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Reduced prefrontal activation during working and long-term memory tasks and impaired patient-reported cognition among cancer survivors post-chemotherapy compared with healthy controls

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Abstract

Background—Patients receiving adjuvant chemotherapy have reported cognitive impairments, which may last years after completion of treatment. Working memory- and long-term memory-related changes in this population are not well understood. In this study we aimed to demonstrate that cancer-related cognitive impairments are associated with under recruitment brain regions involved in working and recognition memory compared to controls.

Method—Oncology patients (n=15) receiving adjuvant chemotherapy with evidence of cognitive impairment by neuropsychological testing and self-report and age/education group-matched, cognitively normal controls (n=14) underwent functional magnetic resonance imaging (fMRI). During fMRI scanning, participants performed a non-verbal 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 left-middle hippocampus compared to controls. Neuroimaging results were not associated with patient-reported cognition.

Conclusion—Decreased recruitment of brain regions associated with working and recognition memory encoding were observed in the oncology group. These results suggest reduced neural functioning post-chemotherapy and corroborate patient-reported cognitive difficulties following cancer treatment, though a direct association was not observed.

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Keywords

fMRI; Cancer-related cognitive impairment (CRCI); working memory; recognition memory; patient-reported outcomes (PRO)

Introduction

Recent studies have shown that cancer patients receiving adjuvant chemotherapy experience cancer-related cognitive impairments (CRCI)[1] that can negatively impact a patient's daily life[2, 3 4]. CRCI manifests as difficulty in real-life routines such as remembering phone numbers[5], or deficits in laboratory tests such as working memory [6] and learning new information (i.e. 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 EEG study has shown that prolonged exposure to chemotherapeutic agents is associated with decreases in hippocampal neurogenesis and theta-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 of CRCI studies using neuroimaging [4, 9] neuropsychological tests[14], and patient-report[15] are not consistent; many brain regions have been implicated, but with high variability from study to study (see recent review by Scherling and Smith[4]). There is also substantial variability 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 aim of this study was to demonstrate that patients who underwent adjuvant chemotherapy experience cancer-related cognitive impairments related to under recruitment of brain regions involved in working and recognition memory compared to controls. In this study we utilized all three approaches (i.e., 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 those involved in recognition, we examined non-verbal 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]. Damage to the MTL has been shown to impact 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.

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 upon 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 where ineligible, 59 refused to participate, and 49 were consented. Healthy controls were recruited through flyers and by word of mouth. Forty-six controls were identified as potentially eligible, 7 were ineligible, 5 refused and 34 were consented. All consented participants, 49 patients and 34 controls, completed neuropsychological tests and patient-reported outcomes (PRO). Participants were then included or excluded from the study based on their neuropsychological performance (see participants section). Controls performing within normal range were selected to group-match the patients on demographics and then underwent the same MRI procedure. In total, 16 patients and 16 controls underwent MRI and were included in the study. Details on the procedures for participant selection, neuropsychological test battery, patient-reported outcome, MRI, behavior, and image processing and statistical analysis are described below.

Participants

Eligibility criteria for patients included solid, non-central nervous system tumor or hematologic malignancy of any stage, physician-rated Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2[25], and completion of 3 or more cycles of chemotherapy within the previous 6 months. Patients or controls were excluded if they had premorbid cognitive dysfunction, or comorbidities known to be associated with cognitive impairment (such as major depression or generalized anxiety[26]). Eligibility criteria for patients included impairment in cognitive domains (≥1 standard deviation below the mean on at least three domains, or ≥1.5 standard deviations below the mean on at least one or more domains, consistent with International Cognition and Cancer Task Force recommendations[23]). Eligibility criteria for controls 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: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail making Tests A and B, Stroop Color-Word Test, Test of Nonverbal Intelligence (TONI-III), Wechsler Adult Intelligence Scale (WAIS-III) Similarities, Digit Span, and Letter-Number Sequencing subscales, and MicroCog Assessment of Cognitive Functioning [27] with reaction time.

Patient-Reported Outcome

A battery of PRO and health-related quality of life (HRQL) measures was administered to participants to quantify patient-reported cognitive problems, overall functional status and well-being. These include: Functional Assessment of Cancer Therapy-Cognitive Function Scale version 1 (FACT-Cog v1) [28], FACT-General (FACT-G)[29], FACT-Fatigue[30], and Hospital Anxiety and Depression Scale (HADS)[31]. All FACT questionnaires assessed for difficulties experienced within the previous 7 days. FACT-Cog v1 (reliability alpha=0.96[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. FACT-G assesses physical, social, emotional, and functional well-being, with higher scores indicating better quality of life. 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 was also provided for each patient.

MRI, Behavior, and Image Processing

All participants who were included in the study underwent magnetic resonance imaging (MRI) on a Siemens 3T Trio scanner. Functional MRI (fMRI) data were acquired using a susceptibility-weighted echo-planar imaging sequence (TR=2200ms, TE=20ms, flip angle=80°, matrix=64×64, resolution=3.4375×3.4375×3mm^3). A T1-weighted MPRAGE image was also acquired (TR=2100ms, TE=4.38ms, flip angle=8, matrix=256×192, resolution=0.859×0.859×1mm^3). During fMRI, participants performed non-verbal n-back (0-, 1-, and 2-back) visual working memory and recognition tasks adapted from Ragland et al [33]. Stimuli were presented to subjects using Cogent 2000 and Cogent graphics software (http://www.vislab.ucl.ac.uk/cogent_2000.php) running in the Matlab environment (Mathworks, Natick MA).

During the n-back task, we employed a blocked design, with each block lasting 33.75sec and repeated 3 times in a pseudo-randomized order. Within each block, 39 fractal images were presented sequentially for 500ms with a 375ms inter-stimulus interval. Participants pressed a button to indicate whether or not the fractal image on the screen was the same as the one shown either 0, 1, or 2 items before (Figure 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 interleaved with 22 new images (foils). Test fractals were presented one at a time in random order for 500ms. 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-prime (d′) (pHits - pFalseAlarms) for each of the 0, 1, and 2-back conditions.

Preprocessing of fMRI data was performed with AFNI and included: exclusion of the first three volumes in each run, slice-timing and motion correction, co-registration to the participant's T1-weighted image, spatial normalization to the Talairach-Tournoux template with atlas regions of interest, and resampling to 3.25mm^3 resolution. Data were then spatially smoothed with Gaussian kernel to a resolution of 8mm FWHM followed by linear

regression with a model hemodynamic response function (HRF) and its temporal derivative for each block and each task. *A priori* regions of interest (e.g., MTL) were analyzed for the recognition task.

Statistical Analysis

For neuropsychological testing, PRO, and n-back behavioral data, student t-tests and effect sizes (Cohen's D) were used to compare groups with SPSS 21.0 (SPSS Inc., Chicago, IL). For recognition memory performance, a 2 × 2 mixed repeated-measures ANOVA and post-hoc t-tests were used to test for the main effects of recognition (hits vs. misses), group and recognition×group interaction. 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 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 $p<0.05$ with individual voxel threshold at $p<0.001$ and 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 found. We therefore 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 showing significant group differences in any of the above comparisons, by conducting Pearson correlation analyses between regional BOLD activity and neuropsychological test and patient-reported cognitive function. For neuropsychological test comparisons, we used 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 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 showed significant group differences. All correlation analyses were performed in patient and control groups separately, and were not corrected for multiple comparisons.

Results

Participant Demographics

Originally 16 oncology patients and 16 healthy controls were included in this study. Three were subsequently removed from analysis because one patient had difficulty understanding directions for the button press and two controls had insufficient trials on the recognition task. A total of 15 oncology patients and 14 controls were included in the final analysis reported here. These subjects showed no group differences in age, education, gender or race

(Table 1). The majority of patients (53.3%) had an ECOG performance status of 0, with 27% at 1 and 20% at 2. Diagnoses included breast cancer (73.3%), colorectal cancer (6.7%), Hodgkin's lymphoma (6.7%), leukemia (6.7%), and myeloma (6.7%).

Neuropsychological Tests

As expected (see eligibility criteria), patients scored significantly lower than controls in most of the cognitive domains, indicating impairment (Table 2). The groups did not differ on Trails A, B, Stroop Interference, TONI-III, and Digits Backwards.

Patient-Reported Outcomes

On 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 compared to controls. Regarding HRQL, on FACT-G patients reported decreased physical and functional well-being, but comparable social and emotional well-being. Compared to controls, patients indicated greater fatigue on the FACT-Fatigue 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 (Figure 2, Table 4). However, moderately reduced effect sizes were observed between groups in d′ and accuracy for 0-back.

N-back fMRI

Oncology patients demonstrated significantly reduced activation compared to controls in the right dorsolateral prefrontal cortex (DLPFC, Brodmann Area 9/10) when the 1-back and 2-back data were averaged and contrasted with the 0-back data (Figure 3, Table 5). These differences remained after covarying for fatigue, anxiety and depression, which can negatively affect working memory performance[36, 37] 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 found a significant main effect of recognition response [$F(1,24)=16.48$, $MSE=0.07$, $p<0.001$, $p\eta^2=0.41$] and a significant recognition response×group interaction [$F(1,24)=6.76$, $MSE=0.072$, $p<0.02$, $p\eta^2=0.22$]. A Post hoc t-test revealed that this interaction was driven by a significant reduction in the proportion of correct hit responses given by patients (55%) compared to controls (75%). We also observed a trend for higher false alarm rates in patients (11%) compared to controls (7%). Overall mean recognition accuracy was statistically poorer for patients compared to controls.

Recognition fMRI

The initial fMRI recognition analysis did not reveal any significant regional differences between groups after correcting for multiple comparisons. Based on *a priori* hypotheses that

the MTL may be especially susceptible to chemotherapy neurotoxicity, we performed an exploratory analysis in this region. We found that a small, 5-voxel cluster of decreased activation in patients in the left-middle hippocampus (p=0.01 voxel-wise uncorrected, Figure 4B).

Correlations Between Task Behavior, Brain Activation, Neuropsychological Performance and Patient-Reported Outcomes Measures

The n-back d′ was normalized to that of the 0-back condition, which was used as pseudo fixation for both groups. For 1-back, d′ performance in patients was positively correlated with WAIS Letter-Number sequencing (r=0.52, p=0.048) and WAIS Similarities (r=0.55, p=0.025). No correlations were observed for 2-back. For the recognition memory task, positive correlations were observed in patients between hits and RBANS attention scores (r=0.69, p=0.006), hits and Trial Making B T-scores (r=0.68, p=0.007), hits and MicroCog time 1 and time 2 standard scores (time 1 r=0.63, p=0.015; time 2 r=0.55, p=0.044). All correlations were uncorrected for multiple comparisons. No correlations were observed in controls between task behavior and any neuropsychological tests. Within DLPFC, where significant group differences were found 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, and 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; a detailed table can be found in Supplementary Table 1. 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 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 showed reduced activation in the DLPFC during a working memory task, as compared with controls. This research extends and helps clarify a growing 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 showing reduced gray matter in frontal and MTL regions [9].

Similarly, studies in human and animal models have linked a pattern of white matter degradation in fronto-temporal circuits to chemotherapy-related cognitive decline[39].

Secondarily, we hypothesized 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- to 2-back (Table 4). Patients showed 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. Due to our criteria on neuropsychological performance, oncology patients showed impairments in executive functioning, manipulation, attention, and working memory. We observed positive correlations between recognition hit rates and RBANS attention scores, Trail Making B and Microcog time 1 and time 2 in patients. The effects of chemotherapy may be 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, 42]. 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 due to limitations in study design outlined below.

Limitations of the study include a relatively small sample size, which likely contributed to the lack of relationship between patient-reported cognitive function and brain activation. Also, we did not assess for pre-existing difficulties, or account for insomnia, sleep/wake deficits or alterations in sleep quality, which has been shown to commonly affect cancer patients[43, 44]. The oncology group was not homogenous in terms of cancer type and gender, and included a large proportion of female breast cancer patients, 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 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, we showed that CRCI was accompanied by under-recruitment of DLPFC and hippocampal regions. Follow-up fMRI experiments should examine specific brain circuitries

to examine the neural mechanisms, including potential compensatory mechanisms underlying CRCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Wagner consulted with Gilead Inc within the past 2 years, interpreting PRO data.

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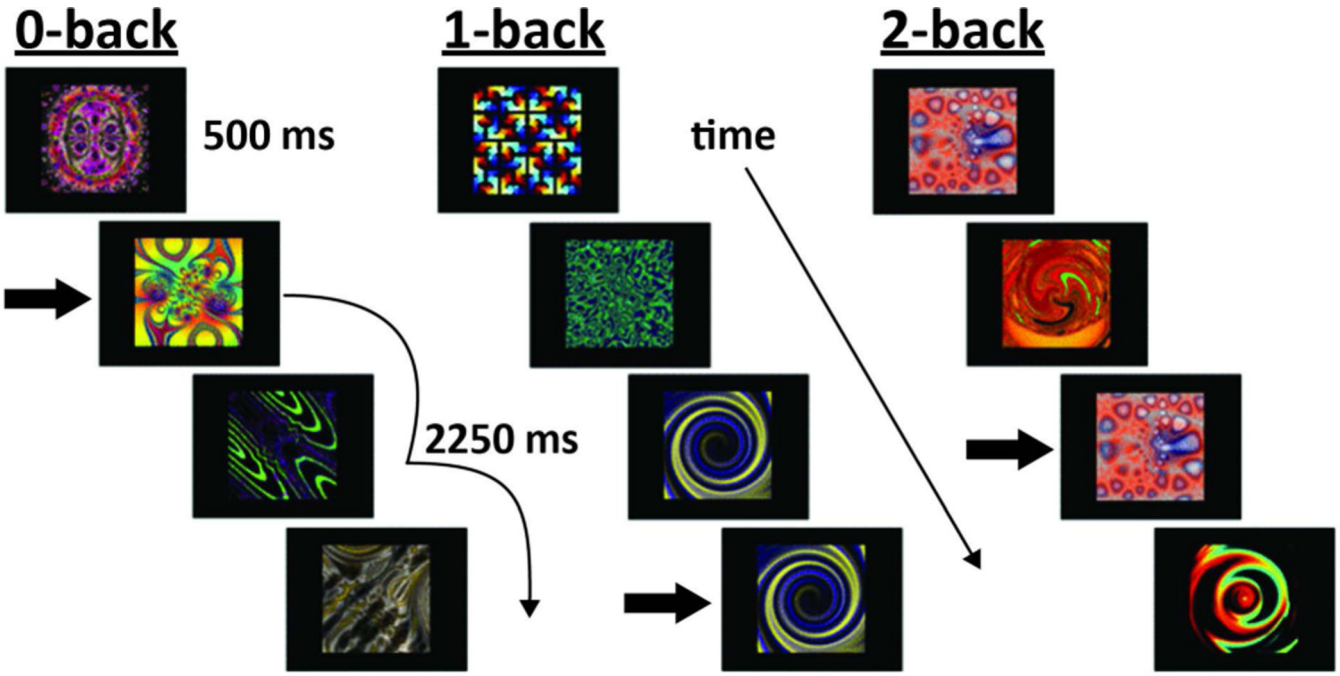

Figure 1. N-back working memory task

In the 0-back condition participants respond whenever the indicated figure appeared, 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. Subjects 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).

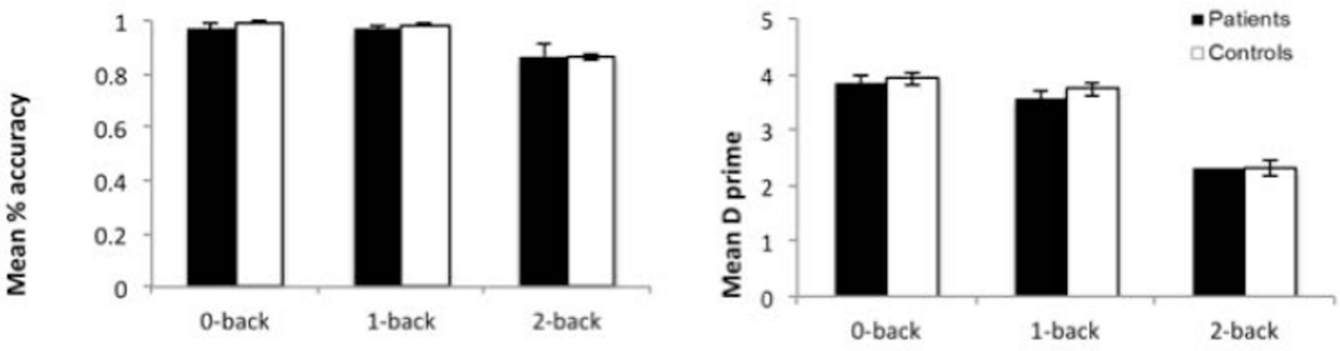

Figure 2. Between-groups behavioral results for the n-back task

Left panel demonstrates mean accuracy and right panel demonstrates mean d-prime. While there were no statistically significant differences between groups for each n-back condition, the differences for the 0- and 1-back conditions showed moderate effects sizes.

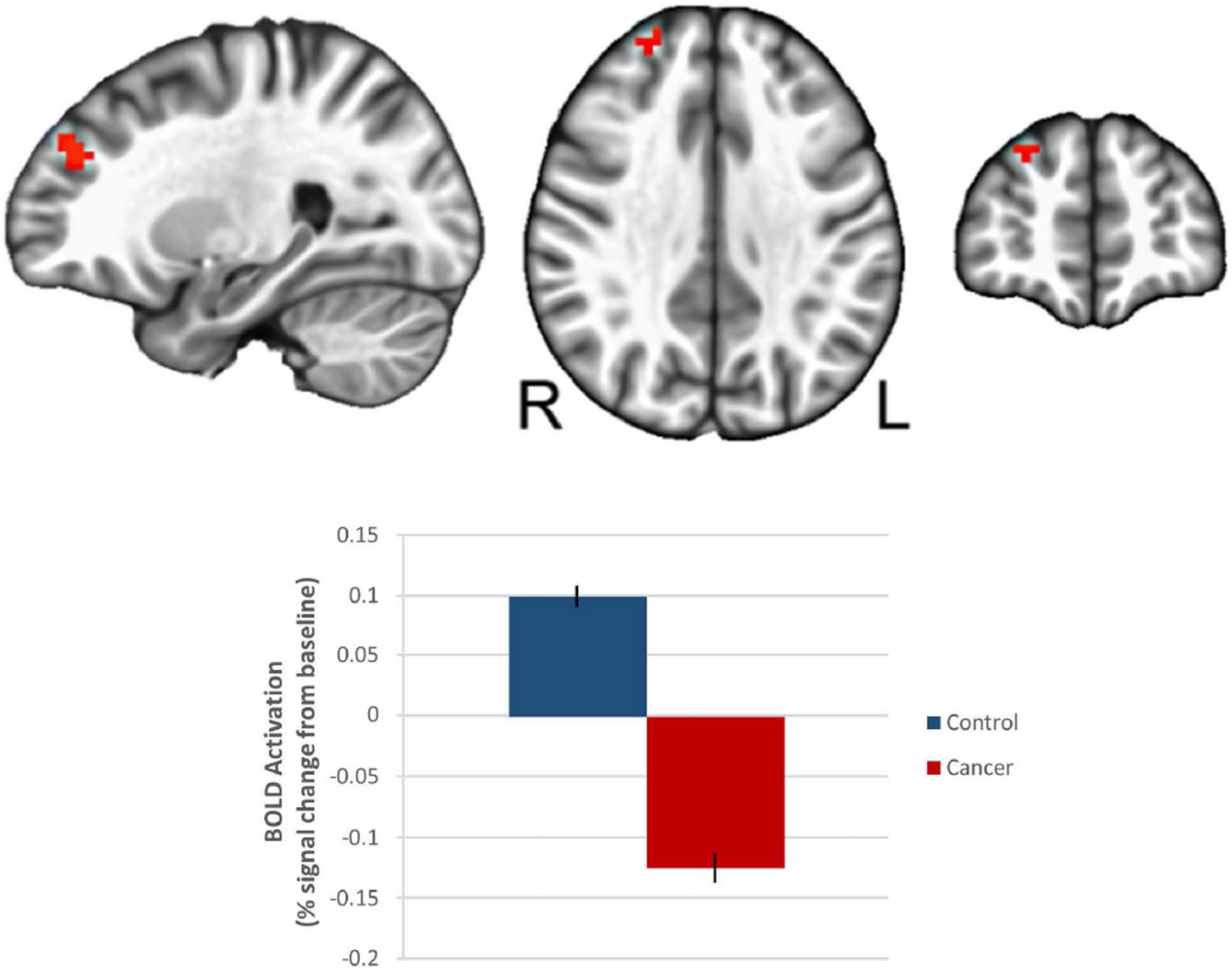

Figure 3. Between-groups functional differences in the right dorsolateral prefrontal cortex for the n-back working memory task

Oncology patients show significantly decreased BOLD activation in right dorsolateral prefrontal cortex as compared with controls.

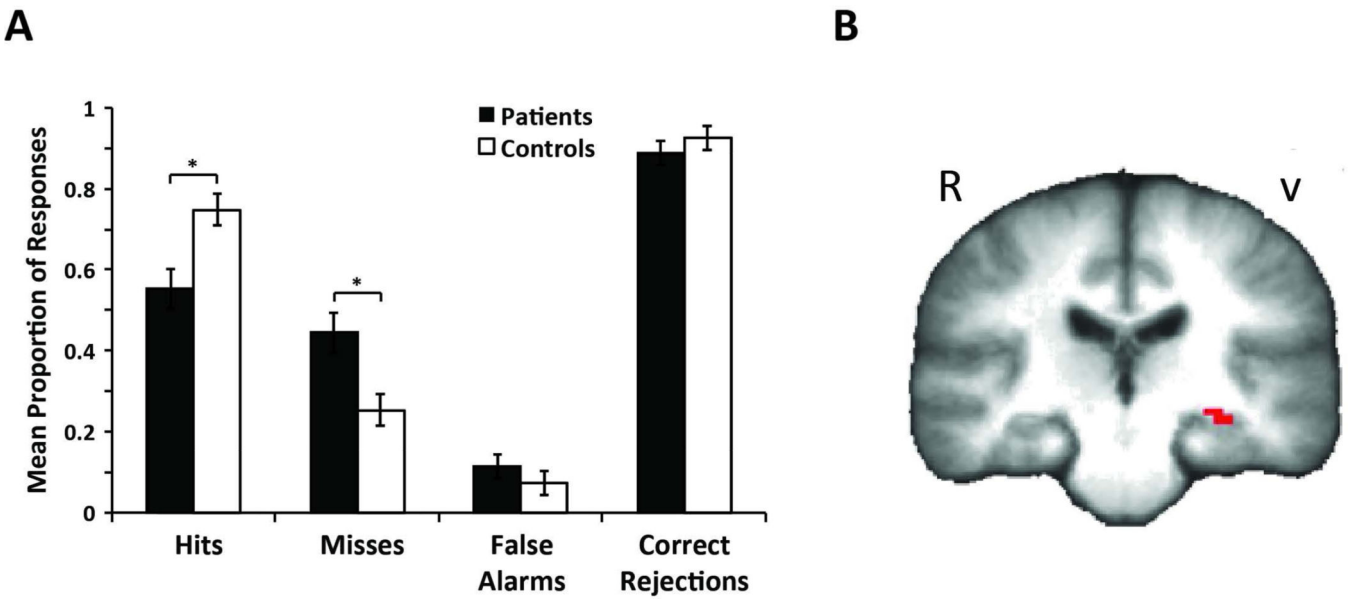

Figure 4. Between-group behavioral and functional differences in recognition task

A. Proportion of hits, misses, false alarms and correct rejections for the visual recognition task. **B**. Controls show increased activation when contrasting hits to correct rejections in the middle hippocampus. Regions of increased activation not displayed also include left lateral parietal cortex, left fusiform gyrus, and left lateral occipital cortex. Conversely, oncology patients showed decreased activation than controls in the left hippocampus.

Table 1

Demographic information for oncology and control groups.

	Oncology Patients (*N*=15)	**Controls (*N*=14)**	**P Value**
Gender (Male/Female)	86.7% female	92.9% female	0.58
Race (Caucasian/AA)	86.7% White, 13.3% Black	78.6% White, 21.4% Black	0.56
Age: mean (SD)	50.7 (± 7.5) years	53.0 (±7.2) years	0.42
Education: mean (SD)	15.6 (±2.3) years	16.8 (±2.2) years	0.16
Handedness (L/R)	1/14	1/13	0.93
Physician-rated ECOG performance status	53.3% 0 26.7% 1 20.0% 2	N/A	--
Cancer diagnosis	73.3% breast 6.7% colo-rectal 6.7% Hodgkin's lymphoma 6.7% leukemia 6.7% myeloma	N/A	--
Extent of disease	20.0% No evidence of disease 26.7% local 13.3% regional 20.0 % metastatic 20.0 % N/A	N/A	--

Table 2

Neuropsychological test scores for oncology patients and controls.

Mean ± SD	Oncology patients	Controls	P Value	Cohen's D
RBANS Percentile				
Immediate memory	39.5±32.7	67.9±14.1	0.006	1.111
Delayed memory	30.0±27.2	55.8±17.6	0.005	1.112
Visuospatial/Constructional	17.7±23.7	57.8±23.8	<0.001	1.684
Language	31.7±20.6	56.0±20.0	0.003	1.196
Attention	44.1±28.6	80.6±21.2	0.001	1.445
Total Index	24.3±19.9	69.1±19.6	<0.001	2.262
Trails A T-score	48.2±7.0	53.6±7.8	0.062	0.723
Trails B T-score	48.9±11.2	55.2±10.6	0.133	0.576
Stroop Interference T-score	48.2±6.5	52.2±5.1	0.076	0.686
TONI-III Percentile	52.0±30.0	55.0±25.4	0.769	0.112
WAIS-III				
Letter-Number age ss	9.9±3.3	12.6±2.6	0.018	0.933
Similarities age ss	10.2±3.0	12.8±2.3	0.014	0.973
Digit Span age ss	9.87±3.4	13.08±2.3	0.009	1.062
Digits forward cumulative percentile	58.8±35.1	31.0±19.4	0.015	0.961
Digits backward cumulative percentile	62.0±33.3	48.6±34.5	0.304	0.398
MicroCog Total Reaction Time ss				
Timer 1	10.5±2.4	12.1±1.9	0.031	0.747
Timer 2	9.2±3.7	11.7±1.9	0.031	0.848

Table 3

Patient-reported outcomes measures for oncology patients and controls.

Mean ± SD	Oncology Patients	Controls	P Value	Cohen's D
FACT-Cog v1				
Perceived Cognitive Impairments (0–80)	38.44±16.11	67.85±8.36	<0.001	2.267
Impact on QOL (0–16)	11.00±4.78	14.93±1.94	0.009	1.063
Comments from Others (0–16)	11 .91±3.47	15.43±1.14	0.002	1.342
FACT-Cog total (0–108)	80.17±14.15	91.76±9.82	0.017	0.945
FACT-G				
Physical Wellbeing (0–28)	18.40±7.60	25.92±2.47	0.002	1.311
Social Wellbeing (0–28)	22.97±2.86	22.38±4.13	0.655	0.168
Emotional Wellbeing (0–24)	20.07±3.41	20.46±2.98	0.741	0.124
Functional Wellbeing (0–28)	18.73±6.51	23.00±4.05	0.045	0.781
FACT-Fatigue (0–52)	33.00±15.03	46.21±5.91	0.005	1.142
HADS				
Anxiety (0–20)	6.40±4.24	3.71±2.46	0.049	0.768
Depression (0–20)	4.07±4.10	1.21±1.48	0.021	0.913

Table 4

N-back working memory behavior results for oncology patients and controls. Results show 0-back and combined 1- 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.

	0 back							1- 2-back combined						
	Mean % accuracy (SD)	**Mean RT (ms) (SD)**	**Sensitivity d′ (SD)**	**Hits (SD)**	**Misses (SD)**	**False Alarms (SD)**	**Correct Rejections (SD)**	**Mean % accuracy (SD)**	**Mean RT (ms) (SD)**	**Sensitivity d′ (SD)**	**Hits (SD)**	**Misses (SD)**	**False Alarms (SD)**	**Correct Rejections (SD)**
Oncology	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)
Controls	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's 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

Table 5

Oncology patients demonstrated significantly reduced activation compared to controls in the right dorsolateral prefrontal cortex (DLPFC, Brodmann Area 9/10) when the 1-back and 2-back data were averaged and contrasted with the 0-back data.

Region With Peak Activation	Hem	"BA"	Center of Mass Coordinates			Peak *T* Value	Cluster Size (in mm^3)	Cluster Size (in voxels)
			L/R	A/P	S/I			
Control subjects > cancer subjects								
Dorsolateral prefrontal cortex	R	9,10	−25	−47	31	3.86	618	18

Table 6

Recognition behavior results for oncology patients and controls

				Old Items		New Items	
	Mean Accuracy (SD)	**Mean RT (ms) (SD)**	**Sensitivity d′ (SD)**	**Hits (SD)**	**Misses (SD)**	**False Alarms (SD)**	**Correct Rejections (SD)**
Oncology	0.72** (0.09)	1227.95 (214.3)	1.99 (1.2)	0.55* (0.2)	0.44* (0.2)	0.11 (0.1)	0.89 (0.1)
Controls	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's d)	1.19	0.20	.86	1.26	0.95	0.40	0.30

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.

* $p<0.05$

** $p<0.01$