Prefrontal Cortex and Executive Function Impairments in Primary Breast Cancer

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**Objectives:** To examine differences in prefrontal-executive function between breast cancer (BC) survivors with and without a history of chemotherapy treatment compared with healthy control women and to determine the associations between prefrontal cortex deficits and behavioral impairments, as well as certain demographic and disease variables.

**Design:** Observational study.

**Setting:** University-based research facility.

**Participants:** Twenty-five women with BC who had received chemotherapy, 19 women with BC who had not received chemotherapy, and 18 healthy female controls, all matched for age and other demographic variables.

**Results:** Women with BC demonstrated significantly reduced activation in the left middle dorsolateral prefrontal cortex and premotor cortex compared with healthy controls. The chemotherapy group also demonstrated significantly reduced left caudal lateral prefrontal cortex activation and increased perseverative errors and reduced processing speed compared with the other 2 groups. Reduced left caudal lateral prefrontal cortex activation was significantly correlated with higher disease severity and elevated subjective executive dysfunction in the chemotherapy-treated women. Older age and lower educational level were associated with increased executive function impairment in the chemotherapy group.

**Conclusions:** These findings provide further evidence of neurological impairment associated with primary BC irrespective of treatment history. The left caudal lateral prefrontal region may be particularly vulnerable to the effects of chemotherapy and/or disease severity and may represent a novel biomarker of subjective executive dysfunction in chemotherapy-treated women. Furthermore, negative effects of chemotherapy on brain function may be exacerbated by such factors as increased age and lower educational level.

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**Breast Cancer (BC) is one of the most common public health problems, with a worldwide estimated incidence of 39 per 100,000 individuals annually.** Although primary BC has not been associated historically with neurological problems, a growing body of evidence suggests that patients are at increased risk for altered brain structure and function. Neurobiological abnormalities may be associated with neurocognitive impairments. These impairments significantly extend disease-related disability, affecting home, educational, and occupational activities. The high prevalence of BC and increasing survival rates contribute to a large and increasing cohort of neurologically affected individuals.

The specific causes of these brain injuries remain unclear because investigations of neurological status in BC survivors have been limited. Abnormal brain function and structure have been associated with chemotherapy treatment, suggesting neurotoxic brain injury, but also have been demonstrated before adjuvant chemotherapy treatment, suggesting a complex interaction of risk factors.

The goal of this investigation was to determine whether profiles of brain activation differ among BC survivors treated with or without chemotherapy compared with healthy control women. This study used a measure of prefrontal-executive function, given that this is the most commonly reported neurocognitive abnormality in BC. The relationships between prefrontal activation and executive function performance also were examined. Potential demographic and treatment-related predictors of executive function and prefrontal activation deficits were explored.

**METHODS**

**STUDY PARTICIPANTS**

Twenty-five female BC survivors who had undergone chemotherapy and surgical procedures, 19 female BC survivors who had undergone surgical procedures only, and 18 healthy female controls with no significant medical his-
therapy regimens varied widely across participants (83% having stage 1 to 2; the no-chemotherapy group ranged in the chemotherapy group had significantly higher stages of disease at the time of evaluation. The BC groups were matched with regard to menopausal status (Table 1). Participants in the BC groups were free of disease and had no history of relapse or recurrence at the time of evaluation. The BC groups were matched for hormonal blockade treatment (tamoxifen citrate), radiation, and time after cessation of therapy. As expected, women in the chemotherapy group had significantly higher stages of BC at diagnosis ($\chi^2=22.0, P<.001$), ranging from 1 to 3, with 83% having stage 1 to 2; the no-chemotherapy group ranged from stage 0 to 2, with 81% having stage 0 to 1. Chemotherapy regimens varied widely across participants (Table 2). Participants were excluded for neurological, psychiatric, or medical conditions known to affect cognitive function (eg, learning disability and brain injury) and any magnetic resonance imaging (MRI) contraindications (eg, non-MRI–safe implants). This study was approved by the Stanford University and the Army of Women institutional review boards; all participants provided informed consent.

### MRI ACQUISITIONS

Functional MRI (fMRI) data were obtained using a T2-weighted13 gradient-echo spiral-pulse sequence (repetition time, 2000 milliseconds; echo time, 30 milliseconds; flip angle, 80° and 1 interleave; field of view, 22.0 cm; matrix, 64x64; and in-plane resolution, 3.4375 mm) with a 3.0-T GE Signa HDx whole-body scanner (GE HealthCare, Milwaukee, Wisconsin). A high-order shimming method was used to reduce field heterogeneity. A high-resolution, 3-dimensional, inversion recovery prepared fast spoiled gradient recalled sequence scan also was acquired to localize functional activation (repetition time, 8.5 milliseconds; echo time, minimum; flip angle, 13°; inversion time, 400 milliseconds; bandwidth, ±31.25 kHz; field of view, 22.0 cm; phase field of view, 0.75 cm; section thickness, 1.5 mm; 124 sections 256×256 pixels at 1 excitation; and scan time, 4:33).

### fMRI TASK

A card-sorting task requiring participants to determine an implicit rule governing the categorization of geometric figures was used to measure prefrontal brain activation associated with executive function. The task consisted of 4 experimental blocks interwoven with 4 control blocks, with 12 trials per block. During the experimental condition, study participants were instructed to “Try to guess the computer’s rule. Does the card shown follow the rule? 1=yes, 2=no.” Then, the participant was shown 12 different cards, 1 at a time, for 3500 milliseconds each. Twenty-four unique cards were each used twice across the experimental condition but never within the same block. Each card depicted 1 to 4 squares, circles, or stars that were blue, green, or red. Rules were based on shape form, number, or color. Trials were followed by a feedback screen indicating, for 450 milliseconds, whether the response was correct. A 50-millisecond interstimulus interval separated feedback and the subsequent trial. The rule remained the same throughout each experimental block.

During the control condition, the study participant was asked to judge whether a single card was red. Feedback was presented after each control trial. Participants were randomized to 3 different versions of the task to control for rule difficulty and presentation order. Task performance data were acquired simultaneously.

### fMRI PREPROCESSING

Using Statistical Parametric Mapping 5 software (http://www.fil.ion.ucl.ac.uk/~fmrill), images were realigned to correct for head movement using least-squares minimization, coregistered and normalized using the segmented anatomical volume, and smoothed to reduce the effects of noise. Individual images were visually assessed for correct spatial normalization. An automated in-house software program, ArtRepair (http://cbsr.stanford.edu/tools), was used to automatically detect and repair artifacts when necessary.

### OUTCOME MEASURES

Executive function was measured using standardized tests administered by trained research staff masked to imaging results.
and group status. The Wisconsin Card Sorting Test Computer Version 4–Research Edition (WCST:CV4) was used as a measure of problem solving and set shifting. The WCST:CV4 was timed to obtain a measure of processing speed. Working memory was assessed using the Digit Span subtest of the Wechsler Adult Intelligence Scale, Fourth Edition.14 The letter fluency section of the verbal fluency subsection of the Delis-Kaplan Executive Function System was used to measure verbal fluency.15 The Behavioral Rating Inventory of Executive Function (BRIEF)16 was administered to assess the participant's subjective perception of executive functioning. The Clinical Assessment of Depression17 was used to screen for current psychiatric symptoms that could confound between-group comparisons. Outcome measures were administered the same day as the MRI scan.

STATISTICAL ANALYSES

fMRI

Statistical analyses of fMRI data were performed using a random-effects model in Statistical Parametric Mapping 5 software.21 Individual contrast images were analyzed using a general linear model to determine voxel-wise t statistics. Then, a 1-sample t test covaried for age was used to define whole-brain within-group activation. Between-group differences in brain activation were calculated using 1-way analysis of variance covaried for age. We used height and extent thresholds of P < .05 and 50 voxels, respectively, corrected for multiple comparisons. Images for 3 patients in the chemotherapy group, 1 patient in the no-chemotherapy group, and 1 healthy control were unusable because of significant motion artifact.

Contrast values from the regions of significant between-group difference were extracted for each participant and entered into a 1-way analysis of variance in SPSS software, version 16.0.2 (SPSS Inc, Chicago, Illinois). The Fisher least significant difference post hoc test was used to conduct pairwise comparisons for analyses with significant (P < .05) omnibus F statistics. Contrast values represented the activation in the experimental condition minus the activation in the control condition.22

Outcome Measures, IMRI Performance, and Exploratory Analyses

Test scores and IMRI task performance metrics were compared between groups using 1-way analysis of variance and pairwise comparisons using SPSS software, as described herein. Within each group, associations between IMRI contrast values and outcome measures were explored. Within each BC group, the relationships among age, educational level, tamoxifen use (yes/no), BC stage at diagnosis (as an indicator of disease severity), menopausal status, outcome measures, and brain activation indices were explored. Only test scores that were significantly different between groups were included; all analyses were conducted using 2-tailed Spearman correlations. Group differences between correlation coefficients were calculated using the Fisher r-to-z transformation (2-tailed).

RESULTS

BRAIN FUNCTION

All 3 groups showed a similar profile of brain activation during the IMRI task, including bilateral cerebellum, basal ganglia, and parietal and dorsolateral prefrontal regions (Figure 1). Significant between-group differences in brain activation were found in the left middle dorsolateral prefrontal gyrus extending into the left inferior frontal gyrus (Brodmann area [BA] 10/46), the left caudal lateral middle frontal gyrus (BA 8), and the left medial frontal gyrus (BA 6) (Table 3). Post hoc analysis indicated that healthy controls showed significantly greater BA 10/46 activation than both BC groups, but the BC groups were not significantly different from each other. The healthy control and no-chemotherapy groups demonstrated significantly greater BA 8 activation than the chemotherapy group, although the healthy control and no-chemotherapy groups were not significantly different. In terms of BA 6 activation, healthy controls showed significantly greater activation than both BC groups, although the BC groups did not differ from each other (Table 3 and Figure 2).

OUTCOME MEASURES AND IMRI PERFORMANCE

The chemotherapy group showed a significantly higher number of perseverative errors on the WCST:CV4 (indicated by lower t scores) compared with healthy controls and longer WCST:CV4 completion time compared with healthy controls and the no-chemotherapy group. The chemotherapy group demonstrated significantly higher subjective executive function difficulties indicated by elevated BRIEF composite scores compared with the other 2 groups (Table 4).

EXPLORATORY ANALYSES

In healthy controls, lower BA 10/46 activation was associated with greater subjective executive function concerns (r = −0.54, P = .03). This correlation was significantly different from that of the no-chemotherapy group (z = −2.2, P = .03) but not that of the chemotherapy group (z = −1.0, P = .32). Increased BA 8 activation was correlated with shorter WCST:CV4 completion time (r = −0.59, P = .006) and was significantly different from those of the chemotherapy (z = −1.9, P = .05) and no-chemotherapy groups (z = −2.6, P = .01).

In the chemotherapy group, lower BA 8 activation was associated with elevated BRIEF score (r = −0.51, P = .02). This finding was significantly different from that for the no-chemotherapy group (r = −2.30, P = .02) but not from that for healthy controls (z = −1.1, P = .25). Higher BC stage at diagnosis was associated with lower BA 8 activation (r = −0.44, P = .049), which was significantly different from that of the no-chemotherapy group (z = −2.2, P = .03). Lower educational level was correlated with increased WCST:CV4 perseverative errors (r = 0.50, P = .01). This finding was not different from that for the other groups. Older age was related to increased WCST:CV4 perseverative errors (r = −0.34, P = .006). This correlation was different from that for healthy controls (z = −2.8, P = .005) and for the no-chemotherapy group (z = −3.1, P = .002).

In the no-chemotherapy group, longer WCST:CV4 completion time was associated with reduced perseverative errors (r = 0.55, P = .02). This correlation was significantly different from that observed in the chemo-
therapy group ($z = -2.6, P = .008$) but not that in healthy controls ($z = -0.9, P = .36$).

**COMMENT**

The findings of this study have important implications for the effects of primary BC on brain function. Survivors of BC demonstrated significantly reduced left middle dorsolateral prefrontal cortex and left medial frontal activation compared with controls, irrespective of treatment history. However, women in the chemotherapy group showed significantly poorer outcome, including additional reductions in left caudal lateral prefrontal function and decreased executive function compared with women not treated with chemotherapy and healthy controls.

Although previous studies\textsuperscript{3,8,11} have shown prefrontal deficits during other executive function tasks and behavioral impairment in chemotherapy-treated women,\textsuperscript{23} the present study contributes findings that are unique, to our knowledge, regarding neurophysiologic and behavioral outcome in BC. Specifically, reduced BA 8 activation was significantly correlated with increased self-reported executive dysfunction in the chemotherapy group, who rated themselves as having more executive deficits. An association between brain function and self-reported executive function was noted for healthy controls involving a different prefrontal region (BA 10/46), although this group rated themselves, on average, as having normal executive function skills. Discordance often is observed between objective and subjective outcome measures in BC, likely due to the often subtle nature of cognitive changes in this group\textsuperscript{23} and the limited sensitivity and ecological validity of most objective measures.\textsuperscript{24} The present findings suggest a potential neurobiological marker of subjective or subclinical executive impairment in chemotherapy-treated BC survivors related to real-world difficulties.

Reduced BA 8 activation was unique to the chemotherapy group and may suggest potential neurotoxic brain injury. Animal studies\textsuperscript{25-28} suggest that chemotherapy regimens are toxic to progenitor cells in the brain, increasing cell death and suppressing cell proliferation. A previous study\textsuperscript{8} demonstrated an association between certain chemotherapies and prefrontal dysfunction. However, too
Table 3. Between-Group Differences in Functional Brain Activation

<table>
<thead>
<tr>
<th>Variable</th>
<th>BA 10/46</th>
<th>BA 8</th>
<th>BA 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value (FDR corrected)</td>
<td>.049</td>
<td>.049</td>
<td>.049</td>
</tr>
<tr>
<td>Cluster size</td>
<td>711</td>
<td>120</td>
<td>58</td>
</tr>
<tr>
<td>F value</td>
<td>8.20</td>
<td>5.90</td>
<td>5.74</td>
</tr>
<tr>
<td>Peak cluster coordinates</td>
<td>−28, 28, 16</td>
<td>−26, 16, 52</td>
<td>−16, 2, 52</td>
</tr>
<tr>
<td>Full cluster description</td>
<td>Left middle dorsolateral prefrontal gyrus extending into left inferior frontal gyrus</td>
<td>Left caudal lateral middle frontal gyrus</td>
<td>Left medial frontal gyrus</td>
</tr>
<tr>
<td>Contrast value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy group, mean (SD) (n=22)</td>
<td>1.90 (3.0)</td>
<td>2.96 (5.1)</td>
<td>.41 (2.1)</td>
</tr>
<tr>
<td>No-chemotherapy group, mean (SD) (n=18)</td>
<td>3.72 (2.4)</td>
<td>7.02 (4.7)</td>
<td>.97 (2.9)</td>
</tr>
<tr>
<td>Healthy control group, mean (SD) (n=17)</td>
<td>6.42 (4.2)</td>
<td>9.95 (8.5)</td>
<td>3.38 (3.5)</td>
</tr>
<tr>
<td>F value</td>
<td>8.74</td>
<td>6.48</td>
<td>5.87</td>
</tr>
<tr>
<td>P value</td>
<td>.001</td>
<td>.003</td>
<td>.005</td>
</tr>
<tr>
<td>d value</td>
<td>1.10</td>
<td>0.97</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; FDR, false discovery rate.

Indicates significantly different from the healthy control group; a, significantly different from the no-chemotherapy group. Effect size is shown in the superscript parenthesis for pairwise comparisons.

Per the Montreal Neurological Institute numbering system.

much variability was reported in chemotherapy regimens among the present sample to address the relationship between treatment protocol and brain function. The BC groups also differed significantly in terms of cancer stage or severity at diagnosis. However, only the chemotherapy group showed an association between disease stage and BA 8 activation. A post hoc comparison of BA 8 activation between the BC groups controlling for disease stage reduced the significance of the finding (F = 1.7, P = .21). However, stage was not a significant covariate (F = 0.2, P = .61) and likely only removed the effect of interest (ie, the group) from the analysis, given that adjuvant chemotherapy and disease stage are highly interrelated. Specifically, treatment regimen and intensity often are influenced by cancer stage, and patients with a higher stage at diagnosis are more likely to receive adjuvant chemotherapy. These findings highlight the importance of continued investigation of the relationship between chemotherapy and brain function in BC.

The BA 8 region is involved in switching attention to alternative competing responses based on learned conditional rules. It is demonstrated herein that increased activation of the BA 8 region was associated with faster completion time on the WCST:CV4 in healthy women. Thus, individuals with abnormalities in this area would be expected to have difficulties in flexibly shifting between response options and/or to experience slower processing speed during rule-governed tasks. Consistently, women in the chemotherapy group showed more perseverative errors than healthy controls, indicating that they tended to persist in responding to an incorrect rule. Also, the chemotherapy group took significantly longer to complete the WCST:CV4 test compared with the other groups. Even though the chemotherapy-treated women took more time on this task, they still made more errors. Thus, slowing down may not be an adequate compensatory strategy for these women. Taking more time may have been helpful for the no-chemotherapy group.

These women showed a uniquely significant correlation between increased WCST:CV4 completion time and lower number of perseverative errors in the context of performance on the WCST:CV4 comparable to that of controls. These findings may suggest that factors specific to the chemotherapy group may have decreased these women’s ability to compensate for certain executive function impairments through simple behavioral adjustments. This may reflect stage of illness, in which slowing down is a first compensatory approach that no longer works when the disease has advanced to the point that increasing prefrontal damage has been incurred.

Decreased BA 10/46 and BA 6 function in both BC groups point to non–chemotherapy-related factors, such as increased WCST:CV4 completion time and lower number of perseverative errors in the context of performance on the WCST:CV4 comparable to that of controls.
as abnormal endocrine function. Tamoxifen and menopause both result in estrogen deficiency, which can impair brain and cognitive function. Although these variables were not related to outcome or brain activation within the BC groups and groups were matched for menopausal status, individual variation in estrogen levels still may exist. Two previous studies have indicated negative effects of tamoxifen on cognitive status and brain function in BC survivors and suggest that women treated with chemotherapy and tamoxifen are at highest risk for cognitive and neurobiological deficits.

The behavioral effects of decreased BA 10/46 and BA 6 activation in survivors of BC are unclear because no significant correlations were observed between activation in these regions and measures of subjective or objective executive function. Also, only the chemotherapy-treated group demonstrated significant differences in executive function performance. Brodmann area 10/46 is responsible for working memory, cognitive control, and monitoring. Brodmann area 6 has been associated with rule-based motor responses, error detection, and maintenance of working memory processes. Thus, a more comprehensive battery of executive function measures may be required to elucidate the relationships between BA 10/46 and BA 6 dysfunction and cognitive outcome in BC.

Cognitive reserve and age also may influence executive function outcome in chemotherapy-treated BC survivors. Individuals with greater cognitive reserve, stemming from genetic and environmental enrichment factors, tend to be less vulnerable to the effects of neurological disease, injury, and senescence. The chemotherapy group showed a significant relationship between higher educational level (a proxy of cognitive reserve) and decreased number of perseverative errors. Also, older women in the chemotherapy group tended to show increased perseverative errors, but aging was not associated with executive function in the other 2 groups. A previous study demonstrated an effect of cognitive reserve and age on processing speed in chemotherapy-treated women. These findings suggest that chemotherapy-treated women may be more vulnerable to the effects of lower environmental enrichment and aging on executive function.

Limitations of this study include its cross-sectional design. Longitudinal studies are necessary to more specifically address the effects of chemotherapy on brain and cognitive outcome. As noted herein, the selection of objective and subjective tests and indices was limited. This approach was taken to focus on the most reliable and salient measures and to reduce the number of statistical tests performed in a relatively small sample. The relatively small sample size may limit the interpretability of the results. For example, a moderate effect size was observed (P = .09, effect size = 0.66) for a difference in BA 10/46 activation between the chemotherapy and no-chemotherapy groups. Power was calculated to be 86% or higher for pairwise omnibus statistics, and effect sizes ranged from 0.66 to 1.20, but larger sample sizes are needed to detect any smaller effects that may exist. Also, as with most such studies of BC, the inherent heterogeneity of this sample in terms of disease and treatment factors may limit the generalizability of these results to other patients.

This study provides further evidence that primary BC may cause measurable brain injury. Women treated with chemotherapy may show additional prefrontal deficits and have difficulty compensating for neurobiological changes such that they also show impaired executive function. The left caudal lateral prefrontal region may be particularly vulnerable to the effects of chemotherapy and/or disease severity and may represent a novel biomarker of subjective or subclinical executive dysfunction in chemotherapy-treated women.

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Author Contributions: Study concept and design: Kesler. Acquisition of data: Kesler and Kent. Analysis and interpretation of data: Kesler and O’Hara. Drafting of the manuscript: Kesler and O’Hara. Critical revision of the manu-

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### Table 4. Outcome Measures and fMRI Task Performance Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy (n=25)</td>
</tr>
<tr>
<td>WCST:CV4 total errors</td>
<td>46 (9.6)</td>
</tr>
<tr>
<td>WCST:CV4 perseverative errors</td>
<td>44 (20.6)</td>
</tr>
<tr>
<td>WCST:CV4 nonperseverative errors</td>
<td>43 (7.4)</td>
</tr>
<tr>
<td>WCST:CV4 time, s</td>
<td>313 (68)</td>
</tr>
<tr>
<td>Digit span</td>
<td>11 (2.1)</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td>BRIEF</td>
<td>64 (13)</td>
</tr>
<tr>
<td>CAD</td>
<td>50 (10)</td>
</tr>
<tr>
<td>fMRI task correct, %</td>
<td>69 (12)</td>
</tr>
<tr>
<td>fMRI task reaction time, ms</td>
<td>1370 (288)</td>
</tr>
</tbody>
</table>

Abbreviations: BRIEF, Behavioral Rating Inventory of Executive Function; CAD, Clinical Assessment of Depression; fMRI, functional magnetic resonance imaging; WCST:CV4, Wisconsin Card Sorting Test Computer Version 4–Research Edition.

*a,b* Indicates significantly different from the healthy control group; *c,* significantly different from the no-chemotherapy group. Effect size is shown in the superscript parentheses for significant pairwise comparisons.

1. Section of the verbal fluency subtest of the Delis-Kaplan Executive Function System.
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REFERENCES


