responsive to working memory demand in this task, high and medium-demand probe activity was contrasted with low demand probe activity separately for each group at each time point, thresholded at $P < .005$ (uncorrected for multiple comparisons) at the voxel-level with a cluster-size threshold of $P < .05$ contiguous voxels. By including all voxels present in any of the group maps at any time point, we generated an executive network mask unbiased to group or time point, which included bilateral inferior and middle frontal gyrus, dorsal anterior cingulate cortex, and bilateral intraparietal sulcus (Fig. 4b).

Calculation of spatial variance

The spatial variance (inconsistency of activation values across all voxels) within the group-defined executive control mask were extracted for each participant's contrast map at each time point for the contrast of high- & medium-demand probes greater than low-demand probes. These values were then submitted to multivariable linear regression models. Spatial variance in activation of the executive network can reflect neural inefficiency with greater sensitivity than mean amplitude (Askren et al. 2014; Berman et al. 2011). Though related concepts, spatial variance is not equivalent to temporal variance (variance in the signal across time in a voxel or group of voxels), which is not reported here. The more traditional mean amplitude measure (the magnitude of the contrast values averaged across all of the voxels within the mask) was also calculated.

Statistical analyses

Demographic and clinical characteristics among groups were compared using Pearson's Chi Square test and analysis of variance (ANOVA). Repeated measures analysis of variance (ANOVA) was implemented to determine patterns of change over time for the three cognitive outcome measures, VMWT performance deficit score, spatial variance in executive network fMRI task-activation, and cognitive complaints (AFI). Additional post-hoc analyses were performed to examine between-group and within-group differences across time points, using t-tests and ANOVAs. Multivariable linear regression models were developed to determine predictors of the three cognitive outcomes at one-year follow-up (M12). During model-building, seven independent variables were selected based on theoretical and statistical considerations (Ahles et al. 2010; Askren et al. 2014; Berman et al. 2014; Cimprich et al. 2005) as potential predictors of cognitive dysfunction: (a) treatment group (chemotherapy, non-chemotherapy, and healthy control) created as dummy variables; (b) pre-treatment measure of the dependent variables, i.e., VWMT performance, spatial variance in executive network activation, and AFI (cognitive complaints); (c) age and (d) years of education as proxy indicators of cognitive reserve; (e) hemoglobin level at M12 as an indicator of cancer

treatment side effects; (f) self-reported worry at M12; and (g) overall physical symptom severity at M12. Mean activation in the executive network was not included as a dependent variable for the regression analysis because the regression model on mean activation in this network did not reach statistical significance ($P \geq .05$).

Results

Sample characteristics

Mean age was 52 years (SD = 9) and groups did not differ by age, race, or menopausal status (Table 1). Healthy controls (HC) were more educated than patients ($P = .006$). The chemotherapy-treated (CT) group had higher stage disease ($P < .001$) and was treated more often with mastectomy ($P < .001$) and lymph node dissection ($P < .001$) than the non-chemotherapy (non-CT) group. Three standard chemotherapeutic regimens were administered in the CT group with 79 % receiving a combination of doxorubicin, cyclophosphamide, and paclitaxel over about a four-month interval. All women in the non-CT group completed radiotherapy and 85 % were receiving anti-estrogen medication (tamoxifen or aromatase inhibitors) at M5 and M12. In the CT group 57 % had started radiotherapy and 29 % were receiving anti-estrogen therapy at M5, coinciding with about one-month post-chemotherapy, whereas 79 % completed radiotherapy and 75 % were receiving anti-estrogen therapy at M12. The CT group had lower hemoglobin at baseline ($P < .001$) and M5 ($P < .001$) than the other groups, but the groups did not differ at M12.

Verbal working memory task performance during fMRI

Repeated measures ANOVA in the three-group model (CT, non-CT, HC) showed no significant group by time interaction for VWMT performance deficit score (Fig. 3a; Table S1; Fig. S1). However, distinctly differing patterns of change were observed among the groups despite similar mean VWMT performance deficit scores at baseline. In particular, the CT group had no change in VWMT deficit score over time, while the HC group showed a significant decline (performance improvement) from baseline to M12 ($P = .001$). Mean scores in the non-CT group were intermediate having improved over time but did not differ significantly from the other two groups at any time point. To confirm pattern differences specifically between the CT and HC groups a post hoc analysis revealed a significant interaction ($P = .039$). These group differences in VWMT performance were clearly evident at M12. Specifically, the overall VWMT score in the CT group was worse than that in the HC group with the CT group performing worse across all levels of task demand (low, $P = .052$; medium, $P = .001$; high, $P = .047$) at M12 than the healthy controls (Fig. 3b, c, d; Table S1). These findings suggest that chemotherapy-treated women experienced cognitive problems even seven months post-chemotherapy.

Spatial variance in executive network activation

Repeated measures ANOVA of spatial variance in task activation in the executive network showed a significant main effect of group ($P = .002$), but no group by time interaction (Fig. 4a; Table S1; Fig. S2). Greater mean spatial variance at baseline was observed in the CT group although group differences were not statistically significant. However, the CT group had greater spatial variance at M12 than HC ($P = .009$) and non-CT groups ($P = .004$). These findings reflect persistent neurocognitive compromise in women treated with chemotherapy. Mean activation within this executive network did not differ across groups and across times ($Ps \geq .30$) (Table S2).

Perceived cognitive dysfunction

No group by time interaction or main effect of group was found in self-reported cognitive complaints, AFI (Fig. 4c; Table S1; Fig. S3). Across groups, there was a significant time effect ($P = .025$) showing a small decline (more complaints) at M5 with return to baseline levels at M12. However, all three groups showed similar scores on perceived cognitive dysfunction at each time point. These findings suggest that changes in self-reported cognitive dysfunction might not be directly associated with breast cancer diagnosis and treatment.

Physical and psychological symptoms

Repeated measures ANOVA showed a significant group by time interaction ($P < .001$) in overall physical symptom severity. Specifically, the CT group had an increase in symptom severity from baseline to M5 ($P < .001$), followed by a small but significant decrease at M12 ($P = .015$). The non-CT group showed a gradual increase in symptom severity from baseline to M12 ($P = .019$), while the change in the HC group was small and not statistically significant (Fig. 4d; Table S1). Repeated measures ANOVA for worry scores revealed a marginal effect of group ($P = .058$). Post-hoc analyses showed greater worry for the CT group than the non-CT ($P = .045$) and the HC groups ($P = .04$) across time points (Fig. 4e; Table S1).

Predicting neurocognitive dysfunction and cognitive complaints

Multivariable regression models were used to determine possible predictors of objectively-assessed

Table 1 Sample characteristics

Characteristics	CT (n = 28)		Non-CT (n = 34)		HC (n = 30)		P[a]
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	
Age (year)		49.68 (9.74)		53.94 (8.42)		51.13 (8.47)	.159
Education (year)		15.09 (2.33)		15.38 (2.07)		16.78 (1.94)	.006
Mini-Mental State Examination (MMSE)[b]		29.46 (0.69)		29.47 (0.79)		29.63 (0.72)	.602
Patient Health Questionnaire (PHQ-8)[b]		3.82 (3.93)		3.62 (3.95)		2.57 (2.88)	.362
Months between baseline and M5		5.07 (1.41)		5.06 (1.07)		5.20 (1.47)	.898
Months between baseline and M12		12.11 (1.85)		11.62 (0.85)		12.33 (1.81)	.169
Race[c]							
White	22 (79)		31 (91)		26 (87)		.362
Non-white	6 (21)		3 (9)		4 (13)		
Stage							
0	0 (0)		11 (32)		–		< .001
I	5 (18)		17 (50)		–		
II	16 (57)		6 (18)		–		
IIIa	7 (25)		0 (0)		–		
Surgery							
Lumpectomy	15 (54)		32 (94)		–		< .001
Mastectomy	13 (46)		2 (6)		–		
Lymph node dissection	16 (57)		2 (6)		–		< .001
Chemotherapy regimen							
Doxorubicin + Cyclophosphamide	1 (4)		–		–		
Doxorubicin + Cyclophosphamide + Paclitaxel	22 (79)		–		–		
Docetaxel + Cyclophosphamide	5 (18)		–		–		
Radiotherapy started							
Before M5	16 (57)		34 (100)		–		< .001
Before M12	22 (79)		34 (100)		–		.006
Endocrine therapy started							
Before M5	8 (29)		29 (85)		–		< .001
Before M12	21 (75)		29 (85)		–		.307
Menstrual status at baseline							
Pre	14 (50)		10 (29)		8 (27)		.219
Peri	2 (7)		5 (15)		7 (23)		
Post	12 (43)		19 (56)		15 (50)		
Hemoglobin (g/dl)							
M0		12.79 (0.83)		13.72 (0.69)		13.18 (0.90)	< .001
M5		12.35 (1.06)		13.37 (0.82)		13.20 (0.85)	< .001
M12		13.07 (0.79)		13.42 (0.74)		13.21 (1.07)	.304

Percentage may not equal 100 because of rounding; Missing hemoglobin values at M0 (CT, n = 1; HC, n = 3), M5 (CT, n = 2; HC, n = 2), and M12 (CT, n = 2; non-CT, n = 1; HC, n = 4)

Abbreviations: *CT*, chemotherapy-treated; *non-CT*, treated without chemotherapy; *HC*, healthy control; *M0*, baseline; *M5*, five-month follow-up; *M12*, twelve-month follow-up

[a] P values are based on one-way ANOVA for continuous variables and chi-square analyses for categorical variables

[b] Screening measures were MMSE for cognitive disorder and PHQ-8 for clinical depression

[c] 86 % Caucasian, 9 % African American, 4 % Asian American, and 1 % American Indian

neurocognitive dysfunction (VWMT performance deficit, spatial variance in executive network activation) and subjective cognitive complaints (AFI) about one year after baseline (Table 2).

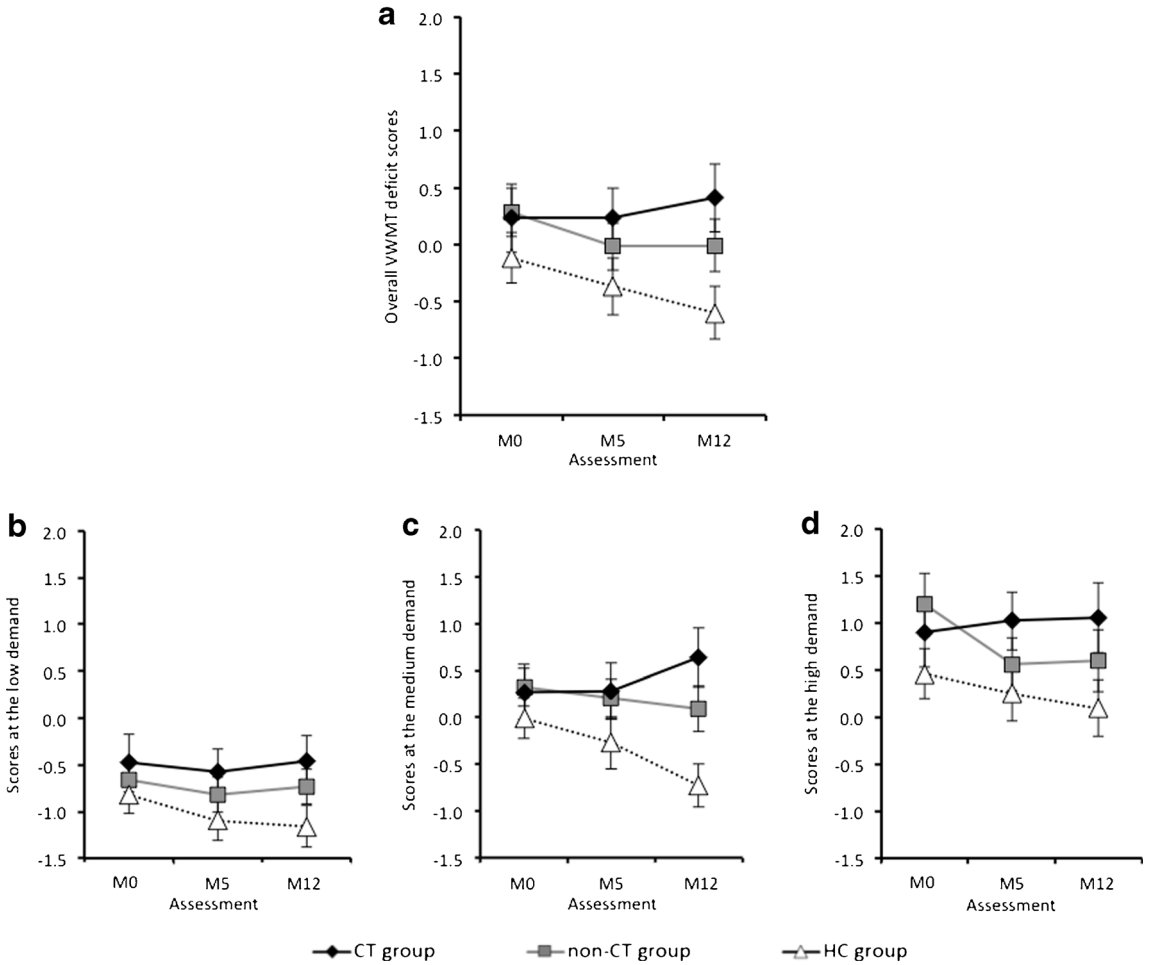

Fig. 3 Changing patterns of VWMT performance deficits by group at baseline, five, and twelve months later. Higher score indicates worse performance. VWMT scores: **a** Overall; **b** Low demand; **c** Medium demand; **d** High demand

Predictors of neurocognitive dysfunction

In the model predicting VWMT performance deficit, being in the CT group rather than HC group (P = .007) and greater baseline performance deficits (P < .001) were significantly associated with worse performance at M12. In the model for fMRI-detected spatial variance in executive network activation, being a member of the CT group rather than the non-CT (P = .002) or HC (P = .003) group and greater spatial variance in the network activation (P = .004) at baseline also predicted greater spatial variance at M12.

Predictors of cognitive complaints

In the model predicting self-reported cognitive complaints, higher levels of cognitive complaints at M12 were significantly associated with greater worry (P = .013) and greater physical symptom severity at M12 (P < .001), as well as greater baseline complaints (P < .001). The predictive effect of symptom severity persisted even after controlling for three cognitive items in the BCPTSS. Although a small but significant correlation (r = .34) was found between worry and physical symptoms, each variable independently accounted for significant variance in the model (Table 2). Together these findings indicate that different risk factors are associated with neurocognitive dysfunction versus subjective cognitive difficulties at M12 (seven months post-chemotherapy).

Discussion

Effective interventions for chemotherapy-associated neurocognitive dysfunction, commonly called ‘chemobrain’, depend on a thorough understanding of its causes, the developmental trajectory, and possible modifiable contributors. In this prospective study of women treated for breast cancer and aged-matched healthy controls we found that the trajectory of fMRI-detected changes in neurocognitive executive network function during VWMT performance from pre-adjuvant treatment to one year post-baseline was worse for women who received chemotherapy compared to those who did not and healthy

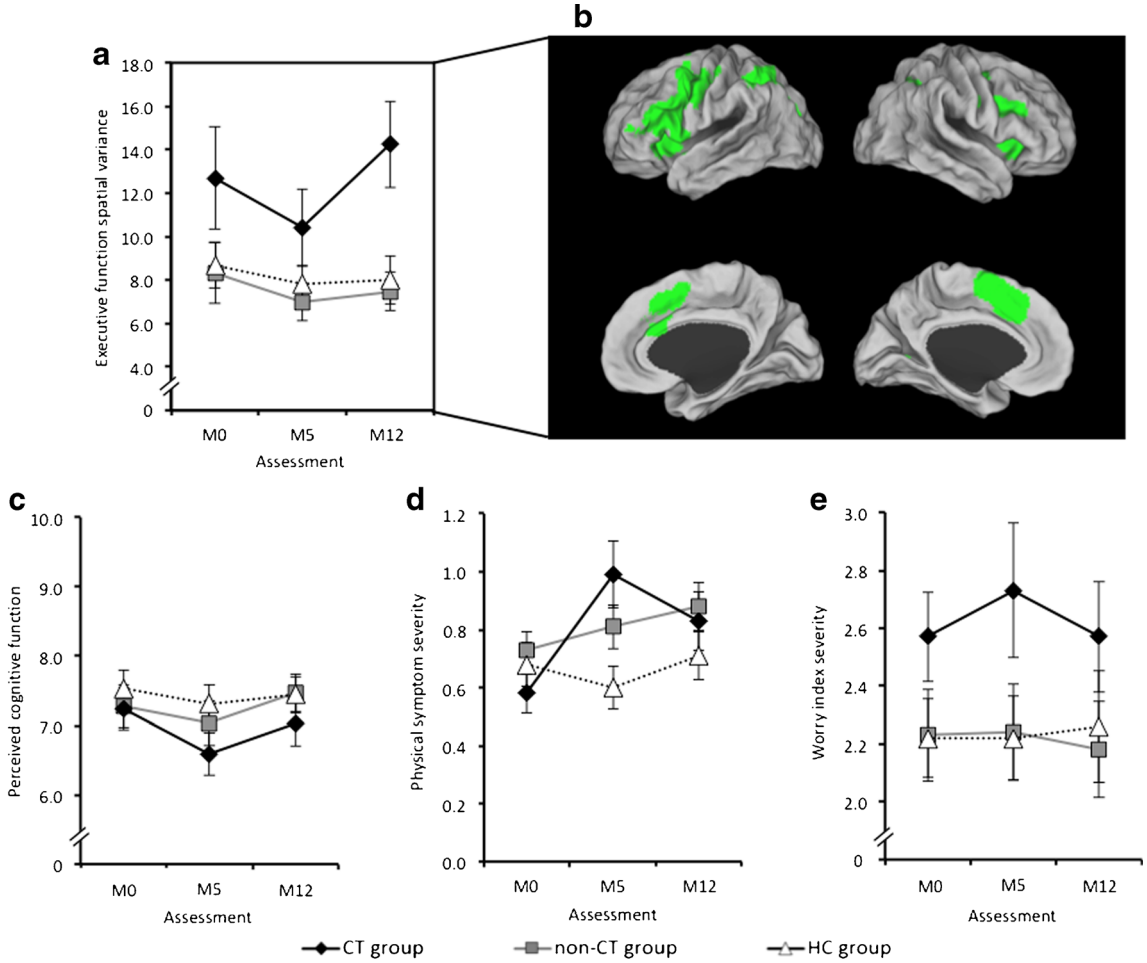

Fig. 4 Patterns of changes in key variables by group over time (M0 = baseline; M5 = five-month follow-up; M12 = twelve-month follow-up). **a** Spatial variance within the executive network which is the brain system responsive to the verbal working memory task used for fMRI analyses, **b** Executive network shown in green which is composed of voxels that were significantly active for any group at any time point, **c** Perceived cognitive dysfunction assessed with AFI (lower scores = more complaints), **d** Physical symptom severity measured with BCPTSS (higher scores = greater severity), and **e** Worry Index severity assessed with TIWI (higher scores = greater severity)

controls. However, we also observed executive network abnormalities before any adjuvant treatment, suggesting that adverse neurocognitive outcomes are not entirely due to chemotherapy treatment. Further we identified that self-reported cognitive complaints at one year post-baseline were associated with worry and physical symptom severity, and not treatment per se.

A measureable difference in neurocognitive indices of executive functioning was found between women treated with chemotherapy and healthy controls over time. Specifically, chemotherapy-treated women showed a persistent deficit in cognitive task performance from baseline to one-year later (seven months post-chemotherapy), while healthy controls displayed continuous improvement over the same period. These findings are consistent with prior studies showing that a subset of women treated with adjuvant chemotherapy (16–60 %) declined in cognitive performance (Shilling et al. 2005; Stewart et al. 2008; Wefel et al. 2010), although a few studies have reported improved cognitive performance over the course of chemotherapy (Fan et al. 2005; Jenkins et al. 2006). Despite heterogeneous neuropsychological tests and statistical models across studies, executive functions are frequently affected following chemotherapy (Jansen et al. 2005). Through targeting executive network function with a theory-based task, our results showed that chemotherapy-treated women did not benefit from repeated testing (practice effect) relative to comparison groups. On average, they had persistent compromise and a widening gap in cognitive performance not observed in the other groups over the one-year follow-up.

Women treated with chemotherapy also showed persistent neural inefficiency as defined by greater fMRI spatial variance in task-related activation of the frontoparietal executive network across time points, compared with non-chemotherapy and healthy control groups. Neuroimaging studies have shown structural and functional changes in frontal and parietal regions before, during, and after chemotherapy (Cimprich et al. 2010; Deprez et al. 2012; McDonald et al. 2012). Our

Table 2 Multivariable regression models predicting objective and subjective cognitive outcomes at M12

Independent Variables	VWMT performance			Spatial variance			Perceived cognitive dysfunction (AFI)		
	Estimate	SE	*P*	Estimate	SE	*P*	Estimate	SE	*P*
CT versus HC	0.79	0.29	.007	6.61	2.06	.002	−0.06	0.29	.827
CT versus non-CT	0.51	0.27	.061	6.12	1.96	.003	−0.34	0.27	.212
HC versus non-CT	−0.28	0.27	.300	−0.49	1.92	.800	−0.28	0.27	.309
Age	0.01	0.01	.433	0.07	0.10	.479	0.01	0.01	.670
Education	0.00	0.05	.974	0.27	0.39	.484	−0.01	0.05	.890
Hemoglobin at M12	−0.03	0.14	.817	−0.68	0.97	.484	0.04	0.14	.750
Worry at M12	−0.01	0.12	.948	−0.63	0.86	.468	−0.32	0.12	.013
Symptom distress at M12	0.04	0.25	.861	0.61	1.75	.728	−1.36	0.26	<.001
Dependent variable at M0	0.77	0.08	<.001	0.25	0.08	.004	0.38	0.08	<.001
F(*P*)	14.05(<.001)			3.51(.002)			17.23(<.001)		
R^2	.58			.26			.63		

Abbreviations: *CT*, chemotherapy-treated; *non-CT*, treated without chemotherapy; *HC*, healthy control; *VWMT*, Verbal Working Memory Task; *AFI*, Attentional Function Index; *M0*, baseline; *M12*, twelve-month follow-up

previous findings demonstrated the usefulness of assessing spatial variance in the task-defined frontoparietal executive network, which appears to be particularly vulnerable in breast cancer (Askren et al. 2014; Cimprich et al. 2010). The current findings also indicate that early changes in spatial variance in task-activation across the frontoparietal executive network, even prior to adjuvant treatment, can serve as an indicator or neuromarker of alterations in attention and working memory function over time. Neural inefficiency prior to chemotherapy may be connected with psychological distress after cancer diagnosis (Berman et al. 2014) and pro-inflammatory immune responses to disease, surgery, or treatment-related symptoms such as fatigue (Askren et al. 2014; Wood and Weymann 2013; Menning et al. 2015).

Although patients treated with and without adjuvant chemotherapy shared similar characteristics of breast cancer diagnosis and surgical treatment, still the pre-chemotherapy group showed greater neural pre-treatment vulnerability in neurocognitive responses that increased over time as compared to the non-chemotherapy patient group. One possible reason is that the anticipation of chemotherapy and related toxic effects, including hair loss, and change in appearance, may be inherently more worrisome and distressing than the prospect of local treatment with radiotherapy. Pre-treatment distress can compound any neurocognitive side effects of chemotherapy resulting in greater neural inefficiency over time. The risk factors affecting pre-treatment neural function need further indepth research to advance prevention of acute and chronic cognitive dysfunction.

The pattern of neurocognitive performance in women not treated with chemotherapy was more similar to that of the healthy control group. At the same time, although mean scores improved and the gap between the CT and non-CT group widened at one year, some women in the non-CT group still experienced persistent cognitive problems with overlapping scores similar to the chemotherapy group. Cognitive problems have not been well studied in women not receiving chemotherapy for breast cancer but these findings suggest further research attention be given to all women treated for breast cancer.

Unlike neurocognitive dysfunction, the one-year trajectory of self-reported cognitive complaints was similar among groups. Although there were no significant differences among groups at any time point, the chemotherapy group did have a small but significant increase in cognitive complaints from baseline to the five-month assessment (one-month post-chemotherapy) without further improvement at one-year. Our results are consistent with evidence suggesting that perceived cognitive problems of attention, memory and executive function do occur in women diagnosed with breast cancer regardless of treatment modality (Myers 2012; Pullens et al. 2010).

Cognitive performance deficits and neural compromise in executive network function at the one year-follow-up were each predicted by the respective cognitive indices assessed *prior to* any adjuvant treatment, as well as by subsequent treatment with chemotherapy. Age, education, hemoglobin, and symptoms did not account for any significant variance in neurocognitive task performance at one year post-baseline. Also, cancer stage was not related to any cognitive outcomes in the patient sample of women with localized early stage disease. In contrast, self-reported cognitive complaints at one year were predicted by co-occurring physical and psychological symptom severity as well as respective baseline levels, regardless of treatment or disease. These findings are consistent with Hermelink et al's proposal that neuropsychological compromise and self-perceived cognitive dysfunction may be

distinct phenomena (Hermelink et al. 2010). Our findings also suggest that these two phenomena may not share common pathogenic mechanisms, and that overall symptom burden is a risk factor for subjective cognitive problems regardless of treatment modality. Physical and psychological symptom burden could be modified by existing evidence-based, targeted interventions such as cognitive-behavioral therapy to treat worry (Covin et al. 2008) and educational intervention for specific symptom management (Given et al. 2008). In addition, executive function training and nature-based interventions may help to improve any co-occurring attention and working memory problems (Cimprich and Ronis 2003; Von Ah et al. 2014).

While considerable research is underway to identify biological mechanisms by which chemotherapy alters neural function (e.g., inflammatory cytokine production, genetic predisposition), research also is needed to explicate the mechanism linking symptom burden and self-reported cognitive problems. One explanation may be that physical and psychological symptoms can increase effort required for even simple tasks, increasing subjective perceptions of dysfunction. Why symptom severity did not predict objective neurocognitive function in this study is not clear. It is possible that the report of symptoms encompasses experience over an extended period of time, while neurocognitive tests sample performance and associated effort on single occasions in highly structured settings (Reuter-Lorenz and Cimprich 2013). It is also possible that the neurocognitive effects of symptom burden may be more apparent in default mode network dysregulation, i.e., neural dysfunction associated with mind-wandering, ruminations, and worry (Reuter-Lorenz and Cimprich 2013). Our previous findings provide some support for this interpretation showing that worry contributed significantly to cognitive dysfunction prior to any adjuvant treatment as it interfered with default mode network deactivation during task performance (Cimprich et al. 2010; Berman et al. 2014).

Strengths of our study included a large sample size relative to other published fMRI studies in breast cancer, a prospective design from pre-adjuvant treatment, two control groups (non-CT and HC) and integration of behavioral, neuroimaging and self-report data. However, sample size was still insufficiently powered to perform further subset analyses, e.g., examining possible differences among women who did or did not receive adjuvant endocrine therapy. Additionally, our study included mostly white, educated women recruited from a comprehensive cancer center, and thus we were unable to address the influence of socioeconomic status, race and ethnicity on cognitive effects of breast cancer treatment.

In conclusion, early compromise of the executive network before any adjuvant treatment can act as a biomarker of risk for longer-term cognitive dysfunction. We found that cognitive performance deficits and neural inefficiency in executive network function generally persisted over succeeding months for patients who received adjuvant chemotherapy compared to those who did not and to healthy controls. Adjuvant chemotherapy was an independent predictive factor in neurocognitive dysfunction of the executive network at one year. In contrast, physical and psychological symptoms, and not breast cancer diagnosis or treatment per se, independently predicted self-reported cognitive complaints. Thus, our findings indicate that multiple factors can influence cognitive outcomes in women treated for breast cancer. These findings support the need for research regarding therapeutic interventions to prevent or reduce neural dysfunction, performance deficits, and subjective cognitive problems. At minimum, approaches are needed: 1) to reduce physical and psychological symptom distress, and 2) to address any co-occurring attention and memory problems, which, left untreated, increase risk for further neurocognitive compromise in women treated for breast cancer.

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Compliance with ethical standards

Conflicts of interest Mi Sook Jung, Min Zhang, Mary K. Askren, Marc G. Berman, Scott Peltier, Daniel F. Hayes, Barbara Therrien, Patricia A. Reuter-Lorenz, and Bernadine Cimprich declare that they have no conflicts of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all participants included in the study.

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