Neuroimaging of Executive Function in Survivors of Pediatric Brain Tumors and Healthy Controls

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Objective: Research on the long-term sequelae of treatment for pediatric brain tumors has identified significant neurocognitive deficits experienced by many survivors. Despite indications of deficits based on cognitive assessment, the identification of specific neurobiological mechanisms of these deficits using neuroimaging techniques has yet to be considered. *Method:* This study used norm-referenced standardized assessment and functional MRI (fMRI) to examine attention and executive functioning deficits of survivors of pediatric brain tumors, as compared with healthy children. *Results:* Survivors of pediatric brain tumors performed more poorly than healthy children on measures of overall cognitive ability, attention, and executive function during testing, as well as on a working memory task during fMRI. Survivors showed lower blood-oxygen level dependent (BOLD) signal in bilateral frontal regions associated with sustained attention (BA6/8) and greater BOLD signal in left cingulate regions associated with complex problem-solving and performance monitoring (BA32) during working memory task completion. Both group and brain activation accounted for significant variance in neurocognitive functioning. *Conclusions:* Survivors of pediatric brain tumor and healthy children differed in brain activation during completion of a working memory task, and brain activation was associated with deficits noted in testing. These findings may improve understanding of mechanisms of cognitive deficits and avenues for intervention for children with brain tumors.

Keywords: brain tumor, children, fMRI, late effects, working memory

Pediatric brain tumors are the most common solid tumor diagnosis of childhood. Over 4,000 children are diagnosed with a brain tumor each year, with over 70% of these diagnoses occurring in children under 15 years of age (Central Brain Tumor Registry of the United States [CBTRUS], 2012). Survival rates currently exceed 70%, and increased attention has been given to late effects experienced by survivors. Research has identified a range of late effects, including significant neurocognitive consequences in a variety of broad (overall intellectual functioning) and specific domains (see Robinson, Kuttesch, et al., 2010 for a meta-analytic review). One especially important domain implicated in studies of deficits in survivors is executive function, as these higher order cognitive processes become increasingly important in adolescence as maturation of the frontal lobes allows children to better integrate complex information and regulate emotions (e.g., Lezak, Howieson, & Loring, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna & Sweeney, 2004). Research on neurocognitive late effects has documented poorer performance on measures of global executive function, as well as more specific skills like working memory and sustained attention (Ullrich, 2009). Moreover, some have suggested that declines noted in global measures (e.g., IQ) may be attributable to deficits in basic processes of sustained attention (Mulhern et al., 1998; Rodgers, Horrocks, Britton, & Kernahan, 1999). The ability to control and sustain attention is essential for more complex executive functions, including successful problem solving, working memory, and engaging in goal-directed behavior.

Relatively little research has examined the neurobiological underpinnings of attention and executive function deficits in survivors of pediatric brain tumors, and most of these studies considered the impact of reduced white matter volumes and integrity (e.g., Aukema et al., 2009; Mulhern et al., 2004). These studies found that reduction in white matter integrity was associated with poorer performance on continuous performance tasks (Mulhern et al., 2004) and slower processing speed (Aukema et al., 2009). However, fewer studies have used functional neuroimaging to explore these associations. Recent neuroimaging studies with other populations have found that neurobiological underpinnings of executive function involve the prefrontal cortex, anterior cingulate cortex, and other frontal and parietal regions, as well as their coordination (Tamnes et al., 2010). These regions are among the last to myelinate, and their development continues through adolescence, leaving them potentially more susceptible to insult during treatment.

Although neuroimaging of these processes in survivors of pediatric brain tumors has been limited, similar studies in other pediatric populations provides a framework for conceptualizing these processes and their possible impact on other areas of functioning. Several of these studies have included an *n*-back task. *n*-Back tasks require an individual to "monitor a series of stimuli and to respond whenever a stimulus is presented that is the same as the one presented *n* trials previously, where *n* is a prespecified integer" (Owen, McMillan, Laird, & Bullmore, 2005, p. 47). For example, in a sample of survivors of traumatic brain injury relative to healthy controls, McAllister et al. (1999) found that although similar neurobiological networks subserved successful completion of an *n*-back task, regional ratios of oxygenated to deoxygenated hemoglobin (i.e., BOLD signal) at different levels of task difficulty differed between groups. Specifically, survivors of traumatic brain injury showed increased BOLD signal in prefrontal and parietal areas at more difficult levels of the *n*-back, whereas healthy children showed minimal relative increases in BOLD signal as task difficulty increased. Similar patterns of compensatory activation were found in a recent study on working memory deficits in survivors of pediatric leukemia (Robinson, Livesay, et al., 2010). In this study, leukemia survivors showed increased BOLD signal in areas of the prefrontal and anterior cingulate cortex, relative to healthy children, at more difficult levels of a verbal *n*-back task.

Research on functional underpinnings of executive function deficits in survivors is an important next step in understanding these deficits following treatment for pediatric brain tumors. This may be particularly useful, as only a subset of survivors experience deficits in these areas. Additionally, few studies to date have examined how patterns of functional activation are associated with task performance and performance on standardized assessment measures outside of the scanner. Therefore, the current study examines attention and working memory in survivors of pediatric brain tumors relative to healthy children and explores the associations among activation in regions of the prefrontal cortex and other indicators of neurocognitive functioning. We anticipated that survivors of pediatric brain tumors would perform more poorly than healthy children on measures of neurocognitive functioning, including measures of attention, overall intellectual functioning, and executive functions, both outside and inside the scanner. We also explored the extent to which group versus patterns of regional brain activation, measured during completion of a working memory task, accounted for variance in neurocognitive functioning.

Method

Participants

Participants were 17 pediatric brain tumor survivors and 15 healthy controls. The 17 brain tumor survivors (10 girls) and 15 healthy controls (9 girls) are a subset of the overall sample of participants in a study of the neurocognitive functioning of survivors of pediatric brain tumor. Twenty-six children who were at least 2 years postdiagnosis were invited to participate in the study. Survivors were identified through the cancer survivorship clinic, the Department of Pediatric Hematology/Oncology, or the Department of Neurosurgery at a university children's hospital. Survivors were invited to participate if they met the following inclusion criteria: (a) 8 to 16 years old at the time of enrollment, (b) completed treatment for a pediatric brain tumor, (c) in first continuous remission, and (d) English speaking. Exclusion criteria included the following: (a) history of a known preexisting neurodevelopmental disorder, (b) history of very low birth weight (< 1500 g), (c) history of secondary malignancies or relapses. Procedures were approved by the Institutional Review Board at Vanderbilt University, and informed consent and assent were obtained from all participants. Of the 26 contacted, 21 agreed to participate and enrolled in the study. Two children declined because of lack of interest, two families had moved out of the area, and one child agreed to participate but relapsed before formal enrollment. Of the 21 who participated in the study, three survivors' data were excluded from the present analyses because of missing data, and one participant's data were excluded because of excessive motion during fMRI.

Twenty-seven healthy children were contacted to serve as a control group, and were matched as closely as possible to the sample of survivors by age and gender. Of these 27, 20 were eligible, agreed to participate, and enrolled in the study. Three children were excluded from initial recruitment because of a preexisting neurodevelopmental disorder, two declined because of lack of interest, and two had orthodontic devices that precluded undergoing MRI. Of the 20 who participated, two healthy controls did not return for their scanning appointment, and three healthy controls' data was excluded because of excessive motion during fMRI, yielding 15 healthy controls included in the present analyses. In addition to the above exclusion criteria, both survivors and healthy controls were required to complete screening per imaging center protocol to detect metallic devices or implants that are incompatible with MRI. Children with braces were also excluded, as metallic orthodontic devices can distort acquired images.

Survivors and healthy controls included in these analyses did not differ in age at participation, gender distribution, race, parent education, family income, history of attention deficit hyperactivity disorder medication by parent report, and history of diagnosis of and/or treatment for psychological problems by parent report ($ps > .05$; Table 1). For survivors, mean age at diagnosis was 6.94 years ($SD = 2.41$; range 2.06–11.62 years) and survivors were on average 5.64 years postdiagnosis ($SD = 2.90$; range 2.14–10.92 years) and 5.29 years posttreatment ($SD = 2.83$; range 2.13–10.92 years) at the time of participation. Tumor pathologies included

Table 1
Group Comparisons on Demographic Information[a]

	Survivors (n = 17)	Healthy controls (n = 15)	t/χ^2	p
Demographics				
Child age	12.60 (2.48)	12.90 (2.78)	−0.33	.74
Child gender	35.3% Female	60.0% Female	1.95	.16
Child race	94.1% White	66.7% White	4.28	.23
Parent marital status	70.6% Married	66.7% Married	2.07	.56
Parent education	4.94 (1.56)	6.00 (0.93)	5.38	.37
Family income	6.53 (2.72)	6.07 (2.46)	5.66	.69
Relevant history				
ADHD meds	11.8% Yes	26.7% Yes	1.16	.28
Mental health Tx	35.3% Yes	13.3% Yes	2.05	.15

Note. For survivors, a mean parent education of 4.94 corresponds to some college education. For healthy controls, a mean parent education of 6.00 corresponds to some post-graduate education. For both groups, family income of 6.53 and 6.07 correspond to an income range of $60,000 to $70,000. ADHD = attention deficit hyperactivity disorder.
[a] Values in parentheses indicate standard deviation.

pilocytic astrocytoma (n = 9), posterior fossa medulloblastoma (n = 4), dysembryoplastic neuroepithelial tumor (n = 3), and craniopharyngioma (n = 1). Tumor locations included the posterior fossa (n = 13), parietal lobe (n = 2), temporal lobe (n = 1), and pituitary gland (n = 1). All survivors underwent surgical resection and five received both chemotherapy and cranial radiation. Of those who received cranial radiation, average cumulative dose was 54.8 Gy (SD = 1.04; range 54.0–56.0 Gy). All participants were right-handed.

Measures

Questionnaires. Parents of participants completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) as a measure of survivors' and controls' emotional and behavioral adjustment. These scales have strong test–retest reliability and criterion validity. The Attention Problems scale reflects symptoms of attention deficit disorder and was the focus of the current analyses. Parents also completed the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) as a measure of survivors' and controls' executive function difficulties in the daily environment. Three composite scores, the Behavioral Regulation Index, Metacognition Index, and General Executive Composite, were calculated. The BRIEF has demonstrated both high internal consistency (α = .80–.98) and test–retest reliability (r = .82).

Cognitive assessment. The Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV; Wechsler, 2003) was administered to children to measure overall cognitive functioning, including general intelligence, working memory, and processing speed. The Wechsler intelligence scales have demonstrated excellent internal consistency (α = .97) and test–retest reliability (r = .93), and convergent and discriminant validity have been established. Subtests of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), a comprehensive battery of tests that assess verbal and nonverbal executive functions, were also administered. These subtests included the Color-Word Interference Test and the Trail Making Test.

Functional neuroimaging. During fMRI, participants completed a letter version of the *n*-back task (Barch, Sheline, Csernansky, & Snyder, 2003), which involves sequences of uppercase consonants and assesses verbal working memory. In the 0-back condition, participants responded to a single target (i.e., V). In the 1-back condition, participants responded when the consonant was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded when the consonant was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the consonant was identical to the one presented three trials prior (e.g., M, T, F, M). Each condition was presented three times in order of increasing difficulty, for a total of 12 blocks. In other words, conditions were presented as 0-back, 1-back, 2-back, 3-back, and repeated in three cycles. Each block contained 15 consonants (trials), 3 of which were target consonants, and a rest period occurred between each condition. This task has been used effectively with children in this age group with no adverse effects (Robinson, Livesay, et al., 2010).

Image Acquisition

Images were collected on a 3 Tesla Philips Achieva (Philips Healthcare, Best, The Netherlands) at the Vanderbilt University Institute of Imaging Science. Imaging consisted of a high resolution 3D anatomical scan using an inversion-prepared spoiled gradient recalled echo sequence, with an inversion time T1 of 400 ms, a repetition time of 15 ms, minimum echo time (3 ms), a matrix size 256×256 for a field of view of $256 \times 256 \times 270$ mm with near isotropic resolution. From this, 33 axial slices obtained at an oblique angle (parallel to the AC-PC plane) were prescribed for the functional data. All functional images were acquired with a gradient echo echo planar imaging pulse sequence, with echo time 30 ms (optimized for $T2^*$ at 3T), flip angle of 70°, repetition time 2000 ms, 33 slices 3.5 mm thick and .35 mm skip, with a field of view of 240×240 (anterior-posterior, right-left) and a matrix size of 80×80 (reconstructed to 128×128) sampled at ± 62.5 kHz. This effectively gives an acquired voxel size of $1.875 \times 1.875 \times$

3.5 mm. During the *n*-back task, each condition contained 15 consonants and a pause between each condition, for a total of 192 dynamic scans per run. Six image volumes were acquired and were discarded to allow magnetization to reach equilibrium before the start of the task.

Data Analysis

FMRI data preparation. Functional data were analyzed using BrainVoyager QX software (Brain Innovation B. V., Maastricht). Functional images from each participant's *n*-back run were corrected for 3D motion and slice-time delays, and linear trends were removed. Additional high-pass filtering was done using a frequency space filter with a cutoff of 2 cycles. Motion correction results were assessed to ensure that all data fell within movement criteria (<3 mm displacement, 3° rotation). One survivor's and three healthy controls' motion exceeded movement criteria, and these participants' data were discarded. All other participants' data fell within movement criteria.

The functional data for each participant were aligned to the participant's high-resolution 3D anatomic dataset. Task time-course reference files were included in individual subject level analyses convolved with a double-gamma haemodynamic response function. Each participant's activation map was normalized to a common reference space (Talairach), using registration techniques. As a result of this technique, the functional data were resampled to a voxel size of 3 × 3 × 3 mm. For the sake of continuity with anatomical images, volume will be described in anatomical voxel size (1 × 1 × 1 mm). For each contrasted load level (e.g., 3-back vs. 0-back), separate whole-brain analyses were completed. These analyses yielded activation maps, and a cluster level threshold was applied to correct for multiple comparisons via 1,000 iterations of a Monte Carlo Simulation. A cluster threshold of 189 voxels was established for examining main effects and interaction patterns of BOLD signal activation. This cluster threshold maintained a significance criterion of $p < .001$. To determine the region in which significant activation occurred, corresponding center-of-gravity coordinates in Talairach space were extracted and regions were defined using Talairach Daemon software (Lancaster et al., 2000). Relevant clusters supported by previous literature were considered further. Finally, between-groups general linear modeling (GLM) analyses were conducted (as described below).

Data analyses. Before hypothesis testing, behavioral, testing, and fMRI data were examined within-group to ensure that individual outliers were not unduly contributing to the results. No data exceeded the threshold of two standard deviations from the group mean, and therefore it is unlikely that individual outliers contribute disproportionally to statistical findings. Independent samples *t* tests were used to compare groups' performance on measures of attention, cognitive functioning, and executive function, as well as parent ratings of executive function in the daily environment; effect sizes (Cohen's *d*) were also calculated for between group comparisons. The individual imaging data were calculated based on a GLM with each level of *n*-back task difficulty as predictors to account for the variance associated with change in the time course of the signal on a voxel-wise level. A random-effects GLM analysis was run and the combined contribution of all subjects from both groups was used to determine relevant regional activation for

increasingly difficult levels of the task. These regions were then used to further interrogate the relationship between activation and other indicators of functioning (see below). Furthermore, a 2 × 2 factor analysis was done to assess the main effects of group, main effect of *n*-back difficulty, and interaction effects. *F* statistics were calculated to measure the degree of activation on a whole-brain level. Bivariate Pearson correlations were conducted to examine the associations among neurocognitive assessment performance, *n*-back task performance, and relative changes in brain activation from the significant clusters described above. For correlation analyses, based on a sample size of 32, correlations of $r > .35$ reached statistical significance at $p < .05$. Finally, analysis of covariance was used to determine whether group or patterns of brain activation, as indicated by relative beta changes, accounted for the variance in neurocognitive functioning. Clusters identified in the between-groups analysis as main effects of group and interaction effects were included.

Results

Questionnaire and Cognitive Assessment

Means, standard deviations, and effect sizes for measures of attention, cognitive functioning, and executive function are reported in Table 2. On the WISC-IV, survivors performed more poorly than healthy children in all domains of functioning ($ps < .05$). Survivors also performed significantly more poorly on the D-KEFS Color-Word Inhibition/Switching task ($p = .011$) and the Trails Letter/Number Switching task ($p = .001$). Based on parent report on the CBCL and BRIEF, survivors displayed significantly more attention problems, as well as problems in executive function in the daily environment, with *t* scores nearly a full standard deviation above the normative mean ($ps < .05$).[1] With the sample of survivors of pediatric brain tumor, time since diagnosis was only associated with perceptual reasoning and overall cognitive ability on the WISC-IV and Color-Word Inhibition/Switching scores on the D-KEFS ($ps < .05$).

Neuroimaging

Task performance. Independent samples *t* tests revealed that groups performed similarly on the *n*-back task in terms of reaction time on all levels of the task ($ps > .05$; see Table 3). Statistically significant differences in accuracy were found between groups. Specifically, survivors' accuracy on the 1-back and 3-back levels, and their overall task accuracy, was significantly worse than healthy controls' ($ps < .05$). Survivors' performance on the 0-back

[1] Because healthy controls' performance fell above the population means on normative measures, one-sample *t* tests were also conducted to determine whether survivors' scores differed from the population mean. On the WISC-IV, survivors performed more poorly than the normative mean on the Working Memory ($p = .003$) and Processing Speed ($p < .001$) indices, and on Full Scale IQ ($p = .020$). On the D-KEFS, survivors performed more poorly than the normative mean on the Trails Letter/ Number Switching task ($p = .005$). Based on parent report, survivors displayed significant difficulties with attention on the CBCL ($p < .001$) as well as significant difficulties in Behavioral Regulation ($p = .003$) and Metacognition ($p = .001$), and on the General Executive Composite ($p = .001$) on the BRIEF.

Table 2
Group Comparisons on Cognitive and Executive Measures[a]

	Survivors (*n* = 17)	Controls (*n* = 15)	*t*(30)	*p*	CI LL	CI UL	Cohen's *d*
CBCL[b]							
Attn problems	59.29 (6.68)	52.87 (4.85)	3.08	.004	2.16	10.69	1.10
BRIEF[b]							
BRI	59.24 (10.84)	49.73 (12.78)	2.29	.029	0.98	18.03	0.81
MI	59.00 (9.52)	51.67 (10.29)	2.22	.034	0.18	14.48	0.78
GEC	59.65 (9.39)	51.13 (10.76)	2.51	.018	1.24	15.79	0.88
WISC-IV[c]							
VCI	100.59 (14.03)	113.73 (10.38)	−2.98	.006	−22.16	−4.13	1.06
PRI	94.12 (17.12)	108.20 (16.51)	−2.36	.025	−26.26	−1.90	0.84
WMI	90.94 (12.47)	101.93 (8.92)	−2.83	.008	−18.92	−3.06	1.01
PSI	84.12 (9.82)	109.73 (12.29)	−6.55	<.001	−33.60	−17.63	2.30
FSIQ	91.82 (13.05)	111.87 (12.58)	−4.41	<.001	−29.33	−10.76	1.56
D-KEFS[d]							
CW Inhib	9.88 (3.33)	11.00 (2.98)	−1.00	.328	−3.41	1.18	0.35
CW Inhib/Sw	8.18 (3.75)	11.20 (2.27)	−2.71	.011	−5.30	−0.75	0.97
Trails L/N	7.65 (3.00)	11.27 (2.58)	−3.64	.001	−5.65	−1.59	1.29

Note. On the CBCL and BRIEF, higher scores indicate more problematic functioning. CI = confidence interval of the difference; LL = lower limit; UL = upper limit; CBCL = Child Behavior Checklist; Attn problems = Attention Problem Scale; BRIEF = Behavior Rating Inventory of Executive Function; BRI = Behavioral Regulation Index; MI = Metacognition Index; GEC = General Executive Composite; WISC-IV = Wechsler Intelligence Scale for Children–Fourth Edition; VCI = WISC Verbal Comprehension Index; PRI = WISC Perceptual Reasoning Index; WMI = WISC Working Memory Index; PSI = WISC Processing Speed Index; FSIQ = WISC Full Scale IQ; D-KEFS = Delis-Kaplan Executive Function System; CW Inhib = D-KEFS color-word inhibition; CW Inhib/Sw = D-KEFS color-word inhibition/switching; Trails L/N = D-KEFS trail making letter/number switching.
[a] Values in parentheses indicate standard deviation. [b] *t* scores with a normative mean of 50 and standard deviation of 10. [c] Composite scores with a normative mean of 100 and standard deviation of 15. [d] Scaled scores with a normative mean of 10 and standard deviation of 3.

and 2-back levels was marginally less accurate than healthy controls' ($p < .10$).

Brain area activation. Between-groups GLM and analysis of covariance was conducted to determine whether survivors and healthy controls differed in their patterns of BOLD signal activation during the *n*-back task. Group by *n*-back task load interactions

were examined first; this analysis yielded one cluster in the left dorsal anterior cingulate cortex (DACC; BA32) where activation significantly differed by group and load level (see Table 4; Figure 1). Further examination of activation patterns indicated that survivors demonstrated greater BOLD signal in the left DACC (BA32) than healthy controls during the 0-back, $t = 3.41$, $p < .01$,

Table 3
Group Comparisons on n-Back Task Performance[a]

	Survivors (*n* = 17)	Controls (*n* = 15)	*t*(30)	*p*	95% CI LL	95% CI UL	Cohen's *d*
Accuracy[b]							
0-back	43.59 (2.81)	44.93 (0.26)	−1.97	.067	−2.83	0.14	0.67
1-back	43.24 (2.88)	44.93 (0.26)	−2.42	.028	−3.23	−0.17	0.83
2-back	41.35 (2.55)	42.87 (1.92)	−1.88	.070	−3.16	0.13	0.67
3-back	37.24 (2.41)	40.87 (1.81)	−4.77	<.001	−5.19	−2.08	1.70
Total	165.41 (9.04)	173.60 (3.18)	−3.50	.002	−13.21	−3.16	1.21
Resp time[c]							
0-back	620.83 (102.10)	591.79 (88.32)	0.84	.405	−41.30	99.38	0.30
1-back	661.13 (127.60)	599.61 (78.69)	1.61	.117	−16.30	139.36	0.58
2-back	763.12 (161.97)	688.30 (151.07)	1.33	.195	−40.44	190.08	0.48
3-back	819.96 (146.67)	830.10 (245.87)	−0.14	.891	−157.72	137.44	0.05
Total	699.18 (104.12)	665.39 (99.49)	0.94	.357	−39.99	107.58	0.33

Note. CI = confidence interval of the difference; LL = lower limit; UL = upper limit; Resp time = response time.
[a] Values in parentheses indicate standard deviation. [b] Scores take into account omission and commission errors. Number indicates total accurate responses of a possible total of 45 (individual levels) or of 180 (total). [c] Response time in milliseconds.

Table 4
Significant Interaction and Main Effects of n-Back Load and Group During the n-Back Task

| | Region | Hemisphere | BA | Talairach Coordinates | | | F | p | # Voxels |
				x	y	z			
ME of Load	MiFG	R	8	33	14	38	18.340	<.000001	12523
	SFG	R	10	26	47	20	9.961	.00001	1049
	ACC	R	32	8.7	30	27	18.221	<.000001	1991
	MeFG	R	10	1.6	45	13	19.206	<.000001	4414
	MeFG	L	6	−0.51	17	44	30.360	<.000001	665
	MiFG	L	8	−24	21	44	12.108	.000001	439
	SFG	L	6	−21	12	54	7.092	.00025	244
	SFG	L	10	−24	47	19	7.576	.00014	389
	PCG	L	6	−24	−1.1	51	23.884	<.000001	421
	PCG	L	6	−40	−5	33	10.853	.000004	2984
ME of Group	MiFG	R	6	32	5.7	39	4.18	<.000001	418
	MeFG	L	8	−3.6	27	42	6.15	<.000001	328
Group × Load Intx	ACC	L	32	−8.9	20	30	4.85	<.000001	256

Note. BA = Brodmann area; MiFG = middle frontal gyrus; SFG = superior frontal gyrus; ACC = anterior cingulate cortex; MeFG = medial frontal gyrus; PCG = precentral gyrus; R = right hemisphere; L = left hemisphere.

1-back, $t = 4.92$, $p < .01$, and 2-back levels, $t = 4.76$, $p < .01$, and marginally greater BOLD signal during the 3-back, $t = 1.74$, $p = .09$. When compared with a baseline, survivors showed a significant increase in BOLD signal in this region during the 1-back, $t = 2.22$, $p = .042$ and 2-back, $t = 2.52$, $p = .023$, whereas healthy children showed a significant decrease relative to baseline during the 1-back, $t = -4.51$, $p < .001$ and 2-back, $t = -4.05$, $p = .001$, indicative of varying amounts of "deactivation."

Between-groups analyses were also conducted to examine the main effect of *n*-back load level and group on BOLD signal activation. Analyses of the main effect of *n*-back load level, collapsing across groups, identified increases in BOLD signal bilaterally in the middle frontal gyrus (MiFG; BA8), superior frontal gyrus (BA6/10), and medial frontal gyrus (MeFG; BA6/10), as well as in the right DACC (BA32) and the left precentral gyrus (BA6). Activation in these areas is consistent with patterns of responding often seen during verbal *n*-back tasks (Owen et al., 2005), and suggests that, as a whole, participants were actively engaged in this task during fMRI. When the main effect of group was examined, collapsing across *n*-back load level, significant differences were noted in clusters in the right MiFG (BA6) and left MeFG (BA8), with healthy control participants demonstrating greater BOLD signal in both regions, regardless of *n*-back level.

Associations Among Domains

Pearson correlations were conducted to examine the interrelationships among child age, gender, BOLD signal activation during the *n*-back task, performance on the *n*-back task, and scores on assessment measures and questionnaires. Child age was not associated with outcome. Child gender was associated with performance on the WISC Working Memory Index (WMI; $r = -.37$, $p = .037$) and Processing Speed Index ($r = -.42$, $p = .017$), and with the D-KEFS Trail Making Task ($r = -.38$, $p = .032$), such that girls performed better than boys. Additional correlations can be found in Table 5. Overall, participants with greater BOLD signal response in the right MiFG (BA6) had higher accuracy scores on the *n*-back task, faster processing speed on the WISC, and better performance on the D-KEFS Trail Making Task. Par-

ticipants with greater BOLD signal response in the left MeFG (BA8) also had higher accuracy scores on the *n*-back task, better performance on most WISC indices, and better performance on the D-KEFS Color/Word and Trail Making Tasks. Finally, participants with greater BOLD signal response in the left DACC (BA32) had worse accuracy scores on the *n*-back task, worse performance on most WISC indices, and had parent ratings of significant executive dysfunction in daily life.

Additional exploratory correlations were conducted within the sample of brain tumor survivors to determine whether time since treatment, chemotherapy, and radiation dosage were associated with performance on the *n*-back task, and scores on assessment measures and questionnaires. Within this small sample of survivors, greater time since treatment was associated with worse performance on the WISC Perceptual Reasoning Index ($r = -.66$, $p = .004$) and FSIQ ($r = -.65$, $p = .004$), and on the D-KEFS Color/Word Switching task ($r = -.62$, $p = .008$).

Finally, analysis of covariance was conducted to determine the extent to which group and BOLD signal activation accounted for aspects of neurocognitive function found to differ between groups. In each analysis, group was entered as the between-subjects covariate and amount of regional BOLD signal activation (as indicated by average beta weights) in the right MiFG (BA6), left MeFG (BA8), and left DACC (BA32) was entered as the independent variable. When predictors of overall cognitive ability, performance on the Trail Making Task, and accuracy on the *n*-back were examined, group accounted for a significant portion of the variance in outcome ($ps < .05$), whereas brain activation did not ($ps > .05$). When the WISC WMI was examined, both group and brain activation in the right MiFG (BA6) accounted for significant portions of the overall variance ($ps < .01$). Similarly, when the WISC Processing Speed Index was examined, both group and brain activation in the left DACC (BA32) accounted for significant portions of the overall variance ($ps < .05$).

Discussion

The development of executive functions during childhood and adolescence is characterized in part by the acquisition and matu-
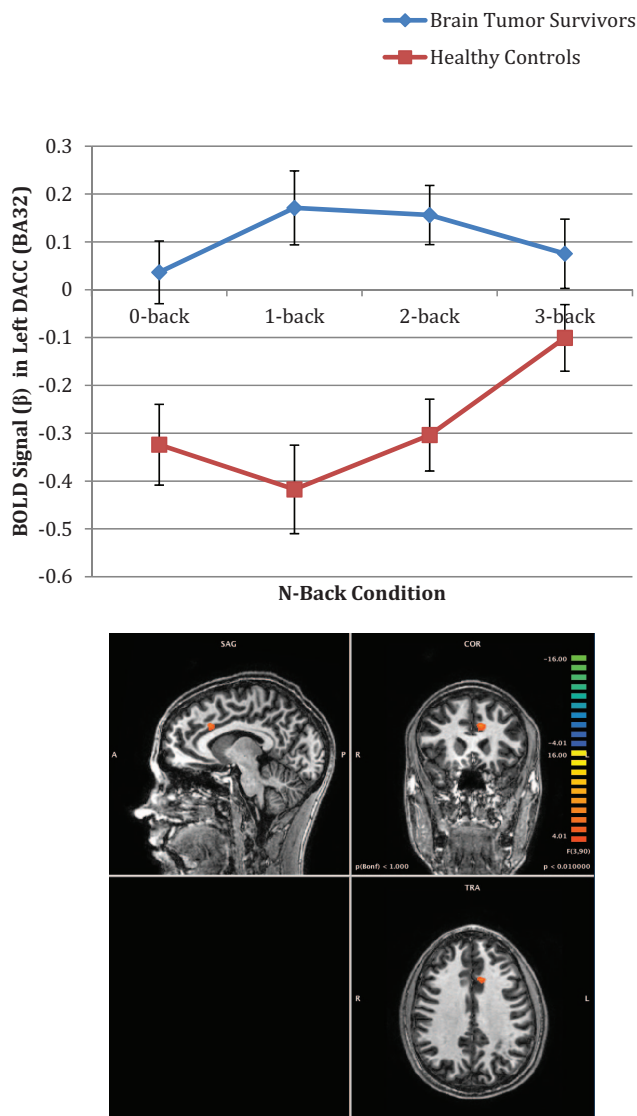
Figure 1. *Note.* Figure depicts average brain activation and corresponding standard error bars in the left dorsal anterior cingulate cortex (DACC; BA32), with center-of-gravity coordinates: x = −8.9, y = 20, z = 30, 256 contiguous voxels. Brain image presented in radiological space (Left = Right).

ration of skills necessary to process and act on increasingly complex information (Luna et al., 2004; Luna & Sweeney, 2004). Working memory, or the ability to hold, manipulate, and retrieve information, is a central component of these higher-order executive processes, and deficits in working memory may impact functioning in a variety of domains. Survivors of pediatric brain tumors are at risk for deficits in executive functions (Ullrich, 2009), and although the neurobiological substrates underlying working memory have been studied in other populations, they have yet to be examined within a sample of survivors of pediatric brain tumors, and the differences in activation between survivors and healthy children is yet unknown.

As hypothesized, survivors in this study performed more poorly than healthy children on several cognitive and neurocognitive tasks. Because the sample of healthy control children performed above average on most of the cognitive tasks, survivors were also compared with normative data and were found to have performed significantly more poorly than normative expectation on measures of working memory, processing speed, overall cognitive ability, and cognitive flexibility. This is consistent with literature outlining the range of late-effects experienced by children with brain tumors after treatment (Robinson, Kuttesch et al., 2010), which documented a mean effect size of Hedges' $g = -0.91$. However, considerable within-group variability highlights the need for better identification of those most at-risk. For example, on the WISC-IV WMI, in the current sample, survivors' scores ranged from 71, which falls in the borderline range and corresponds to the 3rd percentile of a normative sample, to 110, which falls in the high-average range and corresponds to the 75th percentile. This highlights the need for examination of the range of deficits experienced by survivors of pediatric brain tumors, as well as mediators and moderators of risk.

Although survivors of pediatric brain tumors and healthy children recruited similar brain networks during completion of a verbal working memory task, specific differences in magnitudes of activation were found. Specifically, healthy children demonstrated a greater BOLD signal response in areas of the MiFG (BA6) and MeFG (BA8) during task completion. Owen et al. (2005) suggested that activation in such regions underlies maintenance of visuospatial attention, and that this is particularly the case when delays are imposed between stimuli and the response, as occurs in working memory paradigms. Given the positive correlations between *n*-back task performance and activation in these regions, this pattern may indicate that better sustained attention by the healthy controls at more difficult *n*-back levels facilitated better task accuracy. Consistent with this effect, based on parent report on the CBCL, survivors showed significant difficulties with attention relative to healthy children, which is consistent with previous research (e.g., Mulhern et al., 1998; Robinson, Kuttesch et al., 2010). It is possible that survivors who experience deficits in attention also have difficulty engaging requisite brain regions during task completion, or that they are unable to recruit relatively greater amounts of resources to these areas as difficulty increases and corresponding increases in resources are necessary. In a recent intervention study, Zou et al. (2012) examined pre- and postintervention patterns of brain activation during completion of a continuous performance task in survivors of childhood cancer, following participation in a cognitive remediation program. They noted relative increases in activation in BA6 postintervention in survivors, such that their activation was more consistent with that of healthy children. Continuous performance tasks are designed to assess sustained attention, and are similar in presentation modality to the *n*-back task included in the present study (i.e., each involves the sequential presentation of letters). The current findings suggest that attention problems in survivors of childhood brain tumor may show a similar deficit in activation in regions that subserve attention and that these deficits may be amenable to change through cognitive remediation (Zou et al., 2012). Alternatively, some studies have indicated that these regions are involved in maintenance of information in working memory (e.g., Smith & Jonides, 1997). These regions are implicated in tasks requiring executive control and articulatory rehearsal, which are each skills quite necessary to completion of this verbal working memory task. Therefore, the

Table 5
Intercorrelations Among BOLD Signal, Cognitive/Executive Function, and n-Back Task Performance

	n-back	CBCL	BRIEF			WISC-IV					D-KEFS		
	NBAcc	Attn	BRI	MI	GEC	VCI	PRI	WMI	PSI	FSIQ	C/W I	C/W I/S	L/N
MEGp BA6 0-back	.27	−.05	−.13	−.08	−.11	.06	.12	−.08	.46**	.18	.13	.25	.43*
MEGp BA6 1-back	.22	−.02	.02	.00	.01	.03	.07	−.17	.38*	.11	−.02	.15	.30
MEGp BA6 2-back	.36*	−.19	−.21	−.21	−.23	.01	.10	−.05	.43*	.16	.02	.20	.32
MEGp BA6 3-back	.39*	−.21	−.28	−.21	−.26	.17	.29	.05	.55**	.34	.08	.27	.45*
MEGp BA8 0-back	.13	−.01	.06	−.12	−.05	.08	.26	.12	.43*	.27	.38*	.34	.39*
MEGp BA8 1-back	.05	.01	.12	−.03	.04	−.05	−.00	.01	.14	.01	.13	.08	.15
MEGp BA8 2-back	.41*	−.27	−.10	−.22	−.19	.09	.20	.30	.36*	.26	.21	.23	.29
MEGp BA8 3-back	.38*	−.31	−.18	−.32	−.28	.34	.46**	.43*	.58**	.54**	.25	.42*	.41*
Intx BA32 0-back	−.34	.20	.30	.11	.21	−.27	−.18	−.20	−.19	−.25	.05	−.07	−.15
Intx BA32 1-back	−.40*	.30	.32	.33	.36*	−.26	−.34	−.37*	−.35	−.40*	−.03	−.23	−.16
Intx BA32 2-back	−.25	.09	.16	.16	.17	−.26	−.37*	−.34	−.26	−.38*	−.08	−.22	−.15
Intx BA32 3-back	−.06	−.04	.17	−.08	.03	−.16	−.06	−.08	.03	−.08	.11	.09	−.03

Note. CBCL = Child Behavior Checklist; BRIEF = Behavior Rating Inventory of Executive Function; WISC-IV = Wechsler Intelligence Scale for Children–Fourth Edition; D-KEFS = Delis-Kaplan Executive Function System; NBAcc = n-back accuracy total; Attn = Attention Problem Scale; BRI = Behavioral Regulation Index; MI = Metacognition Index; GEC = General Executive Composite; VCI = WISC Verbal Comprehension Index; PRI = WISC Perceptual Reasoning Index; WMI = WISC Working Memory Index; PSI = WISC Processing Speed Index; FSIQ = WISC Full Scale IQ; C/W I = D-KEFS color-word inhibition; C/W I/S = D-KEFS color-word inhibition/switching; L/N = D-KEFS trail making letter/number switching; MEGp = main effect of group; Intx = Group x n-back level interaction.
* $p < .05$. ** $p < .01$.

greater activation found in healthy controls, along with better accuracy, may indicate more successful engagement in working memory during the n-back.

Survivors of pediatric brain tumors demonstrated greater BOLD signal response in the left DACC (BA32) during the n-back, whereas healthy controls showed relative deactivation. This suggests that, even at less cognitively demanding levels of a working memory task, survivors required increased resources in this region. The DACC has been linked to skills including complex problem solving, motivation, and performance monitoring, including error detection. In contrast, healthy controls evidenced relatively lesser deactivation in this region only at the most complex level of the n-back task and never showed a pattern of activation similar to that of survivors. A similar pattern was documented in survivors of pediatric leukemia (Robinson, Livesay et al., 2010). The fact that survivors demonstrated increased BOLD signal in the left DACC throughout the n-back task may indicate this so-called compensatory activation, in which survivors required an increase in resources to this region in order to manage the increase in cognitive load. This is consistent with literature documenting structural reorganization in prefrontal regions in pediatric leukemia (Kesler, Tanaka, & Koovakkattu, 2010). However, survivors of ALL were able to successfully and *accurately* complete the n-back task during fMRI, whereas survivors of pediatric brain tumors performed significantly less accurately than controls. It is possible that similar compensatory processes occur, but given the greater impact of brain tumors on neurocognitive functioning, compensation was unsuccessful at the most difficult task levels. Alternatively, this region has been found to activate during performance monitoring and error detection (e.g., Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001; Rama et al., 2001), and this activation may indicate that survivors were aware of their poorer performance on the more difficult levels of the task. In future studies, use of an event-related design may be useful in further examining patterns of activation tied to correct

versus incorrect responses, and thereby improve understanding the functional processes underlying this pattern of activation. This may be particularly useful in determining whether the pattern of poorer performance and similar response time is indicative of impulsive responding versus nonimpulsive errors related to ability to successfully complete the task.

This study provides evidence that patterns of activation during fMRI are associated with performance on measures of cognitive and executive functioning in children following treatment for a pediatric brain tumor. Overall, the results indicated that more efficient functioning in the healthy controls (as indicated by greater activation in the right MiFG and left MeFG, and less activation in the left DACC during n-back task completion) was associated with better cognitive and executive functioning. Although mean scores for survivors fell within the average range on measures of cognitive and executive function (i.e., within one standard deviation of the normative mean), neurobiological differences as compared with healthy controls were found. It is possible that, for those experiencing milder weaknesses after treatment, neurobiological compensatory processes may be sufficient to maintain adequate functioning. However, those with a more significant decline in performance on standardized testing may show a corresponding change in patterns of neurobiological activation, particularly within the left DACC. Although statistically worse than healthy children, survivors maintained a relatively high degree of accuracy (82.8%) even at the most complex level of the n-back task. Increasing the difficulty level of the task may be useful to clarify whether, and at what point, compensatory processes in this region no longer yield sufficient task accuracy.

Interestingly, the majority of survivors (76%) who participated in this study were treated for a brain tumor arising from the posterior fossa. Weaknesses in cognitive and executive functions have typically been associated with anterior and frontal-subcortical brain systems, although research on "cerebellar cognitive affective syndrome," a constellation of deficits in skills including executive

and visual-spatial coordination, is emerging (e.g., Schmahmann & Sherman, 1998). Indeed, survivors of brain tumors of the posterior fossa have been consistently found to experience deficits in these skills following treatment (Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013). Emerging research has identified broad characteristics of systemic treatment (e.g., cranial radiation therapy) and specific factors such as treatment side effects (e.g., hydrocephalus) that may be important predictors of outcome that impact more global brain function (e.g., Wolfe-Christensen, Mullins, Scott, & McNall-Knapp, 2007). Tumor characteristics and histology and patient characteristics (e.g., age, gender) have also been posited to be related to the nature and extent of deficits (e.g., Glauser & Packer, 1991; Mulhern, Hancock, Fairclough, & Kun, 1992; Nathan et al., 2007). Because of the relatively limited sample size included in this imaging study, we lacked sufficient power to fully incorporate group differences in aspects of diagnosis and treatment into all analyses. However, exploratory analyses suggested that those farther from completion of treatment are at greater risk for deficits. Power was likely insufficient to detect within-group differences for treatment factors (e.g., only five participants received cranial radiation and chemotherapy). Functional connectivity and diffusion tensor imaging analyses may clarify whether it is the direct impact of whole-brain treatment on peripheral brain regions versus a downstream impact of interconnected networks of regions that leads to deficits.

The current study has several strengths that provide unique contributions to this area of research. This is the first study to use fMRI to examine the substrates of working memory deficits in survivors of pediatric brain tumors, as compared with healthy children. The findings contribute to our understanding of the neurobiological processes underlying executive function abilities in survivors. Greater understanding of these processes provides a starting point for examination of the association between patterns of activation and other areas of survivors' functioning. This study also relied on multiple methodological approaches, including neurocognitive assessment using standardized and norm-referenced measures, empirically validated questionnaires, and a well-established verbal working memory task conducted during functional neuroimaging.

Despite these strengths, several limitations need to be considered while interpreting the results. Given the cross-sectional nature of this study, we are unable to speculate as to the timing of the emergence of differences in brain activation, which may be useful in determining ideal intervals for intervention. Although an adequate sample size for imaging research, inclusion of only 17 survivors of pediatric brain tumors, and a lack of detailed disease and treatment-related information, prevented more specific examination of brain activation based on diagnostic and treatment factors. Survivors in this study also represent a small and heterogeneous subset of those treated at one location and may not be representative of the overall population of survivors. Replication in a larger, multisite study is necessary.

Several avenues for future research have been identified based on these findings. This study documents associations among brain functioning and performance on normative-referenced standardized measures. However, survivors of pediatric brain tumors have higher rates of other difficulties, including problems with social and emotional functioning. The role that neurobiological processes play in the emergence of these difficulties is largely unknown.

Research in social–cognitive neuroscience has identified overlapping brain regions subserving executive and psychosocial processes, and this will be important to explore further within this at-risk population. Larger multisite and longitudinal studies tracking the emergence of deficits in these areas are necessary to adequately characterize targets for intervention strategies. For example, although working memory was specifically assessed in this study, deficits in basic attention may precede working memory deficits but have a downstream effect on working memory functioning. Therefore, attention may be the more appropriate skill on which to focus. Recent research in other populations has explored the impact of pharmacologic intervention (Conklin et al., 2007) and cognitive remediation (e.g., Butler et al., 2008; Kesler, Lacayo, & Jo, 2011; Zou et al., 2012) on deficits in these areas, with promising initial results. Although, to our knowledge, no similar study has specifically examined these processes in survivors of pediatric brain tumors, this provides encouraging evidence that interventions may be effective in addressing problematic patterns of brain activation in this at-risk population.

This study replicates prior research documenting cognitive and executive difficulties in survivors of pediatric brain tumors, and extends research by examining related neurobiological processes. These findings contribute considerably to our understanding of these difficulties in this important clinical population, and provide a foundation for research that is directed at exploring the nuances of these associations and their plasticity, with the end goal of improving the posttreatment experience of survivors of pediatric brain tumors.

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