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Pretreatment Worry and Neurocognitive Responses in Women With Breast Cancer

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Objective: Altered cognitive function has been associated with breast cancer treatment, particularly adjuvant chemotherapy, but the underlying neuropsychological mechanisms are not yet understood. Recent research indicates that compromised attention and working memory can exist before adjuvant treatment, implicating psychological distress, such as worry, as a possible contributor to observed alterations in cognitive function. We hypothesized that worry associated with breast cancer diagnosis might influence neurocognitive responses before any adjuvant therapy. ***Design:*** Fifty women, 25 due to receive chemotherapy and 25 due to receive radiation therapy, participated in the study. Women performed a verbal working memory task during functional magnetic resonance imaging scanning to assess neurocognitive responses before any adjuvant treatment and to test the relationship of such responses with self-reports of worry. ***Results:*** Although prechemotherapy participants showed significantly higher levels of worry compared with preradiation participants, higher worry, across both groups, was related to altered brain function. Specifically, increased worry was associated with reduced demand-related deactivation in default-mode regions, such as the precuneus/posterior cingulate. Reduced demand-related deactivation was critically related to worse behavioral performance, which was partially mediated by worry. ***Conclusion:*** Worry appears to be a significant contributor to neurocognitive dysfunction independent of adjuvant treatment for breast cancer. These results suggest that alterations in cognitive function may develop before any chemotherapy treatment and that worry about cancer diagnosis may contribute to reports of "chemo brain" during treatment. Psychological interventions aimed at mitigating worry may help to alleviate cognitive dysfunction associated with life-threatening illness such as breast cancer.

Keywords: worry, default network, working memory, breast cancer, chemotherapy

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When considering breast cancer chemotherapy, people tend to focus on physical distress related to nausea, fatigue, hair loss, and changes in appearance. However, women treated with adjuvant chemotherapy also have reported distressing side effects of altered cognitive functioning, labeled "chemo brain," affecting ability to focus, think clearly, and perform daily tasks. Although reported cognitive deficits vary, a consistent finding is that two basic, functionally connected cognitive processes—selective attention and working memory—may be particularly vulnerable (Tannock, Ahles, Ganz, & van Dam, 2004; Vardy, Wefel, Ahles, Tannock, & Schagen, 2008; Wefel, Vardy, Ahles, & Schagen, 2011). However, the mental toll associated with adjuvant chemotherapy remains difficult to characterize because neither the developmental trajectory nor the fundamental neurocognitive mechanisms are well

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understood (Ahles & Saykin, 2007; Castellon & Ganz, 2009; Wefel et al., 2011).

It is important to note that recent research has shown that neurocognitive deficits can exist even before any adjuvant cancer treatment has begun (Cimprich et al., 2010), adding to the complexity of determining the true sources of diminished cognitive function. In specific, women anticipating adjuvant chemotherapy for breast cancer showed impaired performance on a working memory task during functional magnetic resonance imaging (fMRI) testing compared with healthy women (Cimprich et al., 2010) that could not be attributed to adjuvant treatment. Although various biological factors have been proposed as sources of cognitive impairment in people undergoing cancer treatment, including tumor-related physiological effects and neurotoxic drug side effects (Ahles & Saykin, 2007), it remains unclear why cognitive deficits might occur before any adjuvant chemotherapy.

Although the distressing nature of a cancer diagnosis is generally recognized by health-care providers, its neurocognitive effect has been largely ignored. One factor that may affect cognition is the psychological distress surrounding diagnosis and treatment of cancer. Obtaining a diagnosis of a potentially life-threatening illness such as breast cancer can promote and exaggerate worry (Lampic et al., 1994; Stefanek, Shaw, Degeorge, & Tsottles, 1989), defined as a form of perseverative thinking focused on future events (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). In fact, pretreatment worry has been shown to affect cognition in people diagnosed with cancer by contributing to the formation of negative cognitive representations of illness over the early course of treatment for individuals treated for lung cancer (Lehto & Cimprich, 2009). Heightened worry associated with a cancer diagnosis may produce interfering thoughts that negatively affect cognitive functioning by monopolizing attention and working memory resources. Working memory is critical to proficient cognitive functioning involving the capacity to actively hold and manipulate information "online" for short time intervals (seconds to minutes), which is essential to task performance and higher level cognition (Jonides et al., 2008), including reasoning, decision-making, and problem-solving.

The study presented here examined the potential influence of pretreatment worry on neurocognitive responses during fMRI testing while women with breast cancer completed a working memory task. All participants were women newly diagnosed with breast cancer and due to receive either adjuvant chemotherapy or radiation therapy. Women due to receive radiation therapy were selected as an optimal disease-specific comparison group because both groups received localized breast cancer diagnoses but differed in their treatment plans. We hypothesized that higher levels of pretreatment worry would be associated with alterations in neurocognitive functioning—specifically, impaired working memory performance, and failure to deactivate regions of the default network. The default network represents a set of functionally interconnected brain regions located primarily on the medial wall of each hemisphere (Raichle et al., 2001) that are typically deactivated during attention-demanding tasks. Default network activity and dynamics have been linked to mind wandering and perseverative thinking (Berman, Peltier, et al., 2011; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009). In addition, researchers have found that failures to deactivate regions (or reduce activation) of the default network in response to increased task demand were linked to poorer behavioral performance (Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). Therefore, heightened worry due to a cancer diagnosis could lead to dysregulation of the default network and adversely affect working memory performance.

The study presented here is the first to evaluate whether pretreatment worry contributes to cognitive deficits observed in women before adjuvant treatment. This is an important topic of study because many practitioners and health-care providers attribute cognitive dysfunction in breast cancer solely to the treatment itself, when pretreatment worry may also contribute significantly to neurocognitive dysfunction. Therefore, this study may not only inform the treatment of breast cancer but (also) any serious or life-threatening illness that produces psychological distress.

Method

Participants

Fifty women newly diagnosed with localized (Stage 0 to IIIa) breast cancer were recruited from the University of Michigan Comprehensive Cancer Center, including 25 women in both of the prechemotherapy and preradiation therapy groups. All participants had completed primary surgical treatment, either lumpectomy or mastectomy, with an established treatment plan for adjuvant chemotherapy or radiation therapy. Adjuvant chemotherapy refers to treatment with systemic chemotherapeutic agents that may be given after primary surgical treatment for early-stage breast cancer to reduce the risk of return of the cancer. All participants were prescreened for intact cognitive function (using the Mini Mental Status Examination; Folstein, Folstein, & McHugh, 1975) and absence of clinical depression using the Patient Health Questionnaire (PHQ-8; Kroenke, Spitzer, & Williams, 2001; Kroenke, et al., 2009) on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, text revision* (*DSM–IV–TR*) criteria. All participants were right-handed and met the magnetic resonance imaging (MRI) screening criteria. Women were also excluded if they had locally advanced or metastatic breast cancer (Stage IIIb or higher), secondary diagnosis of a neurological (e.g., stroke, dementia) or psychiatric (e.g., major depression, schizophrenia, substance abuse) disorder, had a debilitating medical condition, or were taking psychoactive medication. All participants provided informed written consent approved by the University of Michigan Institutional Review Board for Medicine. As indicated in Tables 1 and 2, the groups were similar in age and education but differed proportionally in type of primary surgery and postsurgical time interval, mainly because of definitive clinical protocols associated with stage of disease and related treatment criteria.

Table 1
Participant Demographics

Demographic	Prechemotherapy (n = 25) $M \pm SD$ (Range)	Preradiation therapy (n = 25) $M \pm SD$ (Range)
Age	48.76 ± 9.85 (29–66)	52.96 ± 9.18 (30–75)
Years of education	14.72 ± 2.79 (10–22)	15.52 ± 2.00 (12–18)
Time from surgery	24.28 ± 10.83* (10–54)	35.84 ± 19.06 (20–104)

* $p < .05$.

Table 2
Participant Demographics

Demographic	Prechemotherapy (n = 25) Frequency (%)	Preradiation therapy (n = 25) Frequency (%)
Comorbid condition		
Yes[a]	12 (48.0)	13 (52.0)
No	13 (52.0)	12 (48.0)
Type of surgery		
Lumpectomy[b]	13 (52.0)*	23 (92.0)
Mastectomy[c]	12 (48.0)	2 (8.0)
Stage of disease		
0 & I	5 (20.0)	19 (76.0)
II	12 (48.0)	6 (24.0)
IIIa	8 (32.0)	0 (.00)

[a] Including hypothyroidism, hypertension, diabetes, arrhythmia, arthritis, and chronic obstructive pulmonary disease. [b] Including excisional biopsy, simple lumpectomy, and reexcision lumpectomy. [c] Including simple mastectomy and modified radical mastectomy.
* $p < .05$.

Materials and Procedures

Self-reported worry measures. Participants completed two worry measures, the Three-Item Worry Index (TIWI; Kelly, 2004) and a three-item Cancer-Specific Worry instrument (see Supplementary Table S1). The TIWI assesses trait-based (Kelly, 2004) worry and has high concurrent validity because it is reliably correlated with other standard worry measures, such as the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990), the State–Trait Anxiety Inventory (STAI; Spielberger, 1983), and the Worry Domains Questionnaire (WDQ; Tallis, Eysenck, & Mathews, 1992). The Cancer-Specific Worry measure assesses worry related to the life-threat of cancer diagnosis (Lerman, Daly, Masny, & Balshem, 1994). Scores on the general worry and cancer-specific worry measures were strongly correlated and mapped to only one significant factor (accounting for 64% of the variance) in a factor analysis. Thus, all six items were averaged to form a single score for all reported analyses. The internal consistency coefficient of this combined measure was 0.88, indicating satisfactory reliability.

Self-reported cognitive functioning. The Attentional Function Index (Cimprich, Visovatti, & Ronis, 2011) was used to measure subjective perceptions of effectiveness in cognitive functioning in daily life, such as clarity of thinking, performing tasks, and attending to details. Participants were asked to rate themselves on how well they were presently functioning in relation to each item on a scale of 1 (*not at all*) to 10 (*extremely well*). A mean score for overall functioning was used in the analysis. In this sample, the internal consistency was 0.95, indicating satisfactory reliability.

Verbal working memory task. Participants performed a verbal working memory task (VWMT) during fMRI scanning (see Figure 1). The VWMT has been widely used to assess working/short-term memory (STM) performance in healthy younger and older adults (Badre & Wagner, 2005; Jonides et al., 2000; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003). The VWMT was presented using E-Prime (Psychology Software Tools, Inc., http://www.pstnet.com/) and consisted of 192 trials, on which four letters were presented on a screen for 1500 ms. Participants were asked to remember all four letters. After a 3000-ms delay interval, a probe letter was presented for 1500 ms. Participants indicated whether the probe was present in the current memory set. Half of the probes (96 trials) were negative, requiring a "no" response, and half were positive (96 trials), requiring a "yes" response. One fourth (24 trials) of the negative probes were low-demand, meaning that the probe letter had not been presented in at least 3 trials; thus, these probes were unfamiliar and easy to reject. Another one fourth of the negative probes were moderately demanding (i.e., medium-demand) because the probe letter was moderately familiar because it had been present in the previous set. Another one fourth of the negative trials were high-demand because the probe letter had appeared in the previous two memory sets, making the probe letter highly familiar and even more difficult to reject. The final one fourth of negative trials were response conflict trials, but those trials were not included in this analysis because the type of demand was qualitatively different (i.e., the probe did not vary in how many times it was previously presented). Intertrial intervals (ITIs) were jittered and ranged between 1500 and 9000 ms.

fMRI acquisition parameters. Images were acquired on a GE Signa 3 Tesla scanner equipped with a standard quadrature head coil. Functional T2* weighted images were acquired using a spiral sequence with 25 contiguous slices with 3.75 × 3.75 × 5 mm voxels (repetition time [TR] = 1500 ms, echo time [TE] = 30 ms, flip angle = 70°, field of view [FOV] = 24 cm). A T1-weighted gradient echo anatomical overlay was acquired using the same FOV and slices (TR = 225 ms, TE = 5.7 ms, flip angle = 90°). In addition, a 124-slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition (SPGR) in steady-state imaging (TR = 9 ms, TE = 1.8 ms, flip angle = 15°, FOV = 25–26 cm, slice thickness = 1.2 mm).

Each SPGR was corrected for signal in-homogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith, 2002; Smith et al., 2004). These images were then normalized with SPM5 (Wellcome Department of Cognitive Neurology, London, United Kingdom); the normalization parameters for warping to the standard MNI template were recorded and applied to the functional images. Functional images were corrected for differences in slice timing using 4-point sinc-interpolation (Oppenheim, Schafer, & Buck, 1999), corrected for head movement using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), and spatially smoothed with a Gaussian kernel of 8 mm. To reduce noise from spike artifacts, the data were winsorized before normalization (Lazar, Eddy, Genovese, & Welling, 2001) by exploring time courses for each voxel and finding values that were 3 *SD* away from the mean of that voxel's time course. Spikes that were more than 3 *SD* from the mean were made equal to the mean + 3 *SD* and spikes that were 3 *SD* below the mean were made equal to the mean – 3 *SD*.

Behavioral statistical analysis parameters. Analyses were conducted using a general linear mixed model on VWMT accuracy: percentage correct for low, medium, and high negative probe types and correct-trial reaction time (RT). In the model-building process, four independent variables and their interaction terms were considered. The four independent variables were (a) level of demand on the negative VWMT trials (three levels: low, medium, and high) as a categorical within-subjects variable, (b) treatment groups (two levels: prechemotherapy and preradiation) as a between-subjects variable, (c) stage of disease (two levels: 0 & I, II & IIIa grouped for purposes of behavioral analysis) as a

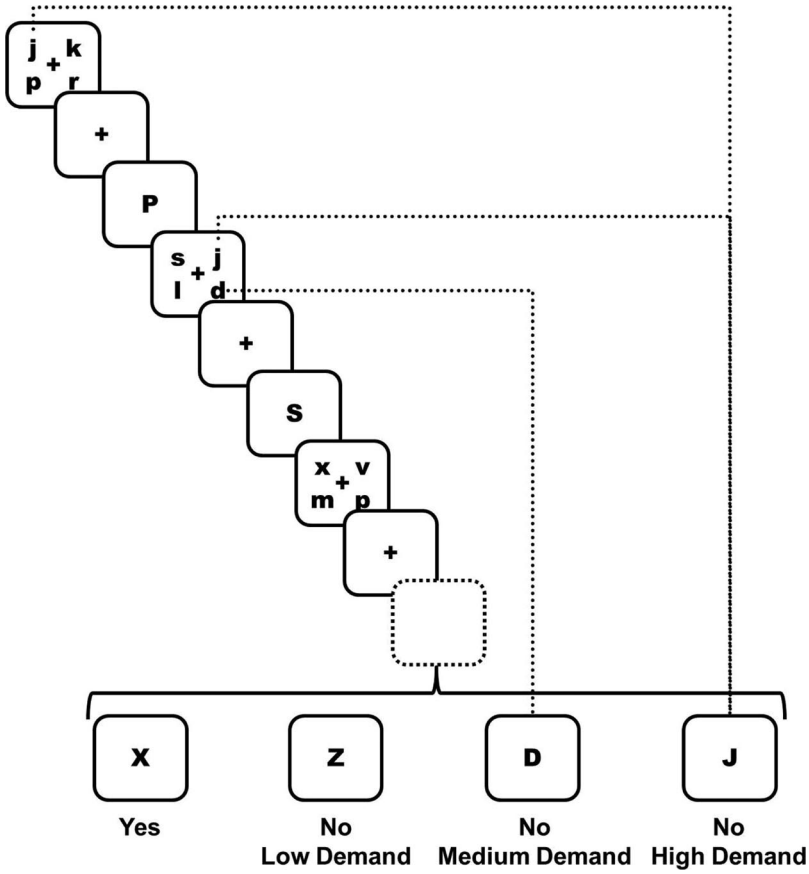

Figure 1. Schematic diagram of the VWMT.

between-subjects variable, and (d) mean reported worry entered as a continuous independent variable. Participants were treated as a random effect in these models. All main effects and significant interactions were included in the final model.

Correlational analyses and regression were implemented to determine the relationship among working memory performance, worry, and brain activation evident with fMRI. Our statistical model specifically tested whether worry was a reliable predictor of working memory performance and brain activity. For these analyses, a single unified performance measure was created by using *Z* scores to combine error rates and RT (Jonides et al., 2000). Combined *Z* scores were created for each condition by summing *Z* scores calculated independently for error rate and RT using the means and standard deviations across all women. Behavioral analyses were conducted using SAS (SAS Institute, 2006).

fMRI statistical analysis parameters. Functional images were entered into a general linear model in SPM5, in which each of the four different probe types—positive, low-demand negative, medium-demand negative, and high-demand negative trials—were modeled. Error trials were modeled separately, but not analyzed. Furthermore, 24 motion parameters were calculated, which included the linear, squared, derivative, and squared derivative of the six rigid-body movement parameters (Lund, Norgaard, Rostrup, Rowe, & Paulson, 2005). A principal component analysis was performed on these 24 motion parameters, and only the first principal component, which accounted for nearly 90% of the motion variance, was included as a covariate in our general linear models.

Whole-brain voxel-wise univariate analyses were performed to identify the brain region activated or deactivated during task performance using a height threshold of $p < .001$ (uncorrected for multiple comparisons) and an extent threshold of 50 contiguous voxels to reduce the probability of type I errors (Forman et al., 1995). Regression analyses were performed within a bilateral precuneus and bilateral posterior cingulate region of interest (ROI) defined based on the Automated Anatomical Labeling Atlas implemented in WFU PickAtlas (Tzourio-Mazoyer et al., 2002). For ROI analyses, a threshold of false discovery rate (FDR) $< .05$, 50 voxels, was used.

Results

Behavioral Results

There was a significant difference in worry between treatment groups, with prechemotherapy participants reporting greater worry than preradiation therapy participants, $t(48) = 3.05$, $p < .01$. It is important to note that self-reported worry was reliably associated with subjective and objective measures of cognitive functioning across both patient groups, suggesting that worry may affect cognitive functioning in women with cancer before any adjuvant chemotherapy or

Table 3
Summary of Behavioral Performance by Group on the VWMT

	Prechemotherapy (n = 25)	Preradiation therapy (n = 25)
	$M \pm SD$	$M \pm SD$
Accuracy of VMT		
Low-demand	.95 ± .09	.98 ± .03
Medium-demand	.92 ± .09	.93 ± .07
High-demand	.89 ± .11	.91 ± .12
Response time of VWMT (ms)		
Low-demand	1,063.88 ± 209.19	1,085.25 ± 155.14
Medium-demand	1,149.26 ± 185.22	1,175.01 ± 171.29
High-demand	1,202.36 ± 182.19	1,228.43 ± 161.71
AFI	7.36 ± 1.49	7.35 ± 1.89
Worry	2.86 ± .77*	2.17 ± .82
Mini Mental State Examination	29.48 ± .71	29.48 ± .71

* $p < .01$.

radiation therapy. Table 3 provides the descriptive behavioral data, and specifics of these analyses are described below.

A general linear mixed model was conducted to assess the effect of level of demand (low, medium, high), treatment group (prechemotherapy, preradiation therapy), worry, and stage of disease (0 & I, II & IIIa) on VWMT accuracy (i.e., % correct) and RT. As expected, demand was reliably associated with accuracy, $F(2, 98) = 9.76$, $p < .001$, and RT, $F(2, 98) = 79.53$, $p < .001$, with worse performance at higher levels of demand. It is important to note that higher worry was reliably associated with lower accuracy, $F(1, 46) = 5.06$, $p < .05$, but it was not significantly related to RT, $F(1, 46) = 2.19$, $p = .15$. Notably, neither treatment group (prechemotherapy or preradiation therapy) nor stage of disease (0 & I, II & IIIa) were related to accuracy or RT in this task: treatment group accuracy, $F(1, 46) = 0.25$, $p = .62$, and RT, $F(1, 46) = 1.00$, $p = .32$; stage of disease accuracy, $F(1, 46) = 0.77$, $p = .38$, and RT, $F(1, 46) = 0.20$, $p = .88$. No significant interactions were found for accuracy or RT (see Supplementary results) because the effects were in the same direction when both groups were analyzed separately. Critically, the significant effect of worry on cognitive performance suggests that worry is more associated with cognitive impairments than either the cancer treatment plan or stage of disease itself.

Self-reported worry was correlated with worse behavioral performance (on a combined Z score of RT and error rate) for all three trial types, attaining significance at high demand ($r = .25$, $p = .08$ for low, $r = .25$, $p = .08$ for medium, $r = .30$ $p < .05$ for high), with higher worry associated with worse cognitive performance (see Figure 2). These relationships were similar when only accuracy data were used, but they were weaker when RT data alone were used, suggesting that much of the effect was carried by accuracy, similar to the results of the general linear model analyses.

Although performance on the VWMT offers an objective and well-characterized measure of cognitive functioning, complaints of chemo brain are often related to self-assessments of performance in daily life. Thus, the relationship of worry to self-reported cognitive functioning in daily life as measured by the Attentional Function Index (AFI) was also assessed. Just as self-reported worry was correlated with performance on the objective VWMT measures, self-reported worry was correlated reliably with AFI scores across all participants, $r = -.57$, $p < .001$ (see Figure 3), suggesting that the more women with breast cancer worry, the more subjective difficulty they experience when performing daily tasks that require concentration. This relationship was significant within both participant groups (preradiation group, $r = -.60$, $p < .001$ and for the prechemotherapy group, $r = -.62$, $p < .001$).

In summary, worry was associated with subjective and objective measures of cognitive performance. This suggests that worry is an important variable for study and may contribute to the cognitive challenges that women with breast cancer face even before beginning adjuvant treatment.

fMRI Results: Effect of Task Demand

The first set of fMRI analyses examined the effect of cognitive demand in the VWMT. Figure 4 displays the neural activation during VWMT performance across both groups. The contrast shown is for high- and medium-demand trials versus low-demand trials. The trials were combined in this way to aggregate trials with memory interference (high- and medium-demand) versus trials that did not have interference (low-demand). Significant activation was found in several regions consistently activated in this task, including the left inferior frontal gyrus (LiFG), the right inferior frontal gyrus (RiFG),

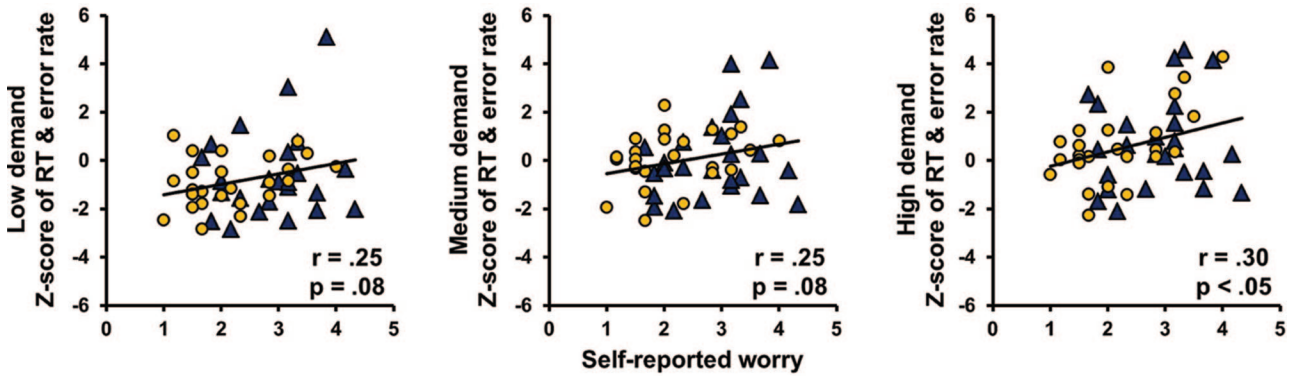

Figure 2. Scatterplot of self-reported worry (x-axis) and Z scores of performance at each level of demand on the VWMT. Prechemotherapy = blue triangles, preradiation therapy = yellow circles.

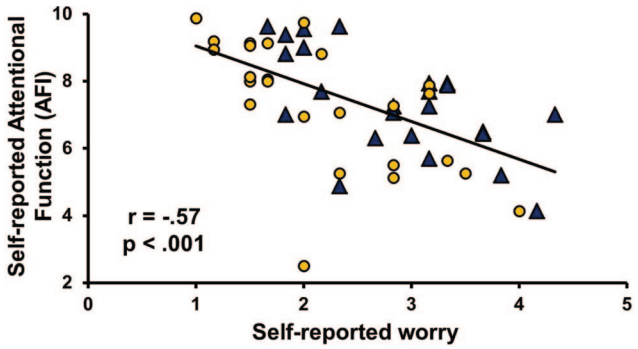

Figure 3. Scatterplot of self-reported worry (*x*-axis) and AFI (*y*-axis) for entire sample ($N = 50$). This relationship also held for the preradiation group, $r = -.60$, $p < .001$, and for the prechemotherapy group, $r = -.62$, $p < .001$. Prechemotherapy = blue triangles, preradiation therapy = yellow circles.

the left and right supplementary motor/anterior cingulate cortex (ACC), and the left inferior parietal lobe (see Supplementary Table S2A; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Nelson et al., 2003). Of note, similar results were observed for the medium-low-demand contrast and the high-low contrast. In addition to these activation effects, deactivation effects were found in areas of the default network (e.g., posterior cingulate/precuenus; see Supplementary Table S2B).

fMRI Results: Worry Associated With Default Network Activity

The behavioral analyses indicated that worry was a significant independent variable in the model predicting performance. Consistent with our hypothesis that worry would be a significant factor in models predicting performance and default network activity, worry was also related to activity in the posterior cingulate/precuneus (see Figure 5). To evaluate this relationship statistically, worry scores were added as a regressor for the high- and medium-low-demand contrast. This regression across the precuneus/posterior cingulate demonstrated a reliable relationship for a large cluster (Montreal Neurological Institute [MNI]: −10, −50, 38; 1662 voxels), with higher worry associated with failure to decrease activation in the precuneus/posterior cingulate as task demands increased.

One could question whether these results are driven by cancer severity and not worry per se. When stage of disease (i.e., cancer severity) was included as a covariate in the worry regression to test that hypothesis, the cluster size was reduced by 37% at the same T threshold ($T = 2.358$), but a large cluster (MNI: 14, −52, 36; 1053 voxels) remained. This suggests that these results are not driven solely by cancer severity.

fMRI Results: Group Differences

To determine whether planned treatment type might influence activation within the posterior cingulate/precuneus, the prechemotherapy and preradiation groups were compared on the high- and medium-low demand contrast. It is interesting to note that there were no significant differences between the two groups for that contrast. This is consistent with the behavioral effects showing that neurocognitive function may be more related to level of worry than to treatment plan.

fMRI Results: Relationship of Behavioral Effects to Activations and Mediation by Worry

To assess whether deficient demand-related modulation of default network regions was associated with compromised task performance, the average of the *Z* scores combining RT and error rate for high- and medium-demand trials was added as a regressor for the high- and medium-low demand activation contrast. Activation in the posterior cingulate/precuneus was found to be correlated with task performance for this contrast such that failure to decrease activation (deactivate) in these regions in response to increased task demand was associated with worse performance (MNI: 0, −58, 14; 202 voxels; MNI: 12, −50, 40; 73 voxels; MNI: −14, −46, 52; 76 voxels).

To test whether worry might mediate the relationship between behavior and deactivation in the precuneus/posterior cingulate, worry was added as a covariate to the ROI analysis relating activation and behavior. With worry scores as a covariate, and holding the T threshold constant ($T = 2.976$), activation within that ROI was reduced by almost 75%, leaving a single smaller cluster (MNI: 0, −58, 16; 89 voxels). This analysis indicates that worry likely contributed to the relationship between activation of the precuneus/posterior cingulate and task performance. Consistent with the behavioral results, including stage of disease as a cova-

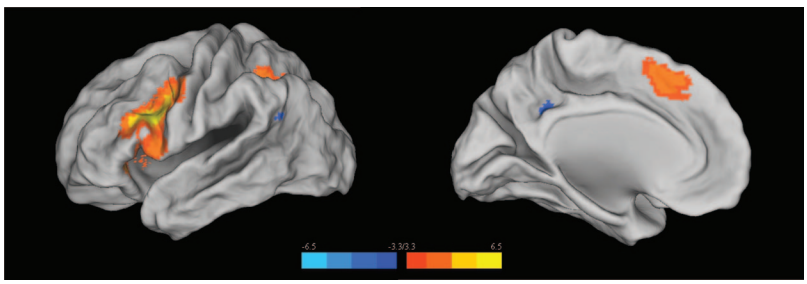

Figure 4. Neural activation for all participants when performing the VWMT. The contrast is for high- and medium-demand–low demand trials. The images are thresholded at $p < .001$ ($T > 3.26$). Blue = deactivation, red/yellow = activation.

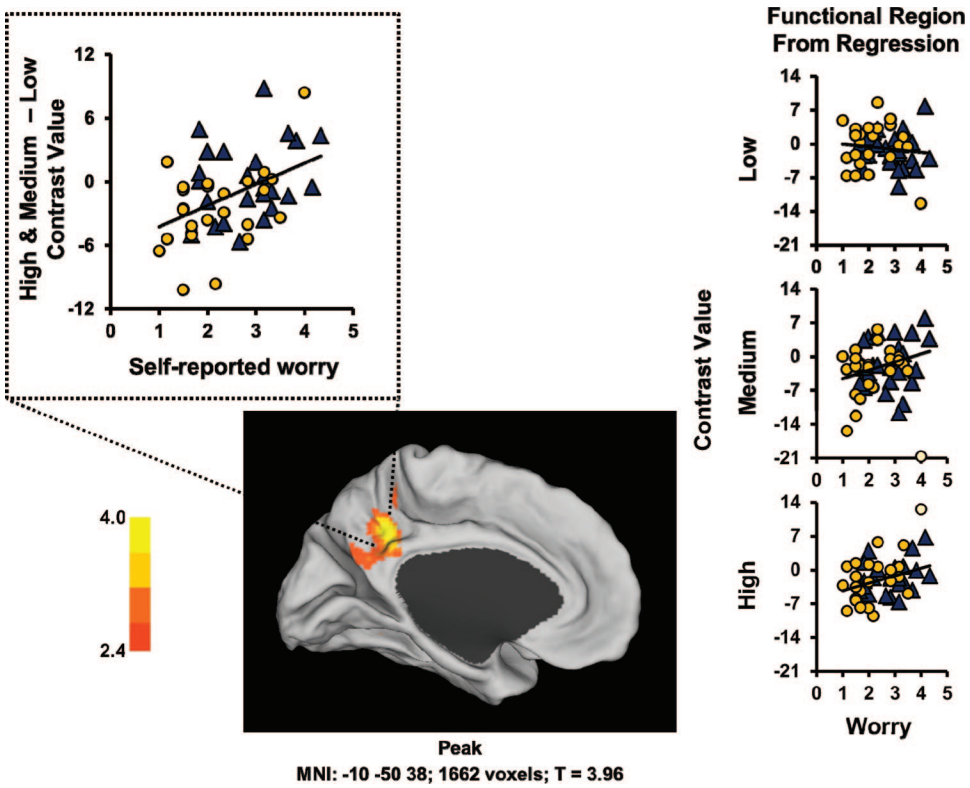

Figure 5. Regression of the contrast of high- and medium-demand–low-demand plotted against worry scores. The correlation in the upper left shows that outliers do not drive the regression and the regression exists for both groups. The correlations at the right are with the functionally defined ROI from the whole-brain regression of the posterior cingulate. No correlation scores are listed because the ROI definition would bias the correlation values. Prechemotherapy = blue triangles, preradiation = yellow circles.

riate, rather than worry, did not reduce the relationship between precuneus/posterior cingulate activation and behavior (MNI: 0, −58, 16; 246 voxels; MNI: 12, −50, 40; 71 voxels; MNI: −14, −46, 52; 73 voxels).

Summary

Increased worry was related to deficient demand-related modulation of the precuneus/posterior cingulate regions of the default network. In addition, failure to deactivate these regions was associated with poorer task performance, an effect that was reduced when worry was added as a covariate. Lastly, cancer severity does not eliminate the association between worry and deactivation of the precuneus/posterior cingulate, nor does it diminish the relationship between performance and deactivation.

Discussion

Cognitive impairments have been found in women newly diagnosed with breast cancer even before treatment begins, suggesting that chemotherapy may not be the sole cause of reported cognitive difficulties (Cimprich et al., 2010). This study was designed to examine whether worry after a cancer diagnosis might contribute to impairments in concentration and working memory in women awaiting adjuvant chemotherapy or radiation therapy for early-stage breast cancer. The results indicated that self-reported worry was significantly associated with objective performance on a test of verbal working memory and perceived cognitive functioning in daily life. These relationships existed even after controlling for treatment group (prechemotherapy vs. preradiation therapy) and stage of disease.

The imaging data indicated that the inability to deactivate regions of the default network, specifically the precuneus/posterior cingulate, in response to higher task demand was correlated with worry; the more women reported worrying, the more they failed to deactivate the precuneus/posterior cingulate in response to increased demand. It is important to note that this relationship existed for both treatment groups and was not explained by stage of cancer disease (i.e., disease severity). Finally, a tight coupling was found between a failure to deactivate default network regions and performance on the cognitive task, suggesting that failure to deactivate is associated with worse behavioral performance. Furthermore, this coupling seemed to be largely a function of worry because including worry as a covariate substantially reduced the relationship between behavioral performance and activation in the precuneus/posterior cingulate.

Other forms of perseverative thinking, such as rumination, have been associated with detrimental thought patterns in people suffering from depression and have been linked to reduced cognitive performance (Berman, Nee, et al., 2011; Berman, Peltier, et al., 2011). Studies have recently found that hyperconnectivity or increased acti-

vation in regions of the default network has been implicated in ruminating (Berman, Peltier, et al., 2011) and off-task thinking/mind-wandering (Christoff et al., 2009). The results presented here indicate that deficient deactivation in regions of the default network when tasks get more demanding may be related to another form of self-referential thinking—namely, worry. Likewise, studies of anxiety have linked worry to compromised behavioral performance, suggesting that worry may be the major factor responsible for impaired performance in multiple contexts (Foa, Franklin, Perry, & Herbert, 1996; Ikeda, Iwanaga, & Seiwa, 1996).

In addition to the effects of worry that characterize the entire sample, this study found a significant group difference in self-reported worry, with women awaiting chemotherapy reporting higher levels of worry than those awaiting radiation therapy. This pretreatment effect is an important clinical finding. It suggests that the anticipation of a systemic chemotherapeutic agent, with possible toxic side effects, may be inherently more worrisome than facing the need for local radiation therapy alone. Women must confront a longer course of treatment with the possibility of distressing side effects (e.g., hair loss, change in appearance) associated with chemotherapy, thereby heightening overall worry. The implications for treatment are especially important because, as shown in the study presented here, worry can significantly compromise cognitive function before any adjuvant treatment, potentially making women more vulnerable to possible cognitive side effects of chemotherapy. Thus, therapeutic interventions to treat worry should be initiated before adjuvant treatment, particularly for women awaiting chemotherapy.

Notably, stage of breast cancer disease (i.e., extent) was not a significant mediator of neural responses nor was it associated with behavioral performance in this sample of women with localized and earlier stage disease. Furthermore, no significant correlation was found between stage of disease and worry. These findings suggest that what may be more important in terms of cognitive response is the extent to which an individual is worrying about her illness, not necessarily its severity. However, this finding warrants further research because the sample was limited to women with early stages of localized and operable disease, and those with higher stages of locally advanced or metastatic breast cancer were not included in this study.

It is also not clear whether worry may continue to influence cognitive performance during and after the course of adjuvant chemotherapy or radiation therapy. In this regard, other researchers did not find that anxiety or depression, often associated with worry, predicted cognitive impairments 1 year after completion of adjuvant chemotherapy (Schagen et al., 1999). Still, there may be differential effects of worry pre- and posttreatment, an issue that also merits further investigation. Likewise, factors such as cumulative fatigue or sleep disturbances might contribute to cognitive impairments over the course of treatment and should be studied.

Overall, these findings implicate worry as an important factor to target for early intervention in women being treated for breast cancer. These results are novel for multiple reasons. First, this is the only study to use functional neuroimaging to specifically examine the potential influence of psychological distress on neurocognitive dysfunction in women with breast cancer before chemotherapy relative to another adjuvant treatment (i.e., radiation therapy), allowing direct comparison of pretreatment effects. These results indicate that symptoms attributed to chemo brain may occur in the absence of treatment, which has important clinical implications. Second, the results of this study link neurocognitive dysfunction with worry and failures to deactivate regions of the default network, and this provides insight into underlying neural mechanisms. Critically, these results highlight the clinical significance of addressing worry in these women with breast cancer. Some treatments, such as cognitive–behavioral therapy, have been effective in treating worry (Covin, Ouimet, Seeds, & Dozois, 2008). In addition, nature-based interventions can be effective in improving cognitive functioning in healthy participants (Berman, Jonides, & Kaplan, 2008; Kaplan & Berman, 2010), in individuals diagnosed with major depression (Berman et al., 2012), and in women treated for breast cancer (Cimprich & Ronis, 2003). Thus, these therapies hold potential for ameliorating worry and optimizing cognitive function in cancer survivors regardless of adjuvant treatment modality. This could also be true for any serious illness that increased psychological distress and worry; that is, these results most likely extend beyond breast cancer.

Although our findings support the hypothesized model in which worry explains the relationship between cancer and brain activation/behavior, we cannot rule out the possibility that brain activation/behavior may mediate the relationship between cancer and worry. However, if the aforementioned interventions that help to reduce worry also are shown to alter brain activity and behavior in breast cancer patients, then we can be more confident that worry is mediating the relationship between cancer and brain activity in behavior. Without experimentally manipulating worry we will not be able to know the true directionality of these effects.

Finally, the findings suggest that complaints of chemo brain may not be solely attributable to chemotherapy. Given the clinical significance of these findings, a broader research agenda is urgently needed to elucidate the potential compounding cognitive effects of psychological distress in women treated for breast cancer.

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Correction to Berman et al. (2013)

In the article "Pretreatment Worry and Neurocognitive Responses in Women With Breast Cancer," by Marc G. Berman, Mary K. Askren, Misook Jung, Barbara Therrien, Scott Peltier, Douglas C. Noll, Min Zhang, Lynn Ossher, Daniel F. Hayes, Patricia A. Reuter-Lorenz, and Bernadine Cimprich (*Health Psychology*, Advance online publication. August 5, 2013. doi: 10.1037/a0033425), the name of author Misook Jung was misspelled as Mi Sook Jung. All versions of this article have been corrected.

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