Original Article

Reduced Prefrontal Activation During Working and Long-Term Memory Tasks and Impaired Patient-Reported Cognition Among Cancer Survivors Postchemotherapy Compared With Healthy Controls

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BACKGROUND: Patients who receive adjuvant chemotherapy have reported cognitive impairments that may last for years after the completion of treatment. Working memory-related and long-term memory-related changes in this population are not well understood. The objective of this study was to demonstrate that cancer-related cognitive impairments are associated with the under recruitment of brain regions involved in working and recognition memory compared with controls. **METHODS:** Oncology patients (n = 15) who were receiving adjuvant chemotherapy and had evidence of cognitive impairment according to neuropsychological testing and self-report and a group of age-matched, education group-matched, cognitively normal control participants (n = 14) underwent functional magnetic resonance imaging. During functional magnetic resonance imaging, participants performed a nonverbal n-back working memory task and a visual recognition task. **RESULTS:** On the working memory task, when 1-back and 2-back data were averaged and contrasted with 0-back data, significantly reduced activation was observed in the right dorsolateral prefrontal cortex for oncology patients versus controls. On the recognition task, oncology patients displayed decreased activity of the left-middle hippocampus compared with controls. Neuroimaging results were not associated with patient-reported cognition. **CONCLUSIONS:** Decreased recruitment of brain regions associated with the encoding of working memory and recognition memory was observed in the oncology patients compared with the control group. These results suggest that there is a reduction in neural functioning postchemotherapy and corroborate patient-reported cognitive difficulties after cancer treatment, although a direct association was not observed. ***Cancer*** **2016;122:258-68.** © *2015 American Cancer Society.*

KEYWORDS: cancer-related cognitive impairment (CRCI), functional magnetic resonance imaging (fMRI), patient-reported outcomes (PRO), recognition memory, working memory.

INTRODUCTION

Recent studies have demonstrated that patients with cancer who receive adjuvant chemotherapy experience cancer-related cognitive impairments (CRCIs)[1] that can have a negative impact on a patient's daily life.[2-4] CRCIs manifest as difficulty in real-life routines, such as remembering telephone numbers,[5] or deficits in laboratory tests, such as working memory[6] and learning new information (ie, encoding).[7] Neuroimaging studies have revealed decreased activity in the frontal cortex during working memory tasks[8] as well as reduced frontal, temporal, parietal, and cerebellar cortical volume[9-11] in these patients. A recent electroencephalogram (EEG) study has demonstrated that prolonged exposure to chemotherapeutic

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This experiment was realized using Cogent 2000 developed by the Cogent 2000 team at the Functional Imaging Library and the Institute of Cognitive Neuroscience and using Cogent Graphics developed by John Romaya at the Laboratory of Neurobiology in the Wellcome Department of Imaging Neuroscience (University College, London, UK).

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agents is associated with decreases in hippocampal neurogenesis and θ-band activity, which may lead to deficits in learning and subsequent retrieval.[12] Furthermore, animal studies suggest a link between chemotherapy-induced cellular damage in the hippocampus and behavioral impairment in visuospatial memory.[13]

Results from CRCI studies that used neuroimaging,[4,9] neuropsychological tests,[14] and patient-report[15] are not consistent; many brain regions have been implicated, but there has been high variability from study to study (for a recent review, see Scherling and Smith[4]. There is also substantial variation in the degree to which these brain differences are related to neuropsychological test domains or patient-reported cognitive function. In addition, whereas some findings support the association between neuroimaging and patient-reported cognitive function,[9,16,17] systematic review of this evidence indicates no clear association across studies.[18]

The objective of this study was to demonstrate that patients who receive adjuvant chemotherapy experience CRCIs related to the under recruitment of brain regions involved in working and recognition memory compared with controls. In this study, we used all 3 approaches (ie, neuroimaging, neuropsychological testing, and patient-reported cognitive function assessments) to evaluate CRCI. Because deficits in working memory and learning can have direct consequences on longer term memory, such as the deficits involved in recognition, we examined nonverbal working memory and visuospatial recognition memory tasks. Recognition memory is the ability to accurately discriminate a novel stimulus from a previously experienced stimulus,[19] and it involves the medial temporal lobe (MTL).[20] It has been demonstrated that damage to the MTL has an impact on both recognition and working memory.[21] Working memory involves prefrontal and frontal parietal networks.[22,23] Therefore, our primary hypothesis was that brain activation during working memory and recognition tasks would be reduced in oncology patients in the prefrontal and MTL brain regions compared with healthy controls. Our secondary hypothesis was that the reduced activation would be associated with impairments in neuropsychological test performance and patient-reported cognition. Finally, we explored whether there was an association between task behavior, neuropsychological test performance, and patient-reported cognitive function.

MATERIALS AND METHODS

Procedure

This study was approved by the Institutional Review Board at Northwestern University and the NorthShore University Health System. After physician referral from affiliated outpatient clinics based on patient report of cognitive difficulty, patients were recruited and consented by research assistants. In total, 185 patients were identified as having reported cognitive impairments; of those, 77 patients were ineligible, 59 refused to participate, and 49 were consented. A group of healthy control participants was recruited through flyers and by word of mouth. Forty-six individuals were identified as potentially eligible for the control group; of these, 7 individuals were ineligible, 5 refused, and 34 were consented. All consented participants, including 49 patients and 34 controls, completed neuropsychological tests and patient-reported outcomes (PRO) measures. Participants were then included or excluded from the study based on their neuropsychological performance (see Participants, below). Controls who performed within the normal range were selected to group-match the patients on demographics and then underwent the same magnetic resonance imaging (MRI) procedure. In total, 16 patients and 16 controls underwent MRI and were included in the study. Details on the procedures for participant selection, the neuropsychological test battery, PRO measures, MRI, behavior, image processing, and statistical analysis are described below.

Participants

Eligibility criteria for patients included a solid, noncentral nervous system tumor or a hematologic malignancy of any stage; a physician-rated Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2[24]; and the completion of 3 or more cycles of chemotherapy within the previous 6 months. Patients and control participants were excluded if they had premorbid cognitive dysfunction or comorbidities known to be associated with cognitive impairment (such as major depression or generalized anxiety[25]). Eligibility criteria for patients included impairment in cognitive domains ($\geq$1 standard deviation below the mean score on at least 3 domains or $\geq$1.5 standard deviations below the mean score on at least 1 or more domains, consistent with International Cognition and Cancer Task Force recommendations[26]). Eligibility criteria for control participants included normal performance on neuropsychological evaluation.

Neuropsychological Tests

Participants completed the following neuropsychological tests designed to assess memory, executive function, problem solving/reasoning ability, visuospatial/constructional ability, language, and attention: the Repeatable Battery for the Assessment of Neuropsychological Status

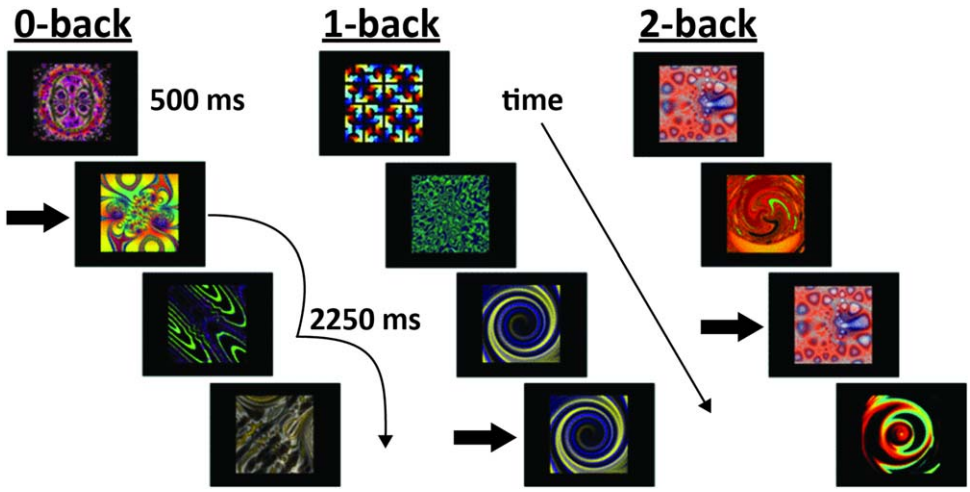

Figure 1. The n-back working memory task is illustrated. In the 0-back condition, participants respond whenever the indicated figure appears, regardless of any figures that preceded it. In the 1-back condition, participants respond whenever the figure is the same as in the previous trial. Participants respond in the 2-back condition whenever the figure matches the stimulus that came 2 trials before it. Arrows indicate correct responses for all conditions. Stimuli courtesy of J. Daniel Ragland (University of Pennsylvania).

(RBANS); Trail Making tests A and B; the Stroop Color-Word Test; the Test of Nonverbal Intelligence (TONI-III); the Wechsler Adult Intelligence Scale (WAIS-III) Similarities, Digit Span, and Letter-Number Sequencing subscales; and the MicroCog Assessment of Cognitive Functioning[27] with reaction time.

PRO Measures

A battery of PRO and health-related quality-of-life measures was administered to participants to quantify patient-reported cognitive problems, overall functional status, and well being. These included: the Functional Assessment of Cancer Therapy (FACT)-Cognitive Function Scale version 1 (FACT-Cog v1),[28] the FACT-General (FACT-G),[29] the FACT-Fatigue,[30] and the Hospital Anxiety and Depression Scale (HADS).[31] All FACT questionnaires assessed for difficulties experienced within the previous 7 days. The FACT-Cog v1 (reliability: $\alpha = .96$[32]) assesses patient-reported cognitive impairment, impact on quality of life, and the extent to which others notice cognitive deficits,[28] with lower scores indicating worse cognitive function. The FACT-G assesses physical, social, emotional, and functional well being, with higher scores indicating better quality of life. The FACT-Fatigue assesses fatigue, with higher scores indicating less fatigue. The HADS measures general anxiety and depression, with higher scores indicating higher levels of anxiety and depression. Physician-rated ECOG performance status also was provided for each patient.

MRI, Behavior, and Image Processing

All participants who were included in the study underwent MRI on a Siemens 3T Trio scanner (Siemens AG, Munich, Germany). Functional MRI (fMRI) data were acquired using a susceptibility-weighted echo-planar imaging sequence (repetition time [TR] = 2200 msec, echo time [TE] = 20 msec, flip angle = 80°, matrix = 64 × 64, resolution = 3.4375 × 3.4375 × 3 mm^3). A T1-weighted magnetization prepared rapid gradient echo (MPRAGE) image also was acquired (TR = 2100 msec, TE = 4.38 msec, flip angle = 8, matrix = 256 × 192, resolution = 0.859 × 0.859 × 1 mm^3). During fMRI, participants performed nonverbal n-back (0-back, 1-back, and 2-back) visual working memory and recognition tasks adapted from Ragland et al.[33] Stimuli were presented to participants using Cogent 2000 and Cogent graphics software (available at: http://www.vislab.ucl.ac.uk/cogent_2000.php; accessed October 2, 2015) running in the MatLab environment (MathWorks, Natick, Mass).

During the n-back task, we used a blocked design, with each block lasting 33.75 seconds and repeated 3 times in a pseudorandomized order. Within each block, 39 fractal images were presented sequentially for 500 msec with a 375-msec interstimulus interval. Participants pressed a button to indicate whether or not the fractal image on the screen was the same as that shown either 0, 1, or 2 items before (Fig. 1). The n-back task served as an indirect encoding phase for the subsequent recognition test. Upon completion of the n-back task, the recognition test consisted of 20 fractal images from the n-back task

TABLE 1. Demographic Information for the Oncology and Control Groups

Variable	Percentage of Participants: Oncology Patients, N = 15	Percentage of Participants: Control Group, N = 14	*P*
Sex: Women	86.7	92.9	.58
Race			
White	86.7	78.6	
Black	13.3	21.4	.56
Age: Mean ± SD, y	50.7 ± 7.5	53.0 ± 7.2	.42
Education: Mean ± SD, y	15.6 ± 2.3	16.8 ± 2.2	.16
Handedness: Left/Right	1/14	1/13	.93
Physician-rated ECOG performance status			
0	53.3	NA	—
1	26.7		
2	20		
Cancer diagnosis			
Breast	73.3	NA	—
Colorectal	6.7		
Hodgkin lymphoma	6.7		
Leukemia	6.7		
Myeloma	6.7		
Extent of disease			
No evidence of disease	20	NA	—
Local	26.7		
Regional	13.3		
Metastatic	20		
NA	20		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available; SD, standard deviation.

interleaved with 22 new images (foils). Test fractals were presented 1 at a time in random order for 500 msec. Participants pressed a button to indicate whether or not they had seen a given fractal in the previous n-back task. Recognition accuracy was calculated as overall mean accuracy ([pHits + pCorrectRejections]/2), and recognition sensitivity was computed using d′ (pHits − pFalseAlarms) for each of the 0-back, 1-back, and 2-back conditions.

Preprocessing of fMRI data was performed using Analysis of Functional NeuroImages (AFNI) software[34] and included the following: exclusion of the first 3 volumes in each run, slice-timing and motion correction, coregistration to the participant's T1-weighted image, spatial normalization to the Talairach-Tournoux template with atlas regions of interest, and resampling to 3.25 mm^3 resolution. Data were then spatially smoothed with Gaussian kernel to a resolution of 8 mm full-width at half max, followed by linear regression with a model hemodynamic response function and its temporal derivative for each block and each task. A priori regions of interest (eg, MTL) were analyzed for the recognition task.

Statistical Analysis

For neuropsychological testing, PROs, and n-back behavioral data, Student *t* tests and effect sizes (Cohen D) were used to compare groups using SPSS version 21.0 (SPSS

TABLE 2. Neuropsychological Test Scores for Oncology Patients and Controls

Measure	Mean Score ± SD: Oncology Patients	Mean Score ± SD: Control Group	*P*	Cohen D
RBANS percentile				
Immediate memory	39.5 ± 32.7	67.9 ± 14.1	.006	1.111
Delayed memory	30 ± 27.2	55.8 ± 17.6	.005	1.112
Visuospatial/constructional	17.7 ± 23.7	57.8 ± 23.8	< .001	1.684
Language	31.7 ± 20.6	56 ± 20	.003	1.196
Attention	44.1 ± 28.6	80.6 ± 21.2	.001	1.445
Total index	24.3 ± 19.9	69.1 ± 19.6	< .001	2.262
Trails A T-score	48.2 ± 7.0	53.6 ± 7.8	.062	0.723
Trails B T-score	48.9 ± 11.2	55.2 ± 10.6	.133	0.576
Stroop interference T-score	48.2 ± 6.5	52.2 ± 5.1	.076	0.686
TONI-III percentile	52.0 ± 30.0	55.0 ± 25.4	.769	0.112
WAIS-III				
Letter-number age, ss	9.9 ± 3.3	12.6 ± 2.6	.018	0.933
Similarities age, ss	10.2 ± 3.0	12.8 ± 2.3	.014	0.973
Digit Span age, ss	9.87 ± 3.4	13.08 ± 2.3	.009	1.062
Digits Forward cumulative percentile	58.8 ± 35.1	31.0 ± 19.4	.015	0.961
Digits Backward cumulative percentile	62 ± 33.3	48.6 ± 34.5	.304	0.398
MicroCog total reaction time, ss				
Time 1	10.5 ± 2.4	12.1 ± 1.9	.031	0.747
Time 2	9.2 ± 3.7	11.7 ± 1.9	.031	0.848

Abbreviations: MicroCog, MicroCog Assessment of Cognitive Functioning; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation; ss, scaled score; TONI-III Test of Nonverbal Intelligence; WAIS, Wechsler Adult Intelligence Scale.

TABLE 3. Patient-Reported Outcome Measures for Oncology Patients and Controls

Measure (Score Range)	Mean Score ± SD		*P*	Cohen D
	Oncology Patients	Control Group		
FACT-Cog v1				
Perceived cognitive impairments (0-80)	38.44 ± 16.11	67.85 ± 8.36	< .001	2.267
Impact on QOL (0-16)	11.00 ± 4.78	14.93 ± 1.94	.009	1.063
Comments from others (0-16)	11 .91 ± 3.47	15.43 ± 1.14	.002	1.342
FACT-Cog total (0-108)	80.17 ± 14.15	91.76 ± 9.82	.017	0.945
FACT-G				
Physical well being (0-28)	18.40 ± 7.60	25.92 ± 2.47	.002	1.311
Social well being (0-28)	22.97 ± 2.86	22.38 ± 4.13	.655	0.168
Emotional well being (0-24)	20.07 ± 3.41	20.46 ± 2.98	.741	0.124
Functional well being (0-28)	18.73 ± 6.51	23.00 ± 4.05	.045	0.781
FACT-Fatigue (0-52)	33.00 ± 15.03	46.21 ± 5.91	.005	1.142
HADS				
Anxiety (0-20)	6.40 ± 4.24	3.71 ± 2.46	.049	0.768
Depression (0-20)	4.07 ± 4.10	1.21 ± 1.48	.021	0.913

Abbreviations: FACT-Cog v1, Functional Assessment of Cancer Therapy-Cognitive Function Scale version 1; FACT-G, Functional Assessment of Cancer Therapy-General Scale; HADS, Hospital Anxiety and Depression Scale; QOL, quality of life; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale.

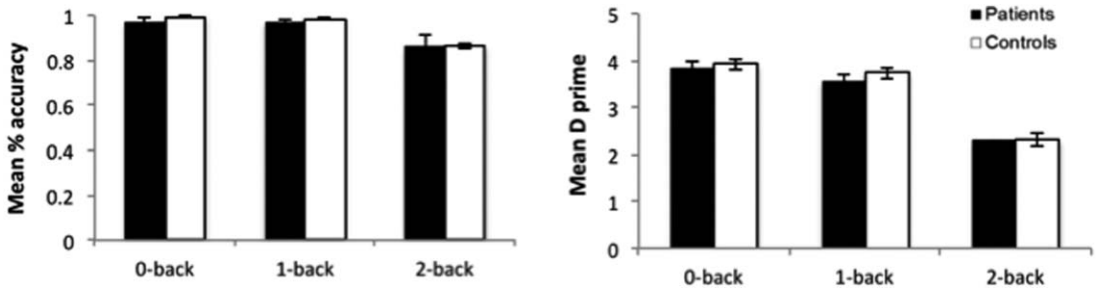

Figure 2. Between-groups behavioral results for the n-back task are illustrated. Bars indicate (*left*) the mean accuracy and (*right*) the mean D-prime value. Although there were no statistically significant differences between groups for each n-back condition, the differences for the 0-back and 1-back conditions indicated moderate effects sizes.

Inc., Chicago, Ill). For recognition memory performance, a 2×2 mixed repeated-measures analysis of variance and post-hoc *t* tests were used to test for the main effects of recognition (hits vs misses) and for group and recognition × group interactions. Effect sizes for these analyses were calculated as partial η^2. For fMRI data, a whole-brain analysis was conducted with mixed-effects meta-analysis (3dMEMA in AFNI) to determine group-level differences after covarying for scores on the FACT-Fatigue and HADS. MEMA uses group-level variation and a precision estimate of the effect of interest from individual participants. For working memory, the n-back data were corrected for multiple comparisons to achieve $P < .05$ with an individual voxel threshold at $P < .001$ and a minimum cluster size ≥ 17 voxels. Each of the 1-back and 2-back conditions was first contrasted with 0-back to examine between-group differences; however, no significant group differences were observed. Therefore, we averaged the 1-back and 2-back conditions to contrast with 0-back and compared across the groups. For recognition, activity corresponding to the correct *yes* (hits) was contrasted with the correct *no* (correct rejections) and compared between groups.

We tested our secondary hypotheses in brain regions that demonstrated significant group differences in any of the comparisons described above by conducting Pearson correlation analyses between regional blood oxygen level-dependent (BOLD) activity and neuropsychological test performance as well as patient-reported cognitive function. For neuropsychological test comparisons, we used

TABLE 4. N-Back Working Memory Behavior Results for Oncology Patients and Controls[a]

Variable	Mean ± SD											
	0-Back Data						1-Back and 2-Back Data Combined					
	Accuracy, %	RT, msec	Sensitivity d′	Hits	Misses	False Alarms	Correct Rejections	Accuracy, %	RT, msec	Sensitivity d′	Hits	Misses	False Alarms	Correct Rejections
Oncology patients	97.18 ± 6.2	638.46 ± 245.1	3.72 ± 0.7	0.98 ± 0.1	0.02 ± 0.1	0.01 ± 0.0	0.99 ± 0.0	92.22 ± 0.07	838.95 ± 247.2	2.87 ± 0.9	0.83 ± 0.1	0.17 ± 0.1	0.03 ± 0.0	0.97 ± 0.0
Control group	99.02 ± 1.5	612.80 ± 180.8	3.91 ± 0.2	0.99 ± 0.0	0.01 ± 0.0	0.01 ± 0.0	0.99 ± 0.0	92.70 ± 0.07	802.60 ± 294.8	3.01 ± 0.8	0.87 ± 0.1	0.13 ± 0.1	0.04 ± 0.0	0.96 ± 0.0
Effect size (Cohen d)	0.48	0.12	0.4	0.13	0.13	0.23	0.23	0.07	0.13	0.17	0.38	0.38	0.42	0.42

Abbreviations: RT, reaction time; SD, standard deviation.
[a] Results indicate 0-back and combined 1-back and 2-back mean accuracy (hits + correct rejections/2), reaction time, sensitivity (d′), hits, misses, false alarms, and correct rejections for oncology patients and controls. Effect sizes are displayed for between-group comparisons.

RBANS subtest percentiles and total index scores, Trail Making A and B T-scores, Stroop T-scores, TONI-III percentiles, WAIS-III subtest scaled scores and cumulative percentiles, and MicroCog 1 and 2 reaction-time scaled scores. For patient-reported cognitive function, we used the FACT-Cog v1 Perceived Cognitive Impairments subscale score and the FACT-Cog v1 total score.

For our exploratory hypotheses, we used Pearson correlation analysis to examine associations between task behavior, neuropsychological test performance, and patient-reported cognitive function measures that exhibited significant group differences. All correlation analyses were performed in the patient and control groups separately and were not corrected for multiple comparisons.

RESULTS

Participant Demographics

Originally, 16 oncology patients and 16 controls were included in this study. Three participants were subsequently removed from analysis, because 1 patient had difficulty understanding directions for the button press, and 2 controls had insufficient trials on the recognition task. In total, 15 oncology patients and 14 controls were included in the final analysis reported here. The groups did not differ in terms of age, education, sex, or race (Table 1). The majority of patients (53.3%) had an ECOG performance status of 0, 27% had a performance status of 1, and 20% had a performance status of 2. Diagnoses included breast cancer (73.3%), colorectal cancer (6.7%), Hodgkin lymphoma (6.7%), leukemia (6.7%), and myeloma (6.7%).

Neuropsychological Tests

In most of the cognitive domains, as expected, patients scored significantly lower than controls, indicating impairment (Table 2) (for eligibility criteria, see Participants, above). The groups did not differ in their scores on the Trails A and B, Stroop Interference, TONI-III, or Digits Backward instruments.

PRO Measures

On the FACT-Cog v1, patients reported significantly more perceived cognitive impairments, a greater impact of cognition on quality of life, and more comments from others regarding their cognition (Table 3). FACT-Cog v1 total scores indicated lower overall cognitive functioning among patients compared with controls. Regarding health-related quality of life, on the FACT-G, patients reported decreased physical and functional well being but comparable social and emotional well being compared with controls. Patients also indicated greater fatigue on

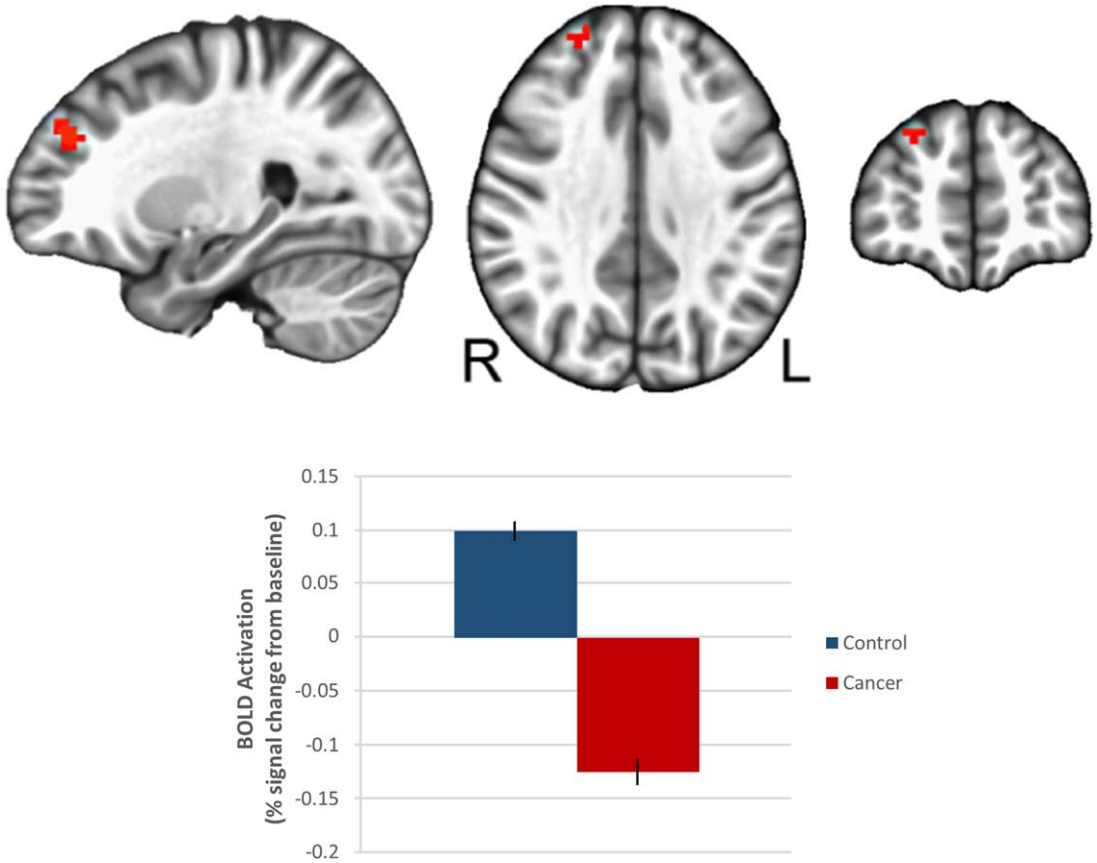

Figure 3. Between-group functional differences in the right (R) dorsolateral prefrontal cortex are illustrated for the n-back working memory task. Oncology patients had significantly decreased blood oxygen level-dependent (BOLD) activation in the right dorsolateral prefrontal cortex compared with controls. L indicates left.

TABLE 5. N-Back Functional Magnetic Resonance Imaging Results[a]

	Region With Peak Activation							
			Center of Mass Coordinates					
Region With Peak Activation	Hem	BA	L/R	A/P	S/I	Peak *T* Value	Cluster Size, mm^3	Cluster Size, Voxels
Control group > oncology patients								
Dorsolateral prefrontal cortex	R	9/10	−25	−47	31	3.86	618	18

Abbreviations: A/P, anterior/posterior; BA, Broadmann area; Hem, hemisphere; L/R, left/right; R, right; S/I, superior/inferior.
[a] Oncology patients demonstrated significantly reduced activation compared with controls in the right dorsolateral prefrontal cortex (Brodmann area 9/10) when the 1-back and 2-back data were averaged and contrasted with the 0-back data.

the FACT-Fatigue instrument and reported higher levels of anxiety and depression on the HADS.

N-Back Behavior

Patients did not differ significantly from controls on working memory behavioral measures (Fig. 2, Table 4). However, moderately reduced effect sizes were observed between groups in recognition sensitivity (d′) and accuracy for 0-back.

N-Back fMRI

Oncology patients demonstrated significantly reduced activation compared with controls in the right dorsolateral prefrontal cortex (DLPFC) (Brodmann area 9/10) when 1-back and 2-back data were averaged and contrasted with

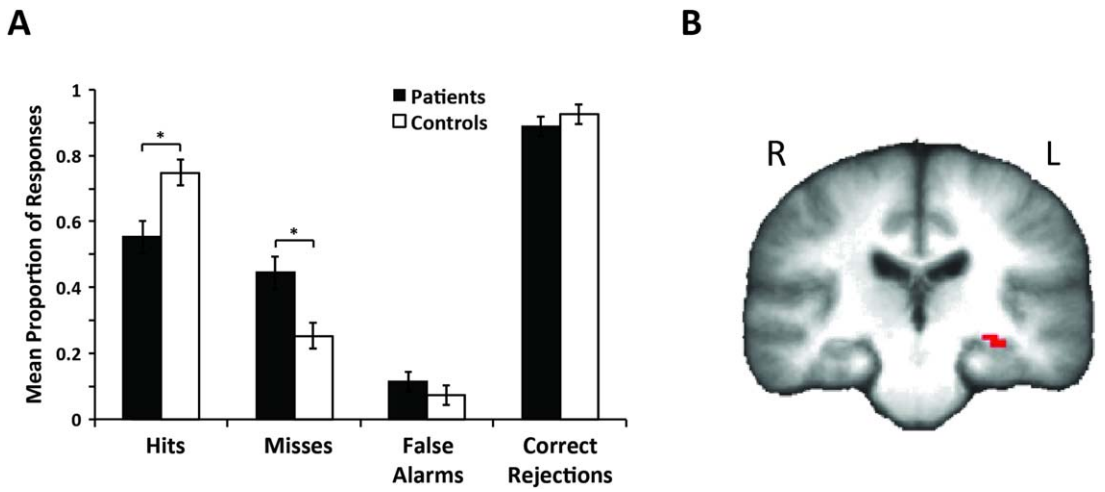

Figure 4. Between-group behavioral and functional differences are illustrated in the recognition task. (A) The proportions of hits, misses, false alarms, and correct rejections are illustrated for the visual recognition task. (B) Controls had increased activation when contrasting hits to correct rejections in the middle hippocampus (red area). Regions of increased activation that are not displayed also included the left lateral parietal cortex, the left fusiform gyrus, and the left lateral occipital cortex. Conversely, oncology patients had decreased activation compared with controls in the left hippocampus.

TABLE 6. Recognition Behavior Results for Oncology Patients and Controls[a]

	Mean ± SD						
				Old Items		New Items	
Variable	Accuracy	RT, msec	Sensitivity d′	Hits	Misses	False Alarms	Correct Rejections
Oncology patients	0.72 ± 0.09[b]	1227.95 ± 214.3	1.99 ± 1.2	0.55 ± 0.2[c]	0.44 ± 0.2[c]	0.11 ± 0.1	0.89 ± 0.1
Control group	0.82 ± 0.08	1336.33 ± 728.2	3.26 ± 1.7	0.75 ± 0.1	0.25 ± 0.2	0.07 ± 0.1	0.92 ± 0.1
Effect size: Cohen d	1.19	0.20	0.86	1.26	0.95	0.40	0.30

Abbreviations: RT, reaction time; SD, standard deviation.
[a] Displayed are estimates of mean recognition accuracy ([pHits + pCorrectRejections]/2), reaction time, recognition sensitivity (d′ = pHits − pFalseAlarms), and proportions of hits, misses, false alarms, and correct rejections for oncology patients and controls. Effect sizes are displayed for between-group comparisons.
[b] $P < .01$.
[c] $P < .05$.

0-back data (Fig. 3, Table 5). These differences remained after covarying for fatigue, anxiety, and depression, which can negatively affect working memory performance[35,36] and were greater in patients compared with controls (Table 3).

Recognition Behavior

Behavioral results from the recognition task are displayed in Table 6 and Figure 4A. We observed a significant main effect of recognition response ($F[1,24] = 16.48$; mean squared error[MSE] = 0.07; $P < .001$; $p\eta^2 = 0.41$) and a significant recognition response × group interaction ($F[1,24] = 6.76$; MSE = 0.072; $P < .02$; $p\eta^2 = 0.22$). A post-hoc *t* test revealed that this interaction was driven by a significant reduction in the proportion of correct hit responses from patients (55%) compared with controls (75%). We also observed a trend toward higher false-alarm rates in patients (11%) compared with controls (7%). Overall mean recognition accuracy was statistically poorer for patients compared with controls.

Recognition fMRI

The initial fMRI recognition analysis did not reveal any significant regional differences between groups after correcting for multiple comparisons. On the basis of a priori hypotheses that the MTL may be especially susceptible to chemotherapy neurotoxicity, in the patient group, we performed an exploratory analysis in this region and observed a small, 5-voxel cluster of decreased activation in the left-middle hippocampus ($P = .01$ voxel-wise, uncorrected) (Fig. 4B).

TABLE 7. Patient Correlations Between Neuropsychological Measures and Patient Self-Reported Outcome Measures That Differed Significantly Between Patients and Controls

Variable	FACT-Cog Perceived Cognitive Impairments	FACT-Cog Impact on QOL	FACT-Cog Comments From Others	FACT-G Total Score	Physical Well Being	Functional Well Being	Fatigue	HADS Anxiety	HADS Depression
RBANS immediate memory	−0.402	−0.264	−0.054	−0.417	−0.498	−0.3	−0.285	0.266	0.052
RBANS delayed memory	0.041	0.004	−0.085	−0.562[a]	−0.288	−0.590[a]	−0.198	0.155	0.466
RBANS visuospatial/ constructional	−0.22	−0.193	−0.453	−0.095	−0.109	0.008	−0.1	0.364	0.096
RBANS language	0.078	0.327	−0.314	0.086	0.116	−0.082	0.044	−0.351	−0.212
RBANS attention	0.048	−0.132	0.096	−0.562[a]	−0.451	−0.509	−0.362	0.325	0.191
RBANS total index	−0.26	−0.252	−0.25	−0.608[a]	−0.556[a]	−0.555[a]	−0.465	0.406	0.3
Stroop interference T-score	0.312	0.206	−0.199	−0.204	−0.188	−0.237	−0.17	−0.008	0.359
WAIS Letter-Number	0.135	−0.295	0.074	−0.647[b]	−0.626[a]	−0.695[b]	−0.611[a]	0.06	0.626[a]
WAIS Similarities	0.34	−0.341	0.195	−0.295	−0.121	−0.373	−0.247	0.016	0.315
WAIS Digit Span	0.038	−0.276	−0.073	−0.584[a]	−0.41	−0.525[a]	−0.33	0.269	0.624[a]
WAIS Digit Forward percentile	0.163	0.348	0.213	0.577[a]	0.396	0.519*[a]	0.307	−0.333	−0.556[a]
MicroCog time 1	0.236	−0.031	0.718[b]	−0.386	−0.259	−0.369	−0.171	−0.02	0.216
MicroCog time 2	0.246	−0.273	0.635[a]	−0.366	−0.16	−0.378	−0.21	0.044	0.2

Abbreviations: FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function Scale; FACT-G, Functional Assessment of Cancer Therapy-General Scale; HADS, Hospital Anxiety and Depression Scale; MicroCog, MicroCog Assessment of Cognitive Functioning; QOL, quality of life; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WAIS, Wechsler Adult Intelligence Scale.
[a] $P < .05$.
[b] $P < .01$.

Correlations Between Task Behavior, Brain Activation, Neuropsychological Performance, and PRO Measures

The n-back d′ was normalized to that of the 0-back condition, which was used as pseudofixation for both groups. For 1-back, d′ performance in patients was positively correlated with WAIS Letter-Number Sequencing ($r = 0.52$; $P = .048$) and WAIS Similarities ($r = 0.55$; $P = .025$). No correlations were observed for the 2-back condition. For the recognition memory task, positive correlations were observed in patients between hits and RBANS attention scores ($r = 0.69$; $P = .006$), hits and Trial Making B T-scores ($r = 0.68$; $P = .007$) and between hits and MicroCog time 1 and time 2 standard scores (time 1, $r = 0.63$ [$P = .015$]; time 2, $r = 0.55$ [$P = .044$]). All correlations were uncorrected for multiple comparisons. No correlations were observed in controls between task behavior and any neuropsychological tests. Within the DLPFC, in which significant group differences were observed on the n-back task, no significant correlations were observed between DLPFC BOLD activity and any neuropsychological test or PRO measure for either group.

For controls, MicroCog time 1 was positively correlated with functional well being and FACT-G total scores and was negatively correlated with HADS depression. RBANS attention was positively correlated with FACT-Cog comments from others. For patients, numerous correlations were observed between PRO and neuropsychological measures, as detailed in Table 7. For example, slower reaction times on the MicroCog tests were associated with more negative comments from others regarding their cognition. Surprisingly, physical and functional well being were negatively associated with performance on the RBANS total index score and the WAIS letter-number scaled score. Similarly, FACT-G total scores were negatively correlated with several measures of memory and working memory, and a higher level of self-reported depression symptoms was correlated with better performance on working memory tasks. None of the correlations survived multiple comparison correction.

DISCUSSION

The primary finding of this study was that oncology patients exhibited reduced activation in the DLPFC during a working memory task compared with controls. This research extends and helps clarify a growing body of literature that links working memory deficits in oncology patients to aberrant activity in frontal brain regions.[16,17] Our results remained unchanged after covarying for fatigue, depression, and anxiety, suggesting that oncology

patients did not recruit the right DLPFC sufficiently to perform this task. Another finding was that oncology patients exhibited hypoactivation during visual recognition in the left hippocampus, a brain region involved in encoding and retrieval in episodic memory and in the maintenance of learned information. These functional deficits are consistent with findings in oncology patients exhibiting reduced gray matter in the frontal and MTL regions.[9] Similarly, studies in human and animal models have linked a pattern of white matter degradation in frontotemporal circuits to chemotherapy-related cognitive decline.[37]

Our secondary hypothesis was that patients would differ from controls on behavioral correlates of working memory and visuospatial recognition memory. For the working memory task, moderate effect sizes indicated that oncology patients performed worse than controls as task difficulty increased from 0-back to 2-back (Table 4). Patients had more missed items in recognition performance, suggesting that oncology patients may have a specific problem encoding and maintaining initially acquired information. This is plausible considering that the participants viewed the fractals without knowing that they would later perform a recognition task.

Finally, we explored associations between task behavior, neuropsychological test performance, and patient-reported cognitive function. Because of our neuropsychological performance criteria, oncology patients had impairments measured in executive functioning, manipulation, attention, and working memory. We observed positive correlations between recognition hit rates and RBANS attention scores, Trail Making B scored, and MicroCog time 1 and time 2 in patients. The effects of chemotherapy may have been driving the deficits in both behavior and neuropsychological performance, resulting in this patient-specific correlation. However, chemotherapy-related impairments, including cancer-related symptom burden, may also contribute to these deficits and will need to be examined in future studies. A growing number of studies reported associations between patient-reported cognitive function and activation or connectivity, even in the absence of impaired performance on neuropsychological tests.[10,16,38] However, in the current study, neuroimaging correlates were not significantly associated with PRO measures, including patient-reported cognitive impairments, fatigue, depression, and anxiety. This may be because of limitations in study design, as outlined below.

Limitations of this study included a relatively small sample size, which likely contributed to the lack of a correlation between patient-reported cognitive function and brain activation. Also, we did not assess for preexisting difficulties or account for insomnia, sleep/wake deficits, or alterations in sleep quality, which commonly affect cancer patients.[39,40] The oncology group was not homogenous in terms of cancer type or sex and included a large proportion of women with breast cancer, which may have resulted in differences in activation and behavior. Furthermore, our paradigm combined encoding of each new image into working memory, reorganization, and inhibition, which made the task particularly difficult as the load increased. Future research should explicitly address differences between encoding and retrieval phases of memory tasks and should attempt to separate the effects of chemotherapy from cancer by assessing patients before and after chemotherapy as well as comorbid symptoms, such as fatigue, sleep disturbances, and emotional distress. We are currently conducting a more comprehensive study of cognition, brain activation, and brain circuitry in CRCI to address many of these limitations.

In summary, the current results demonstrate that CRCI is accompanied by under-recruitment of the DLPFC and hippocampal regions. Follow-up fMRI experiments should examine specific brain circuitries to identify the neural mechanisms, including potential compensatory mechanisms, underlying CRCI.

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CONFLICT OF INTEREST DISCLOSURES

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