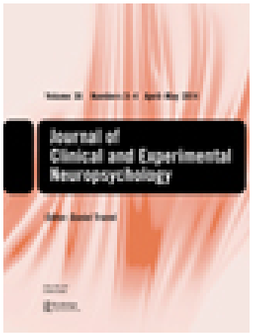

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Prechemotherapy alterations in brain function in women with breast cancer

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Despite clinical reports of cognitive deficits associated with cancer chemotherapy, the underlying brain mechanisms are not clear. This research examined selective attention and working memory using functional magnetic resonance imaging (fMRI) in women before chemotherapy for localized breast cancer. Patients were tested with an established selective attention and working memory task during fMRI. Compared with healthy controls, patients showed (a) bilateral brain activation in high-demand task conditions with recruitment of additional components of attention/working memory circuitry, and (b) less accurate and slower task performance. Results indicate compromised cognitive functioning before any chemotherapy and raise key questions for further research.

Keywords: Breast cancer; Cognitive function; Selective attention; Working memory; Adjuvant chemotherapy; Functional magnetic resonance imaging.

INTRODUCTION

An accumulating body of research provides evidence of cognitive deficits associated with adjuvant chemotherapy for breast cancer (Ahles & Saykin, 2001; Institute of Medicine and National Research Council of the National Academies Committee on Cancer Survivorship, 2006; Phillips & Bernhard, 2003; Rugo & Ahles, 2003; Saykin, Ahles, & McDonald, 2003; Tannock, Ahles, Ganz, & van Dam, 2004) that vary in scope, severity, and incidence (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006). Despite diverse, unexplained cognitive deficits seen across studies, attention and working memory have been implicated as being vulnerable to effects of chemotherapy in certain women (Ahles et al., 2007; Anderson-Hanley et al., 2003; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006). Attention and working memory are prerequisites for effective functioning in higher level cognitive domains including learning, decision making, and problem solving (Mesulam, 2000; Posner, 1995; Posner & Dehaene, 1994; Posner & Snyder, 1975). Further, our previous work (Cimprich, 1992, 1993, 1998, 1999; Cimprich & Ronis, 2001, 2003) and that of others (McAllister et al., 2004; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005) implicates impairment of these basic processes as key sources of cognitive deficits associated with breast cancer diagnosis and treatment. The purpose of this preliminary study was to examine prechemotherapy functional neural brain activation patterns during functional magnetic

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resonance imaging (fMRI) testing of selective attention and working memory in women with breast cancer.

Cognitive impairment has been documented during and following adjuvant chemotherapy for breast cancer. The reported incidence of moderate to severe cognitive impairment in women during chemotherapy for breast cancer has varied widely, but has been estimated at 16% to 48%, compared with 4% to 11% in age- and education-matched controls (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Tchen et al., 2003). The incidence of cognitive problems has been shown to persist and even increase following chemotherapy (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995).

Less is known about possible cognitive deficits in the pretreatment period prior to adjuvant chemotherapy. Previous research, however, has suggested that the basic cognitive processes of selective attention and working memory are vulnerable to fatigue and decline early in the breast cancer illness trajectory prior to any treatment (Cimprich, 1992, 1993, 1998, 1999; Cimprich & Ronis, 2001, 2003). Few studies (Ahles et al., 2007; Hermelink et al., 2007; Hurria et al., 2006; Jenkins et al., 2006; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004), however, have assessed cognitive function prior to adjuvant chemotherapy for breast cancer to determine whether deficits might already be present, and none have focused specifically on possible problems of selective attention and working memory. Further, in existing studies, cognitive impairment has often been characterized in a dichotomous way, which is cognitively impaired or not, based on varying criteria applied to standard neuropsychological tests, obscuring any subtle losses in cognitive function (e.g., Ahles et al., 2007; Jenkins et al., 2006; Wefel et al., 2004). It is important to note that even subtle losses in selective attention and working memory, which might not be detected using standard neuropsychological tests, may present cognitive challenges to an individual dealing with complex treatment decisions and the multiple demands of a life-threatening illness such as breast cancer (Cimprich, 1992, 1993; Cimprich & Ronis, 2003; Kaplan & Kaplan, 1982). Further, such subtle losses in basic cognitive function may be at the source of complaints expressed by many women treated with chemotherapy and labeled "chemo brain" (Wefel, Witgert, & Meyers, 2008).

According to current cognitive neuroscience theory, selective attention is one of several executive processes that are crucial for the integrity of higher order cognitive and social-affective functions (see E. E. Smith & Jonides, 1999, for review). Selective attention is the cognitive ability to focus awareness on some relevant information in the environment while ignoring other information. Selective attention provides inhibitory control for many aspects of cognitive function including working memory, learning, and higher order "executive" functions such as decision making, problem solving, and effective social functioning (Mesulam, 2000; Posner, 1995; Posner & Dehaene, 1994; Posner & Snyder, 1975). A close functional connection between selective attention and working memory is widely recognized, and both systems are integral components of effective cognitive functioning (Baddeley, 1992; Engle, 2002; Lezak, 2004; Mesulam, 2000; Posner, 1995; E. E. Smith & Jonides, 1999). Even simple lapses in selective attention, such as momentary distraction, can interfere with working memory and reduce effectiveness in daily functioning (Kaplan & Kaplan, 1982).

Numerous neuroimaging studies have documented that in healthy adults selective attention and working memory demands activate the anterior executive attention system (Posner, 1995; Posner & Dehaene, 1994)—namely, regions of the prefrontal cortex and the anterior cingulate (Barch, Braver, Sabb, & Noll, 2000; Cohen, Botvinick, & Carter, 2000; Cohen et al., 1997; Corbetta, Miezen, Dobmeyer, Shulman, & Peterson, 1991; D'Esposito et al., 1995; Fiez et al., 1996; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Milham et al., 2001; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003; Reuter-Lorenz, Marshuetz, Jonides, & Smith, 2001; Sakai, Rowe, & Passingham, 2002; Thompson-Schill et al., 2002). For verbal tasks this activation is typically lateralized to left prefrontal regions, although right prefrontal activity has been reported in senior adults and in some patient populations (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006; Reuter-Lorenz & Cappell, 2008). Therefore, in the present pilot work our imaging analyses focus on prefrontal (left and right PFC) and anterior cingulate cortices (ACC).

The specific objectives of the study were to (a) identify regions of brain activation during a selective attention and working memory task in breast cancer patients prior to adjuvant chemotherapy, and (b) compare these activation patterns to those obtained from women without breast cancer. It was hypothesized that diagnosis-related alterations in functional activation would be detectable in the ACC and PFC, particularly during high selective attention demand. It was also expected that such alterations would be evident in behavioral measures of accuracy and response time.

METHOD

Sample

A total of 19 women were assessed with fMRI, including 10 women newly diagnosed with invasive breast cancer whose treatment plan included adjuvant chemotherapy and 9 women without breast cancer who served as healthy controls. Patients were eligible if they were 25 years of age or older and had a clinical diagnosis of primary breast cancer with a treatment plan for adjuvant chemotherapy. Patients were excluded if they had a previous history of cancer or secondary diagnosis of a neurological (e.g., stroke, dementia) or psychiatric (e.g., schizophrenia, depression, substance use) disorder, had a debilitating medical condition, or were taking psychoactive medications. All eligible women were identified while they were being evaluated for newly diagnosed Stage I–III invasive breast cancer in a single multidisciplinary breast cancer clinic at the University of Michigan Comprehensive Cancer Center (UMCCC). The control group consisted of women who had a negative mammogram within the

past year and were recruited from the same screening population of women who were apt to be diagnosed and treated for breast cancer at the UMCCC. The controls had no history of cancer and were screened with the same exclusion criteria as those for the patients. All participants scored greater than 24 on the Mini-Mental State Examination, indicating intact cognitive function (Folstein, Folstein, & McHugh, 1975). All participants also were right-handed (by self-report) and passed the fMRI screening criteria. Patients underwent fMRI testing with the cognitive task prior to the start of chemotherapy, and healthy controls were tested within a year of a negative screening mammogram. All participants provided informed written consent approved by the University of Michigan Institutional Review Board for Medicine.

Functional magnetic resonance imaging procedures

Prescanning procedures

The fMRI safety screening was performed to ensure that there were no contraindications to the scanning procedure. The participant was instructed in the selective attention and working memory task and practiced 10 trials of the computerized test to ensure that she understood how to perform the task before entering the scanner. The participant was instructed (a) that communication would be maintained through an intercom during the scanning procedure, and (b) how to signal the staff if needed. Demographic data were obtained from the participant prior to the scan.

Cognitive testing during fMRI

A modified Verbal Working Memory Task (VMT; Jonides et al., 1998; Nelson et al., 2003; Reuter-Lorenz et al., 2001) was used during fMRI to assess the brain activation related to selective attention and working memory. Like the Stroop test, the modified VMT produces interference and response conflict, but these effects are not subjectively obvious and, therefore, produce less frustration for the research participants. At the start of each VMT trial, a memory set of four lowercase letters is presented in a square pattern around a central fixation cross for 1,500 ms. After a 3,000-ms delay, a 1,500-ms probe is presented that consists of a single uppercase letter. On 50% of the trials, this probe will be a member of the current memory set, and for 50% of the trials, it is a letter that is not in the current memory set. Participants are instructed to respond "yes" with their right index finger using a key pad if the probe matches (positive trial) any of the four letters in the current memory set. If the probe letter does not match (negative trial) the current memory set, the participant is instructed to respond "no" using the right middle finger. The length of the intertrial interval (ITI) varied: 96 ITIs of 1.5 s, 48 ITIs of 3 s, 24 ITIs of 4.5 s, 16 ITIs of 6 s, 4 ITIs of 7.5 s, and 4 ITIs of 9 s. It takes about 30 min to complete 192 trials of the task.

In the low-demand condition, participants must make a "no" response to a probe that has not appeared in the previous two trials (not familiar). In the more demanding conditions, the negative probe appears in the preceding one (familiar) or two (highly familiar) trials, increasing the tendency to respond positively. The behavioral measures were accuracy and response time (measured from probe onset until the key press). There were 96 positive trials requiring "yes" responses and 96 negative trials requiring "no" responses. Half of the negative probes were low demand, and the other half comprised the two high-demand test conditions.

The VMT was presented visually with MRI-compatible goggles (Resonance Technologies, Inc.) using E-Prime (Beta 5.0 version) software (Psychology Software Tools, Inc.) and the IFIS 9.0 system (MRI Devices Corp.). A finger pad unit was used for response collection. Head movement was minimized using standard procedures involving instruction on the importance of remaining still, foam padding, and a light restraint band across the participants' foreheads that gives them tactile feedback on their head position.

Image acquisition

Images were acquired using a 3T MRI scanner (General Electric) equipped with the standard quadrature headcoil. Functional T2* blood-oxygenation-level-dependent (BOLD) images were acquired using a reverse spiral sequence with 30 contiguous axial 4-mm slices (time to repetition, TR = 1,500 ms; echo time, TE = 25 ms; flip angle = 70 degrees; field of view, FOV = 24 cm). A T1-weighted gradient echo (GRE) anatomical image also was acquired using the same FOV and slices as the functional scans (TR = 250 ms, TE = 3.6 ms, flip angle = 90 degrees). In addition, a 60-slice, high-resolution set of anatomical images was acquired using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (TR = 36 ms, TE = 6 ms, flip angle = 35 degrees, FOV = 24 cm, 2.5-mm slice thickness). The T1 images were acquired at the start of the scanning session, and the SPGR images were acquired at the end of the scanning session.

Neuroimaging and statistical analyses

Except as indicated, image analysis was done using SPM5 (Wellcome Department of Cognitive Neurology, London). Functional images were corrected for slice time differences using a local sinc interpolation program (Oppenheim, Schafer, & Buck, 1999). SPGR images were corrected for signal inhomogeneity and were coregistered to the T1 images. The skull was removed from the SPGR images using the BET (brain extraction tool) from FSL (S. M. Smith, 2002); then the images were normalized to the T1 template in the Montreal Neurological Institute (MNI) space. Next, the same normalization patterns were applied to the functional images. After spatial normalization, functional images were smoothed with an 8-mm full width at half maximum Gaussian filter. All images were high-pass filtered and scaled to a global mean intensity of 100.

Event-onset times for the probes of the trial types including positive probe and three kinds of negative probe types—not familiar, familiar, and highly familiar—were

convolved with the canonical hemodynamic response function to predict probe-related activity in the brain. Statistical parametric maps (SPMs) were generated using *t* statistics to identify regions activated according to the model. The image analyses used conventionally acceptable thresholds to examine predefined regions of interest (ROIs). The areas used as ROIs were derived from published research with healthy adults using a similar working memory task during brain imaging (Jonides, Marshuetz, Smith, Reuter-Lorenz, & Koeppe, 2000; Milham et al., 2001; Nelson et al., 2003). These studies have shown activation of specific frontal brain regions involving the inferior frontal gyrus in the prefrontal cortex during the working memory task. Specifically, we focused on ROIs derived from Jonides et al. (2000) for the left prefrontal cortex sites (Talairach coordinates: $x = -51$, $y = 21$, $z = 11$, radius of ROI = 10 mm; Brodmann's area, BA, 45), and the homologue in the right frontal area (Talairach coordinates: $x = +51$, $y = 21$, $z = 11$, radius of ROI = 10 mm; BA 45). The anterior cingulate cortex (ACC) site was derived from Milham et al. (2001; the union of two relevant sites in BA 32: $x = 8$, $y = 20$, $z = 42$; also $x = 0$, $y = 10$, $z = 44$, radius of ROI = 10 mm). Each of the above predefined ROIs was examined as a single contiguous unit. Group comparisons of activation levels in the ROIs were made using a *t* test for independent samples and a standard statistical threshold of $p < .05$. Additionally, an exploratory whole-brain analysis was performed using a statistical threshold of $p < .01$, uncorrected for multiple comparisons, extent threshold 10 voxels, to identify other possible alterations in brain function in response to the working memory task.

Statistical data analyses

Mixed-effects analysis of variance (ANOVA) modeling (SAS Version 9.2) was used to examine patient and control group differences in the negative-probe VMT trials in (a) response time and accuracy and (b) brain activation levels in the predefined ROIs—namely, the left and right inferior frontal gyrus (IFG) in the prefrontal cortex and the anterior cingulate cortex (ACC) in the medial frontal cortex. In the mixed-effects ANOVA, the correlations between ROIs for a given trial, and between trials for a given patient, are explicitly estimated and incorporated into subsequent statistical tests. Linear contrasts were used to compare activation of different ROIs during a given trial, activation of a given ROI between trials, and the accuracy and response time across different trial types. These differences were further compared again using linear contrasts between patients and controls. In all analyses, the familiar (medium-demand) and highly familiar (high-demand) conditions were contrasted with the not-familiar (low-demand) condition. The rationale for using the not-familiar negative-probe condition as the control was that the contrasts would then reflect differing levels of selection demand (low vs. medium and high) and interference resolution. The significance level for mixed-effects ANOVA comparisons was set at $p < .05$. Brain activation values were weighted by the inverse of the within-ROI variance, so that ROIs with internally consistent activations were weighted higher than ROIs with heterogeneous activation.

RESULTS

The patient group was younger (mean age = 45 ± 8 years) than the control group (mean age = 52 ± 10 years), but not significantly so (see Table 1). While both groups were relatively well educated (mean years = 17), the patient group had fewer years of education than the control group. The majority ($n = 6$) of the patients were diagnosed with Stage II breast cancer; of the remaining patients, 3 were Stage I, and 2 were Stage III. All patients had completed a surgical procedure prior to testing, with most ($n = 8$) having had breast conservation/excisional biopsy; 2 women underwent modified radical mastectomy. All patients were tested prior to any chemotherapy with an average time interval between surgical procedure and testing of 25 days ($SD = 10$; range: 4–42 days). The time interval between surgical procedure and testing varied of necessity based on patients' decision making for adjuvant chemotherapy and recovery time post surgery. The patient with the shortest postsurgical interval of 4 days before testing had an outpatient excisional biopsy under local anesthesia with little interference in function.

TABLE 1
Demographic characteristics

	Total (N = 19)			*Patients (n = 10)*			*Controls (n = 9)*		
	n (%)	*Mean years ± SD*	*Min/max*	*n (%)*	*Mean years ± SD*	*Min/max*	*n (%)*	*Mean years ± SD*	*Min/max*
Age		49 ± 9	30/64		45 ± 8	30/61		52 ± 10	31/64
Education		17 ± 3	12/20		15 ± 2	12/19		18 ± 2*	14/20
Race									
Caucasian	17 (89)			10 (100)			7 (88)		
Other[a]	2 (11)			0 (0)			2 (22)		
MMSE[b]			29/30			29/30			29/30

[a]Asian, African-American. [b]Mini-Mental State Examination.
*$p < .05$.

Group comparisons in behavioral performance

The response time and accuracy of the VMT for patients and controls are presented in Table 2 in low- (not-familiar), medium- (familiar), and high-demand (highly familiar) conditions. Patients had consistently higher (slower) mean response times over the three conditions than did controls, but the group mean differences (highly familiar and familiar contrasted with not familiar) were not statistically significant. However, patients had lower mean accuracy in the medium- and high-demand conditions than did the controls, and the group differences were statistically significant in the high-demand (highly familiar vs. not-familiar) condition (estimated mean difference = –.10, *SEM* = .04, $t = -2.56$, $p = .015$).

Group comparisons in brain activation patterns

Regions of interest analysis

Figure 1 illustrates group differences in ROI comparisons. In the predefined ROI of the left IFG in the prefrontal cortex, a significant group difference in brain activation levels was observed in the not-familiar versus familiar (medium-demand) condition (estimated mean difference = 0.03173, *SEM* = 0.01479, $t = 2.15$, $p = .03$), with patients showing a larger difference in activation than the controls. There was no significant group difference in the highly familiar versus not-familiar condition, with patients and controls showing similar differences in levels of activation in the left IFG. This finding of increased activation in the left IFG in both controls and patients in the highly familiar contrast is consistent with the greater selection demand reflected in this condition (Nelson et al., 2003). In contrast, in the predefined ROI of the right IFG, significant differences between groups were observed in the familiar (medium-demand; estimated mean difference = 0.04229; *SEM* = 0.01387, $t = 3.05$, $p = .0026$) and the highly familiar (high-demand; estimated mean difference = 0.03584, *SEM* = 0.01450, $p = .014$) conditions versus the not-familiar condition, with patients showing larger differences in activation in the right IFG in the medium- and high-demand conditions. In the predefined ROI within the ACC, no significant differences in brain activation levels were found in the comparisons between patient and control groups on the familiar (medium-demand) and highly familiar (high-demand) versus not-familiar (low-demand) conditions.

Exploratory whole-brain analysis

A whole-brain analysis was done for the purpose of hypothesis generation for future research, comparing the familiar and highly familiar versus not-familiar conditions.

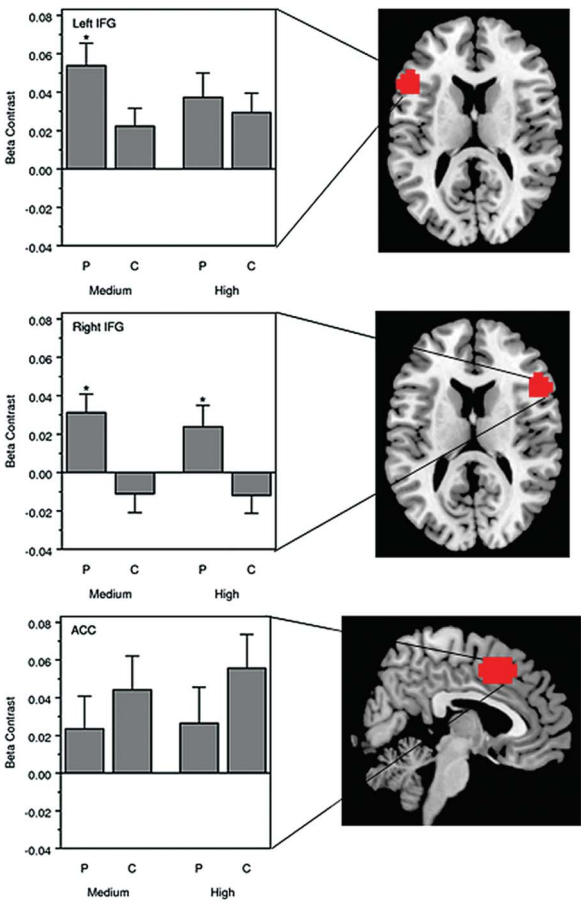

Figure 1. Mean beta contrast (+*SEM*) in brain activation regions of interest for patients (P) and controls (C). IFG = inferior frontal gyrus. ACC = anterior cingulate cortex. Medium: familiar minus not familiar. High: highly familiar minus not familiar. * $p < .05$, patients > controls. To view a color version of this figure, please see the online issue of the Journal.

TABLE 2
Response time and accuracy for controls and patients

	Response time (ms)				*Accuracy*			
	Controls (n = 9)		*Patients (n = 10)*		*Controls (n = 9)*		*Patients (n = 10)*	
Conditions	*Mean ± SD*	*Min/max*	*Mean ± SD*	*Min/max*	*Mean ± SD*	*Min/max*	*Mean ± SD*	*Min/max*
Not familiar	962.5 ± 70.098	841.1/1,068.9	1,048.1 ± 192.4	820.8/1,421.3	.966 ± .035	.917/1	.983 ± .029	.917/1
Familiar	999.0 ± 90.07	824.6/1,107.0	1,097.6 ± 187.6	776.5/1,377.4	.921 ± .049	.833/.958	.876 ± .094	.722/.958
Highly familiar	1,024.1 ± 105.0	809.8/1,194.1	1,118.8 ± 172.2	828.9/1,426.7	.972 ± .036	.917/1	.887 ± .121*	.667/1

*Controls > patients, $p < .05$.

TABLE 3
Whole-brain activation in high-demand conditions in patients and controls

Brain region		*Controls*	*Patients*
Left IFG	BA 44, 45	+	+
	BA 46, 47		+
Right IFG	BA 46		+
Right LIF	BA 10, insula		+
ACC	BA 6, 24, 32	+	
Left parietal	BA 7		+
Right parietal	BA 7, 40		+

Note. + = areas of activation; BA = Brodmann area; IFG = inferior frontal gyrus; LIF = lateral inferior frontal area; ACC = anterior cingulate cortex.
Statistical threshold is $p < .01$, uncorrected for multiple comparisons, extent threshold 10 voxels.

Table 3 illustrates the brain activation patterns for controls and patients. Specifically, the control group showed activation in the left IFG and the ACC, regions that are typically activated for this task. In contrast, in the patient group, additional components of the attention/working memory circuitry in both hemispheres were activated while performing the more demanding task.

DISCUSSION

Women awaiting chemotherapy for breast cancer may have reduced efficiency in attention and working memory brain systems prior to treatment with adjuvant chemotherapy. The findings of this preliminary study indicate compromised cognitive function in behavioral responses and brain activation patterns during performance of a demanding task requiring attention and working memory in women prior to adjuvant chemotherapy for breast cancer compared to women without breast cancer. Specifically, the breast cancer group showed significantly less accuracy in the high-demand condition of the verbal working memory task than did the cancer-free controls. Importantly, differences in brain activation patterns occurred in predefined ROIs in the prefrontal cortex in the higher demand task conditions between patients and participants in the control group. Furthermore, in the breast cancer group, additional components of the attention/working memory circuitry in both brain hemispheres were activated during the more demanding task. Overall, the findings demonstrate significantly decreased accuracy in performance, a tendency to slower responses, and greater vulnerability in functioning of the attention and working memory brain systems in middle-aged women with breast cancer prior to any adjuvant chemotherapy.

Similar functional differences in attention and working memory have been demonstrated in neuroimaging studies of healthy adults related to aging (Jonides et al., 2000; Reuter-Lorenz, 2002; Reuter-Lorenz et al., 2000, 2001). Specifically, using positron emission tomography (PET), Reuter-Lorenz and colleagues (2000, 2001) showed striking age differences in the patterns of brain activation in PFC during working memory tasks. Behaviorally, the older adults (65–75 years) showed significantly slower response times and less accuracy in the task than did younger adults, indicating that the tasks were more demanding for the older participants. Weaker activation in the left PFC and unexpected activation in the right PFC suggest that recruitment of additional sites of brain activation may compensate for the reduced effectiveness in brain functioning. Interestingly, brain activation patterns of the middle-aged breast cancer patients in this study were similar to those of the older (65–75 years) healthy individuals as reported by Reuter-Lorenz and colleagues (2001), suggesting reduced effectiveness in brain functioning prior to any chemotherapy.

A recent study of possible effects of chemotherapy in monozygotic twins by Ferguson and colleagues (Ferguson, McDonald, Saykin, & Ahles, 2007) reported a similar pattern on fMRI of recruitment of additional sites of brain activation in response to a demanding task in the twin with breast cancer 22 months following chemotherapy, compared to her unaffected sibling. In that clinical report, the twin with breast cancer also reported substantially more cognitive complaints than her unaffected sibling, although both scored within normal ranges on neuropsychological tests.

Taken together, these findings raise questions about the independent impact of chemotherapy alone on cognitive function in women treated for breast cancer. While multiple physiological toxic effects of chemotherapy on brain function have been proposed (Ahles et al., 2007; Barton & Loprinzi, 2002; Ferguson et al., 2007; Saykin et al., 2003) and require further investigation, none of these would adequately explain the prechemotherapy findings of reduced efficiency of attention and working memory. Given the known detrimental effects of fatigue on attention and working memory (Cimprich, 1992, 1993, 1998, 1999; Cimprich & Ronis, 2001, 2003) in women newly diagnosed with breast cancer, the possible compounding effect of fatigue and potential sleep loss on cognitive problems associated with adjuvant chemotherapy needs to be considered.

This study demonstrated congruence between performance on behavioral measures and brain activation patterns by indicating that poorer performance was associated with more regions of brain activation in the breast cancer group. In particular, more difficulty in performing the demanding cognitive task was associated with altered recruitment of brain regions known to mediate selective attentional control and working memory.

The interpretation of these findings is limited by the size and nature of the sample and other questions that were not addressed in this preliminary study. First, in this small convenience sample it is not possible to determine the generalizability of the findings. Also, the patient group tended to be younger and less educated than the noncancer controls. However, we examined this issue with an analysis of covariance of the behavioral and imaging data controlling for age and education. Although the analysis of covariance showed no significant influence of age and education on the findings, it is possible that this sample of middle-aged and relatively well-educated women lacked sufficient diversity to detect such possible

effects. Although potential participants were screened and excluded from the study for clinical depression or history of major psychiatric disorder, the possible influence of depressive symptoms on cognitive performance still needs to be controlled in future work. Finally, the possible differential effects of other factors, such as extent of primary surgery for breast cancer and fatigue, on brain function need further examination.

Despite the above limitations, the findings of this study indicate that use of fMRI can provide considerable sensitivity in detecting linkages between alterations in behavioral performance and correlates of brain functioning. The study provides preliminary evidence that basic cognitive processes of attention and working memory may be compromised prior to any chemotherapy in women treated for breast cancer. The findings raise a number of questions for further research with larger, diverse samples of women treated for breast cancer, including the following: (a) whether brain alterations in attention and working memory prior to adjuvant chemotherapy are exacerbated (more pronounced) during and following chemotherapy; and (b) whether such alterations can be linked to subjective complaints of cognitive deficits in women treated for breast cancer.

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