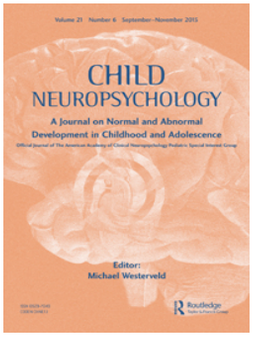

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Functional neuroimaging of working memory in survivors of childhood brain tumors and healthy children: Associations with coping and psychosocial outcomes

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Purpose: Pediatric brain tumors are the second most common cancer diagnosis in individuals under age 20 and research has documented significant neurocognitive, psychosocial, and emotional late effects. Associations among these deficits have not been adequately considered and the role of survivors' coping with stress in relation to deficits is unknown. Further, research has yet to examine neurobiological processes related to neurocognitive, psychosocial, and emotional difficulties in survivors through the use of functional neuroimaging. *Method*: Questionnaire measures and functional neuroimaging were used to examine the neurocognitive, psychosocial, and emotional functioning and coping responses of survivors of pediatric brain tumors ($N = 17$; age 8–16) and healthy children ($N = 15$). *Results*: Survivors experienced elevated levels of psychosocial and behavioral/emotional difficulties relative to healthy controls and normative data. Increases in brain activation in prefrontal and other anterior regions in response to a working memory task were associated with better psychosocial functioning, use of engagement coping strategies, and less use of disengagement coping strategies. Regression analyses suggest coping accounts for a significant portion of the association between brain activation and behavioral/emotional functioning. *Conclusions*: This study extends late-effects research by examining neurobiological processes associated with psychosocial and emotional difficulties. These findings contribute to our understanding of difficulties in survivors and provide a foundation for research exploring these associations and mediators of deficits in future longitudinal studies.

Keywords: Neoplasm; Working memory; Psychosocial; Late effects; Coping.

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Over 4,000 children are diagnosed with a brain tumor each year, and more than 70% of these diagnoses are in children under 15 years of age (Central Brain Tumor Registry of the United States [CBTRUS], 2012). Improvements in treatment have resulted in an increasing number of survivors, and increased rates of neurocognitive, psychosocial, and emotional difficulties among survivors are well documented (e.g., Panigrahy & Bluml, 2009; Schultz et al., 2007). Foremost among documented late effects are neurocognitive deficits, including deficits in working memory, attention, processing speed, and executive functions (see Robinson et al., 2010, for a meta-analytic review). Survivors experience higher rates of internalizing problems (e.g., Fuemmeler, Elkin, & Mullins, 2002; Schultz et al., 2007), diminished social competence (e.g., Schulte & Barrera, 2010; Schultz et al., 2007), poor social skills, and difficulties with peer relationships (e.g., Boydell, Stasiulis, Greenberg, Greenberg, & Spiegler, 2008). Although research clearly suggests that survivors experience difficulties in these areas, the associations among these problems are not well understood. The interrelationships among executive functions, psychosocial functioning, and emotional functioning are important to examine in survivors of pediatric brain tumors and may improve understanding of the predictors and implications of these deficits.

Social cognitive affective neuroscience implicates several brain regions as playing a role in executive, psychosocial, and emotional functioning, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), orbitofrontal cortex, and posterior parietal cortex (e.g., Amodio & Frith, 2006; Mah, Arnold, & Grafman, 2004; Robinson et al., 2010; Yeates et al., 2007). The PFC, for example, plays a central role in integrating social, affective, and cognitive aspects of behavior (e.g., Satpute & Lieberman, 2006). Neural bases of executive function implicate the PFC, ACC, and parietal regions, as well as their coordination (Tamnes et al., 2010), and functional neuroimaging studies have documented patterns of prefrontal and parietal activation in both adolescents and adults during executive function tasks (e.g., Kwon, Reiss, & Menon, 2002; Nelson et al., 2000). Studies examining activation specifically in response to working memory tasks in children and adolescents have similarly identified prefrontal-parietal networks (Nelson et al., 2000; Thomas et al., 1999). Research with populations known to be at risk for deficits in working memory, including pediatric traumatic brain injury (McAllister et al., 1999), acute lymphocytic leukemia (Robinson et al., 2010), and brain tumors (Robinson et al., in press), has demonstrated that survivors recruit greater amounts of oxygenated hemoglobin to prefrontal and cingulate regions during working memory task completion, relative to healthy controls, perhaps indicating patterns of compensatory activation.

Prefrontal and parietal regions are important for working memory, and it is possible that executive function ability, particularly working memory, may play a key role in facilitating social and emotional functions via overlapping neural networks. Indeed, research examining the neurobiological underpinnings of emotion regulation and coping has implicated similar brain regions. For example, the ACC and areas of the PFC have been linked to self-regulation, emotion regulation, and complex social-problem solving (e.g., McRae et al., 2012; Ochsner, Bunge, Gross, & Gabrieli, 2002; Yeates et al., 2007). These skills depend on the ability to attend to relevant aspects of a situation, to mentally manipulate (reappraise) aspects of the situation or one's responses to it, and to evaluate the acceptability and consequences of reactions. These strategies rely heavily on executive functions including working memory, cognitive flexibility, and sustained attention. The association between executive function, on one hand, and emotion regulation and coping,

on the other, suggests that the development of skills to regulate emotions and to cope with stress may parallel the development of the PFC (e.g., McRae et al., 2012).

One possible predictor of psychosocial and emotional difficulties in survivors of pediatric brain tumors is the skill with which survivors cope with stress and interpersonal problems and regulate their emotions. Although the association between neurocognitive function, most importantly executive function, and coping skills in survivors of pediatric brain tumors has not been examined, research with other populations provides a framework for the conceptualization of these associations (Campbell et al., 2008; Compas, Campbell, Robinson, & Rodriguez, 2009). Several important cognitive abilities, including attention and working memory, are related to coping strategies such as cognitive reappraisal or problem solving (Campbell et al., 2008; Hocking et al., 2011; Schmeichel, Volokhov, & Demaree, 2008). Therefore, brain tumor survivors who experience neurocognitive late effects may be unable to use these coping skills effectively, leaving survivors more vulnerable to social and emotional difficulties.

The present study was guided by a conceptualization of coping as "conscious, volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000, p. 89). A model of coping that includes three factors—primary control engagement, secondary control engagement, and disengagement coping—has been supported in confirmatory factor analytic studies with diverse samples of children and adolescents (e.g., Compas et al., 2006; Connor-Smith et al., 2000; Wadsworth, Rieckmann, Benson, & Compas, 2004; Yao et al., 2010). Primary control coping strategies include efforts to change the stressor or situation itself and include problem solving, emotional modulation, and emotional expression. Secondary control coping strategies aim to manipulate or adjust one's own reactions to the stressor and include strategies like positive thinking, cognitive restructuring, acceptance, and distraction. Disengagement coping responses include avoidance, denial, and wishful thinking. Studies of children and adolescents coping with chronic illness (including cancer) have found that secondary control coping responses are associated with lower levels of emotional and behavioral problems, whereas disengagement coping has been associated with higher levels of emotional and behavioral problems (Compas, Jaser, Dunn, & Rodriguez, 2012).

The current study examined coping, social, and emotional functioning, attention, and functional brain activation in a sample of pediatric brain tumor survivors and a sample of healthy children. We hypothesized that survivors of pediatric brain tumors would report more social problems, attention problems, and internalizing problems relative to healthy controls, as well as lower social competence. Across domains, we hypothesized that the use of primary and secondary control coping would be positively associated with social competence and negatively associated with attention problems, social problems, and internalizing symptoms, and the use of disengagement coping would be positively associated with attention problems, social problems, and internalizing symptoms, and negatively associated with social competence, regardless of group. Whereas the goal of previous analyses with this sample was to examine differences in brain activation across *groups* in response to a working memory task (see Robinson et al., in press), the present analyses focused on associations among several domains of functioning including brain activation, coping, and aspects of psychosocial and emotional functioning. We expected that survivors would show a relative increase in oxygenated blood across increasing levels of *N*-back difficulty (i.e., increased blood-oxygen level dependent (BOLD) signal) to

areas of the prefrontal, anterior cingulate, and parietal cortices in response to a verbal working memory task completed during functional magnetic resonance imaging (fMRI), as previous research has found that those at risk for working memory deficits may exhibit compensatory activation in regions relevant to task completion, perhaps to an even greater extent than healthy individuals (e.g., McAllister et al., 1999; Robinson et al., 2010). Further, we predicted that an increased BOLD signal would be positively associated with the use of engagement coping and social competence and negatively associated with the use of disengagement coping and with attention problems, social problems, and internalizing symptoms. These analyses were also conducted within a sample of healthy controls to determine whether across-domain associations were unique to the sample of brain tumor survivors or occurred similarly in healthy children. Finally, we hypothesized that coping would partially account for the association between brain activation and behavioral, emotional, and social problems.

METHOD

Participants

Data from 17 survivors (10 girls) and 15 healthy controls (9 girls) were included in these analyses. These participants represent a subset of the overall sample of participants in a study of the neurocognitive and psychosocial functioning of survivors of pediatric brain tumor. Twenty-six children at least 2 years postdiagnosis were initially 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 large children's hospital. Survivors were invited to participate if they met the following inclusion criteria: (a) 8–16 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 (a) history of a known pre-existing neurological disorder (e.g., epilepsy, neurofibromatosis) or certain neurodevelopmental disorders (e.g., autism spectrum disorder, learning disability), (b) history of very low birth weight (<1500 grams), or (c) history of secondary malignancies or relapses. Children with a history of attention deficit/hyperactivity disorder (ADHD) were not excluded. Procedures were approved by the Institutional Review Board, 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 due to lack of interest, two families had moved out of the area, and 1 child agreed to participate but relapsed prior to formal enrollment. Of the 21 who participated in the study, 3 survivors' data were excluded from the present analyses due to missing data, and 1 participant's data were excluded due to excessive motion during fMRI.

Twenty-seven healthy children were contacted to serve as a control group for the study. Three of the 27 children were excluded due to a pre-existing neurodevelopmental disorder, 2 declined due to lack of interest, and 2 had orthodontic devices that precluded undergoing an MRI. Of the 20 who were eligible, agreed to participate and enrolled in the study, 2 healthy controls did not return for their scanning appointment, and 3 healthy controls' data were excluded due to excessive motion during the 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

Table 1 Group Comparisons on Demographic Information.[a]

	Survivors (n = 17)	Healthy Controls (n = 15)	t/X^2	p	d/φ
Demographics					
Child Age	12.60 (2.48)	12.90 (2.78)	−0.33	.74	0.11
Child Gender	35.3% Female	60.0% Female	1.95	.16	
Child Race	94.1% Caucasian	66.7% Caucasian	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	0.83
Family Income	6.53 (2.72)	6.07 (2.46)	5.66	.69	0.18
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 postgraduate education. For both groups, family income of 6.53 and 6.07 correspond to an income range of $60,000 to $70,000. Tx = Treatment.

[a]Values in parentheses indicate standard deviation.

MRI. Children with braces were excluded, as metallic orthodontic devices can distort images.

Survivors and healthy controls did not differ in terms of age at participation, gender distribution, race, parent education, family income, history of ADHD medication, and history of diagnosis of and/or treatment for psychological problems (ps > .05; see Table 1). All survivors underwent surgical resection and 5 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). Children who received adjuvant treatment (i.e., chemotherapy and/or cranial radiation) and children who only underwent surgical resection did not differ on any measure of brain activation, psychosocial functioning, or coping. 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 completion (SD = 2.83; range 2.13–10.92 years) at the time of participation. Tumor pathologies included 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); no tumors overlapped with brain regions included in analyses. All participants were right-handed.

Procedure

Parents of brain tumor survivors were sent a letter from a physician informing them of the study. Approximately 2 weeks later, families were contacted by the study coordinator who assessed their interest in participating and eligibility. Potential healthy controls were identified through responses to a mass e-mail distributed to faculty and staff at a large university and medical center. Participating families completed the study in one full-day or two half-day sessions, per their preference. Study participation included neurocognitive assessment, questionnaire measures, and an fMRI session. Neurocognitive assessments included measures of overall cognitive functioning, memory, visual-spatial

integration, and executive function; between-group comparisons of some assessment measures have been reported elsewhere (see Robinson et al., in press) but generally indicate poorer performance across measures by survivors of pediatric brain tumors. Additionally, parents and children completed several questionnaires assessing various domains of functioning, including psychosocial, emotional, and behavioral problems, executive function, and coping.

All neuroimaging was conducted on a 3Tesla Philips Achieva (Philips Healthcare, Best, The Netherlands) dedicated for research. Mock scanner facilities were used to introduce children to the scanning environment, to explore physiological and response pad devices, and to learn how each computerized task ran and would appear during the scan. Protocols were run via computer in an adjacent room, and task stimuli appeared via a rear-mounted projector. Participants responded to questions using buttons on the response pad, and they were able to communicate reciprocally with study personnel throughout the scan through headphones and a microphone.

Measures

Emotional and Behavioral Problems. Parents and children provided information about social, emotional, and behavioral problems by completing the Child Behavior Checklist (CBCL) and Youth Self-Report (YSR), respectively, which assess internalizing, externalizing, and social problems in children and adolescents (Achenbach & Rescorla, 2001). These scales have strong test-retest reliability and criterion validity. In the following analyses, attention, social problems, and internalizing symptoms were assessed using the Social Competence (SC), Anxious/Depressed (AD), Social Problems (SP), and Attention Problems (AP) scales.

Coping. Parents and children completed the Social Stress version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000), a measure of coping and stress reactivity associated with stressful interpersonal and peer relationships. Based on previous research on the association between coping as measured by the social stress version of the RSQ and executive function (Campbell et al., 2008), the current study focuses on coping responses comprising the three coping domains: Primary Control coping (i.e., problem solving, emotional modulation, emotional expression), Secondary Control coping (i.e., acceptance, cognitive restructuring, positive thinking, distraction), and Disengagement coping (i.e., avoidance, denial, wishful thinking). The RSQ has been shown to have good test-retest reliability, internal consistency, and convergent and discriminant validity (e.g., Connor-Smith et al., 2000).

Functional Neuroimaging. During fMRI, participants completed the *N*-back task, which is designed to assess working memory. The letter version of the *N*-back task (Barch, Sheline, Csernansky, & Snyder, 2003) involves sequences of uppercase consonants. 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 letter was presented for 1900 ms

and a 100 ms intrastimulus interval was used throughout the task. 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), three of which were target consonants. Children responded using the response pads and response accuracy and reaction time were recorded. This task has been used effectively with children in this age group with no adverse effects (Robinson et al., 2010).

Image Acquisition

Imaging consisted of a high-resolution three-dimensional anatomical scan using an inversion-prepared spoiled gradient recalled echo sequence (IR-SPGR), with an inversion time (T1) of 400 ms, a repetition time (TR) of 15 ms, a minimum echo time (TE; 3 ms), a matrix size 256 × 256 for a field of view (FOV) of 256 × 255 × 270 mm with near isotropic resolution. From this, 33 axial slices obtained at an oblique angle (parallel to the anterior commissure-posterior commissure plane) were prescribed for the functional data. All functional images were acquired with a gradient echo planar imaging pulse sequence, with a TE of 30 ms (optimized for T2* at 3T), a flip angle of 70°, a TR of 2000 ms, 33 slices 3.5 mm thick and 0.35 mm skip, with an FOV of 240 × 240 (anterior-posterior, right-left) and a matrix size of 80 × 80 (reconstructed to 128 x 128) sampled at +/-62.5 kHz. This effectively yields an acquired voxel size of 1.875 × 1.875 × 3.5 mm and a total coverage area of 126.7 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 prior to the start of the task.

Data Analysis

Data Reduction. For measures of emotional and behavior problems and coping, parent and child report scores were converted to *z*-scores and the mean of the parent and child *z*-scores were used to create a composite score. This yielded one overall indicator for each participant of social competence, symptoms of anxiety and depression, social problems, attention problems, and use of primary control, secondary control, and disengagement coping.

fMRI Data Preparation. Functional data were analyzed using BrainVoyager QX software (Brain Innovation B. V., Maastricht). The functional data for each participant's *N*-back run were corrected for three-dimensional motion and slice-time delays, and linear trends were removed. Additional high-pass filtering and smoothing were done using a frequency space filter with a cutoff of two cycles. Motion correction results were assessed to ensure that all data fell within a predefined criteria (<3 mm displacement, 3° rotation). All participants included in these analyses had data that fell within movement criteria.

The functional data for each participant were aligned to the participant's high-resolution three-dimensional anatomic dataset. *N*-back data were modeled using a block design and task time-course reference files were included in individual subject level analyses convolved with a double-gamma hemodynamic 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 functional voxel size of 3 x 3 x 3 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 27 functional voxels was established for examining within-group patterns of BOLD signal activation. This cluster threshold maintained a significance criterion of $p < .001$, which was deemed likely to adequately reduce the likelihood of Type 1 error in subsequent analyses. For the brain tumor group, within-group general linear modeling (GLM) analyses were conducted (as described below). These analyses calculated all significantly activated voxels, both positively and negatively, during all levels of the *N*-back task. 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).

Data Analyses. Prior to hypothesis testing, 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 determine whether groups differed on social competence, symptoms of anxiety and depression, social problems, attention problems, and use of primary control, secondary control, and disengagement coping. Next, individual imaging data were calculated based on a GLM with each level of *N*-back task difficulty as predictors to account for variance associated with change in the time course of the signal on a voxelwise level. Subject-level analyses were conducted to examine changes in BOLD signal activation at increasingly difficult levels of the *N*-back task relative to the 0-back baseline condition. In the within-group analyses for the sample of brain tumor survivors, composite *t*-test statistics were calculated to measure the degree of activation in each cluster. These identified clusters were then force prescribed to the healthy control participants, and composite *t*-test statistics for identical clusters were calculated for this sample. Clusters from the within-group analyses for the sample of healthy controls were also completed and clusters were force prescribed to the brain tumor sample. Additional independent samples *t*-tests were conducted to determine whether groups differed in activation in these regions. Next, pooled within-group correlations were conducted to examine the associations among emotional and behavioral problems, coping, and relative changes in brain activation. Correlations were also examined separately for each group to explore whether associations were unique to one group or were similar across groups. Fischer's *z*-tests were used to test whether correlations differed significantly between groups. Finally, hierarchical linear regressions were conducted to ascertain the individual and total contributions to variance in symptoms of emotional and behavioral problems accounted for by group, by brain activation, and by coping.

RESULTS

Between-Group Analyses

Based on the parent report on the CBCL, survivors demonstrated reduced social competence and elevated social problems and attention problems relative to healthy controls ($ps < .05$). Survivors reported reduced social competence relative to healthy

controls ($p < .05$). Groups did not differ in their use of the three types of coping (see Table 2).[1] Survivors and healthy controls had similar average reaction times on the *N*-back task. Survivors performed significantly less accurately than healthy controls on the 1-back and 3-back levels ($p < .05$) and marginally less accurately on the 0-back and 2-back levels ($p < .10$; see Table 2).[2]. All participants maintained generally high levels of accuracy throughout the task (i.e., exceeding 82%).

Table 2 Group Comparisons on Cognitive, Emotional, and Behavioral Functioning.[a]

	Survivors (n = 17)	Healthy Controls (n = 15)	t	p	Cohen's d
Emot/Behav[b]					
CBCL Soc Comp	41.53 (8.00)	49.27 (10.03)	−2.72	.011	0.85
CBCL Anx/Dep	59.94 (8.22)	55.80 (10.81)	1.19	.245	0.43
CBCL Soc Prob	62.71 (6.96)	54.53 (8.38)	2.91	.007	1.06
CBCL Attn Prob	59.29 (6.68)	52.87 (4.85)	−3.39	.002	1.21
YSR Soc Comp	42.00 (8.36)	48.40 (6.08)	−2.32	.028	0.88
YSR Anx/Dep	58.47 (10.60)	54.93 (4.70)	0.340	.737	0.43
YSR Soc Prob	60.18 (7.87)	56.13 (4.73)	1.38	.179	0.62
YSR Attn Prob	59.65 (11.38)	56.33 (4.19)	−0.10	.923	0.03
Coping[c]					
PR—Primary	0.21 (0.03)	0.21 (0.04)	−0.12	.905	0.04
PR—Secondary	0.24 (0.05)	0.27 (0.06)	1.21	.238	0.42
PR—Disengagement	0.16 (0.03)	0.15 (0.01)	−1.36	.184	0.49
SR—Primary	0.18 (0.04)	0.21 (0.06)	1.28	.210	0.45
SR—Secondary	0.26 (0.06)	0.24 (0.05)	−0.79	.434	0.28
SR—Disengagement	0.16 (0.02)	0.16 (0.03)	−0.61	.549	0.21
N-Back Accuracy[d]					
0-back	43.59 (2.81)	44.93 (0.26)	−1.97	.067	0.67
1-back	43.24 (2.88)	44.93 (0.26)	−2.42	.028	0.83
2-back	41.35 (2.55)	42.87 (1.92)	−1.88	.070	0.67
3-back	37.24 (2.41)	40.87 (1.81)	−4.77	<.001	1.70
Average Accuracy	165.41 (9.04)	173.60 (3.18)	−3.50	.002	1.21
N-Back Response Time[e]					
0-back	620.83 (102.10)	591.79 (88.32)	0.84	.405	0.30
1-back	661.13 (127.60)	599.61 (78.69)	1.61	.117	0.58
2-back	763.12 (161.97)	688.30 (151.07)	1.33	.195	0.48
3-back	819.96 (146.67)	830.10 (245.87)	−0.14	.891	0.05
Average Response Time	699.18 (104.12)	665.39 (99.49)	0.94	.357	0.33

Note. CBCL = Child Behavior Checklist; YSR = Youth Self-Report; PR = Parent report; SR = Self-report.
[a]Values in parentheses indicate standard deviation. [b] *T*-scores with a mean of 50 and a standard deviation of 10. [c]*Z*-scores with a mean of 0 and a standard deviation of 1. [d]Scores include omission and commission errors. Number indicates total accurate responses out of 45 (individual levels) or out of 180 (total). [e]Response time in milliseconds.

[1] Because ratings of healthy controls' social problems, internalizing symptoms, and attention problems fell above the population means on normative measures, one-sample *t*-tests were also conducted to determine whether survivors' scores differed from the normative sample mean. On the CBCL and YSR, both parents and survivors reported significantly reduced social competence, and elevated internalizing symptoms, social problems, and attention problems (ps < .01).

[2] A between-group comparison on CBCL and YSR attention problems, and on *N*-back task performance, was previously reported elsewhere (see Robinson et al., in press) and is presented here in summary due to inclusion in additional subsequent analyses.

Table 3 Correlations Among Coping and Psychosocial and Emotional Functioning.

	Primary Control Coping	Secondary Control Coping	Disengagement Coping
Pooled Within-Group Correlations for Entire Sample (N = 32)			
Social Competence	.06	.32	−.13
Anxiety/Depression	−.35*	−.78**	.53**
Social Problems	−.34	−.69**	.23
Attention Problems	−.22	−.53**	.29
Correlations for Sample of Brain Tumor Survivors (n = 17)			
Social Competence	.02	.45	−.30
Anxiety/Depression	−.44	−.76**	.70**
Social Problems	−.35	−.67**	.42
Attention Problems	−.34	−.56*	.52*
Correlations for Sample of Healthy Controls (n = 15)			
Social Competence	.07	.18	.13
Anxiety/Depression	−.26	−.72**	.34
Social Problems	−.35	−.61*	−.10
Attention Problems	.33	.14	−.01

**$p < .01$. *$p < .05$.

Pooled within-group correlations, summarized in Table 3, indicated that primary control coping was significantly negatively correlated with symptoms of anxiety/depression ($p < .05$). Secondary control coping was significantly negatively correlated with symptoms of anxiety/depression ($p < .01$), social problems ($p < .01$), and attention problems ($p < .01$). Finally, disengagement coping was significantly positively associated with symptoms of anxiety/depression ($p < .01$). Correlations were also run separately for each group to determine whether patterns of association were unique to one group or were consistent across groups. Although no statistically significant differences among the magnitude of correlations were found, correlations were generally larger within the brain tumor sample.

fMRI Analyses

Levels of activation for the contrasting load demands for the N-back tasks are presented in Table 4. In the sample of survivors of pediatric brain tumors, we observed increased activity of the left dorsolateral prefrontal cortex (DLPFC; BA9) and right superior frontal gyrus (SFG; BA8) in the 2-back condition compared with the 0-back condition ($p < .001$). Increased activity in the right dorsal anterior cingulate cortex (DACC; BA32), right anterior prefrontal cortex (APFC; BA10), and right supramarginal gyrus (SMG; BA40) was observed for the 3-back vs 0-back condition ($p < .001$). These clusters were then prescribed onto the sample of healthy children and activity level was extracted for subsequent analyses. Although not sufficient to reach the significance threshold of $p < .001$ used for fMRI analyses, healthy controls did show relative increases in activation in each region. A significant between-group difference in the magnitude of activation was only noted for the DLPFC (BA9).

Levels of activation for contrasting load demands were also extracted for the sample of healthy controls. In the 2-back versus 0-back condition, we observed increased activity in the right DLPFC (BA9) and bilaterally in the precuneus (BA7) and SMG (BA40). In

Table 4 Significant Within-Group BOLD fMRI Responses During the N-Back Task.

				Talairach Coordinates			BT Survivors		Healthy Controls			BT v. HC Contrast	
	Region	Hemi	BA	x	y	z	*t*	*p*	*t*	*p*	# Voxels	*t*	*p*
Clusters with Significant Activation: Brain Tumor Survivors													
2-back vs. 0-back	SFG	R	8	1.6	17	47	6.35	< .001	3.83	.003	96	−0.20	.842
	DLPFC	L	9	−39	7.4	30	6.32	< .001	1.92	.102	92	2.22	.034
3-back vs. 0-back	APFC	R	10	37	44	21	7.80	< .001	2.17	.077	157	0.90	.377
	SMG	R	40	32	−53	36	5.93	< .001	3.24	.011	339	0.94	.356
	DACC	R	32	8.8	21	39	7.19	< .001	3.63	.005	117	0.05	.961
Clusters with Significant Activation: Healthy Controls													
2-back vs. 0-back	DLPFC	R	9	40	18	37	0.52	.541	4.78	< .001	141	−3.65	.001
	PCN	R	7	26	−63	35	2.06	.097	4.66	< .001	394	−2.63	.014
	SMG	R	40	35	−49	40	2.52	.063	4.83	< .001	869	−2.45	.020
	PCN	L	7	−21	−65	35	1.80	.210	4.50	< .001	247	−3.58	.001
	SMG	L	40	−33	−47	37	2.53	.066	4.56	< .001	328	−1.65	.110
3-back vs. 0-back	DLPFC	R	9	35	28	33	2.54	.029	4.54	< .001	149	−1.78	.086
	MiFG	R	6	24	2.5	59	1.30	.411	4.43	< .001	123	−3.77	.001
	SMG	R	40	36	−46	39	2.72	.037	4.72	< .001	654	−1.87	.071
	DACC	R	32	1.7	17	42	2.11	.124	4.98	< .001	3816	−4.38	<.001
	SMG	L	40	−35	−50	37	1.67	.232	4.73	< .001	821	−2.41	.022

Note. Hemi = hemisphere; BA = Brodmann Area; SFG = Superior Frontal Gyrus; DLPFC = Dorsolateral Prefrontal Cortex; APFC = Anterior Prefrontal Cortex; SMG = Supramarginal Gyrus; DACC = Dorsal Anterior Cingulate Cortex; PCN = Precuneus; MiFG = Middle Frontal Gyrus; *R* = Right hemisphere; *L* = Left hemisphere.

the 3-back versus 0-back condition, we observed increased activation in the right DLPFC (BA9), right middle frontal gyrus (BA6), right DACC (BA32), and bilateral SMG (BA40). When these clusters were prescribed onto the sample of brain tumor survivors, survivors showed relative increases in activation nearing significance thresholds in only the right precuneus (BA7) and bilateral SMG (BA40) during the 2-back versus 0-back contrast, and in the right DLPFC (BA9) and right SMG (BA40) during the 3-back versus 0-back contrast. Healthy controls' relative increases in activation significantly exceeded the relative increases noted in the sample of survivors for nearly all clusters (see Table 4, Figures 1 and 2).[3]

Pooled within-group and individual-group correlations were calculated to examine the associations among BOLD signal activation, psychosocial and emotional functioning, and coping (see Table 5). When groups were combined, greater relative increases in activation in the SFG (BA8) were associated with fewer symptoms of anxiety/depression and social problems. Greater relative increases in activation in the DLPFC (BA9) were also associated with fewer symptoms of anxiety/depression. In terms of coping responses, greater relative increases in activation in the SFG (BA8) were associated with more use of secondary control coping strategies, and greater relative increases in activation in the DLPFC (BA9) were associated with more use of secondary control coping strategies and less use of disengagement coping.

Hierarchical linear regressions were conducted to determine the extent to which group, brain activation, and/or type of coping accounted for the variance in measures of social competence, social problems, and attention problems. Regression models were run if (a) between-group differences were found in measures of emotional/behavioral problems and (b), in accordance with recommendations for joint significance testing (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002), marginal or significant associations were found among activation in a given brain region, coping subtype, and emotional/behavioral outcome measure. Based on pooled within-group correlation analyses, two hierarchical linear regressions were conducted testing group, brain activation, and coping as predictors of social competence (see Table 6). Group was a significant predictor of social competence when entered in the first step of the regression and remained a significant predictor in the second and third step of the regression. Relative increases in activation in the SFG (BA8) and DLPFC (BA9) during more difficult levels of the *N*-back task were not significantly associated with social competence when added in the second step, and coping was not a significant predictor when added in the third step.

One regression was conducted to examine the extent to which group, brain activation, and coping predicted social problems (see Table 7). Group was a significant predictor of social problems when added in the first step of the regression. When brain activation in the SFG (BA8) was added in the second step, both brain activation and group significantly predicted social problems. However, when secondary control coping was added in the third step of the model, only group and coping remained significant predictors.

Finally, two hierarchical linear regressions were conducted testing group, brain activation, and coping as predictors of attention problems (see Table 8). In analyses predicting attention problems, group was a significant predictor when entered in the first step of the regression. In one regression, when brain activation was added in the second step, brain activation in the SFG (BA8) was not a significant predictor, but group

[3] Color images depicting each area of functional activation are available in the online publication of this article as supplemental material.

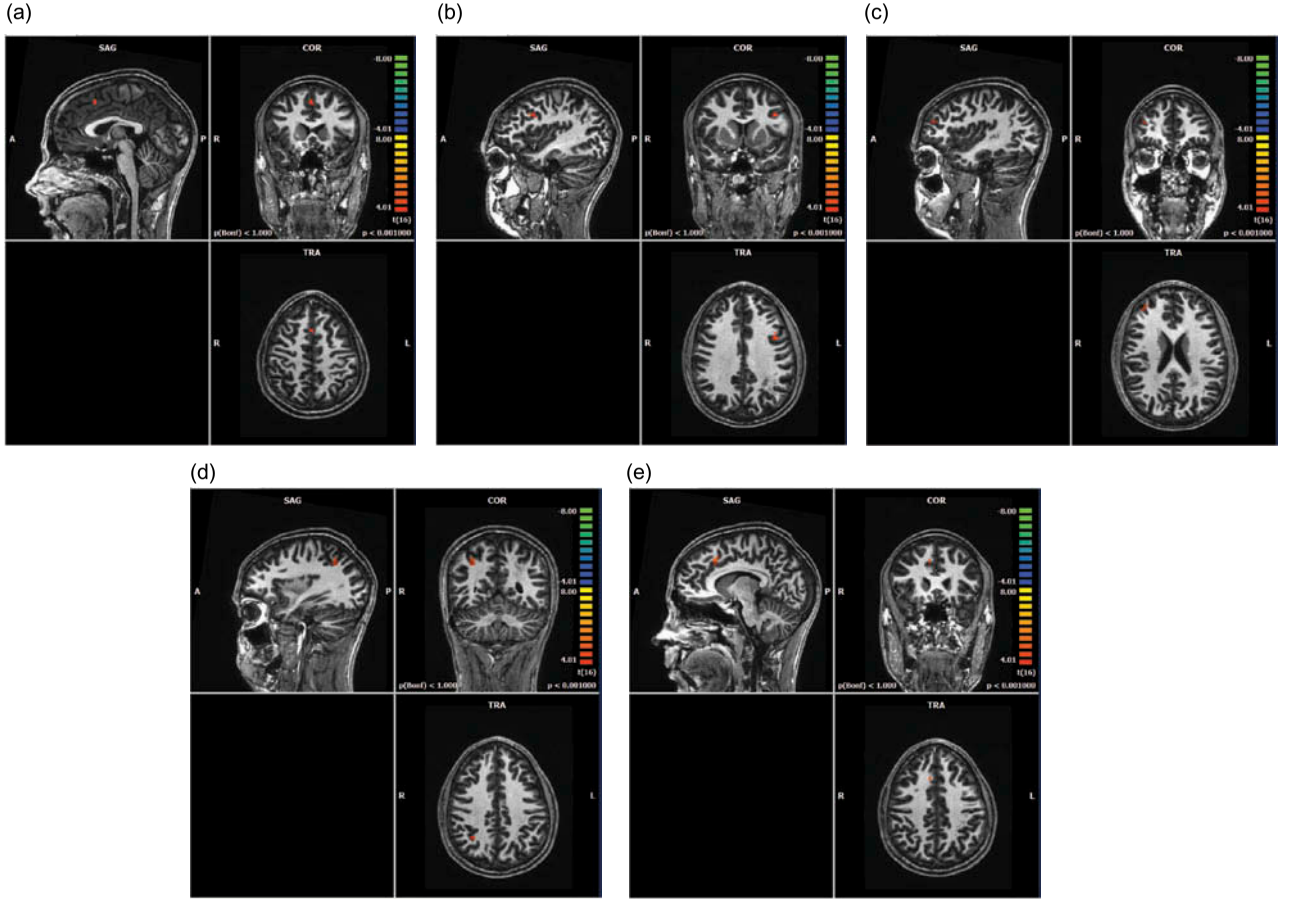

Figure 1 (a) 2v0-back Activation in BT Cluster 1: Right Superior Frontal Gyrus; (b) 2v0-back Activation in BT Cluster 2: Left Dorsolateral Prefrontal Cortex; (c) 3v0-back Activation in BT Cluster 1: Right Anterior Prefrontal Cortex; (d) 3v0-back Activation in BT Cluster 2: Right Supramarginal Gyrus; (e) 3v0-back Activation in BT Cluster 3: Right Dorsal Anterior Cingulate Cortex.

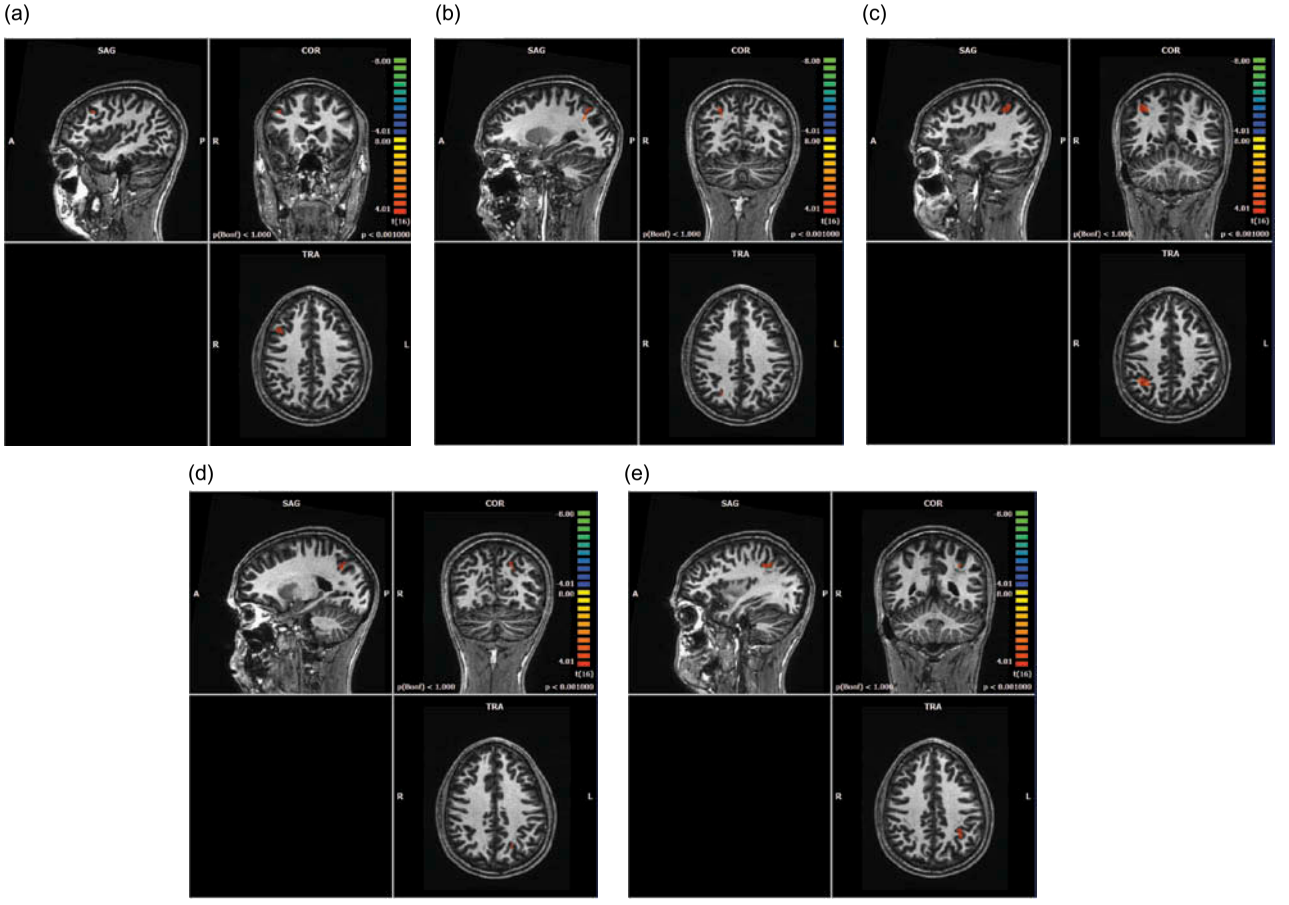

Figure 2 (a) 2v0-back Activation in HC Cluster 1: Right Dorsolateral Prefrontal Cortex; (b) 2v0-back Activation in HC Cluster 2: Right Precuneus; (c) 2v0-back Activation in HC Cluster 3: Right Supramarginal Gyrus; (d) 2v0-back Activation in HC Cluster 4: Left Precuneus; (e) 2v0-back Activation in HC Cluster 5: Left Supramarginal Gyrus; (f) 3v0-back Activation in HC Cluster 1: Right Dorsolateral Prefrontal Cortex; (g) 3v0-back Activation in HC Cluster 2: Right Middle Frontal Gyrus; (h) 3v0-back Activation in HC Cluster 3: Right Supramarginal Gyrus; (i) 3v0-back Activation in HC Cluster 4: Right Dorsal Anterior Cingulate Cortex; (j) 3v0-back Activation in HC Cluster 5: Left Supramarginal Gyrus.

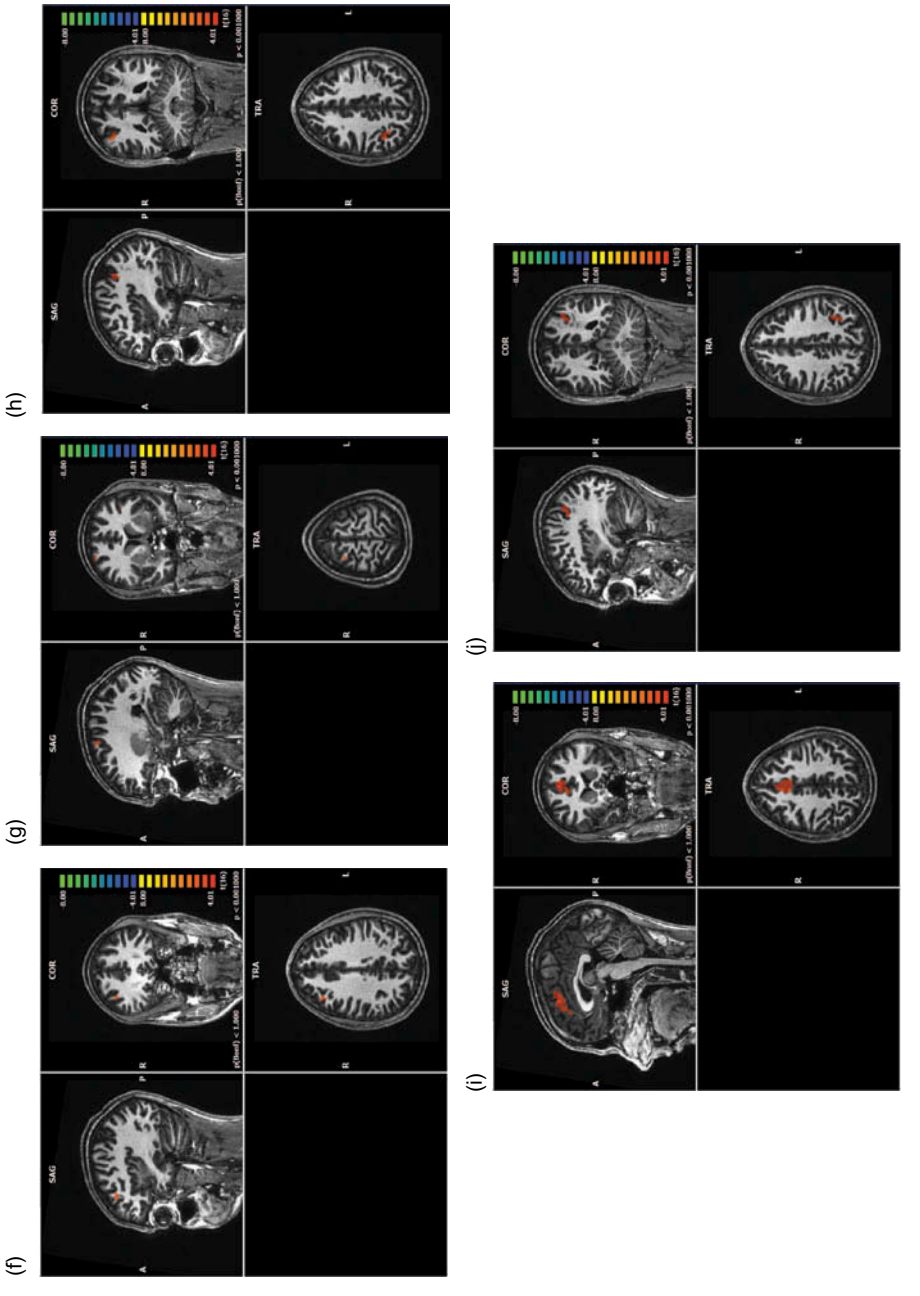

Figure 2 Continued

Table 5 Correlations among Brain Activation, Coping, and Psychosocial and Emotional Functioning.

	SCom	A/D	SProb	AtProb	PCC	SCC	DEC
Pooled Within-Group Correlations for Entire Sample (N = 32)							
2-back vs. 0-back							
R SFG (BA8)	.34	−.58**	−.38*	−.34	−.03	.50**	−.25
L DLPFC (BA9)	.02	−.42*	−.23	−.18	.16	.37*	−.43*
3-back vs. 0-back							
R APFC (BA10)	.29	−.33	−.13	−.03	.28	.29	−.30
R SMG (BA40)	.14	−.20	−.02	−.05	.18	.04	−.21
R DACC (BA32)	.33	−.34	−.26	−.34	.12	.34	−.23
Correlations for Sample of Brain Tumor Survivors (n = 17)							
2-back vs. 0-back							
R SFG (BA8)	.35	−.67**	−.45	−.12	.20	.46	−.53*
L DLPFC (BA9)	−.15	−.49*	−.32	−.61**	.29	.35	−.61**
3-back vs. 0-back							
R APFC (BA10)	.40	−.57*	−.21	−.30	.26	.59*	−.37
R SMG (BA40)	.21	−.40	−.13	−.07	.09	.18	−.30
R DACC (BA32)	.39	−.37	−.20	.04	.40	.43	−.33
Correlations for Sample of Healthy Controls (n = 15)							
2-back vs. 0-back							
R SFG (BA8)	.35	−.59*	−.34	.13	−.17	.54*	.01
L DLPFC (BA9)	.21	−.12	.05	.25	−.04	.32	−.13
3-back vs. 0-back							
R APFC (BA10)	.27	−.20	−.01	.55*	.33	.17	−.30
R SMG (BA40)	.07	.12	.11	.32	.22	−.08	−.11
R DACC (BA32)	.23	−.31	−.30	.04	−.07	.29	−.08

Note. SFG = Superior frontal gyrus; DLPFC = Dorsolateral prefrontal cortex; APFC = Anterior prefrontal cortex; SMG = Supramarginal gyrus; DACC = Dorsal anterior cingulate cortex; Soc Comp = Social Competence scale; Anx/Dep = Anxiety/Depression scale; Soc Prob = Social Problems scale; Attn Prob = Attention Problems scale; PCC = Primary control coping; SCC = Secondary control coping; DEC = Disengagement coping.

**$p < .01$. *$p < .05$.

Table 6 Hierarchical Linear Regressions: Predictors of Social Competence.

Step	Predictors	β	$t(p)$	R^2	ΔR^2	ΔF
SFG and Secondary Control Coping						
Step 1: Group	Group	−0.46	−2.82**	.22	.22	7.92**
Step 2: SFG BOLD Signal Change	Group	−0.46	−2.88**	.30	.09	3.54
	SFG	0.30	1.88			
Step 3: Secondary Control Coping	Group	−0.45	−2.85**	.33	.03	1.02
	SFG	0.20	1.12			
	SCC	0.18	1.01			
DLPFC and Secondary Control Coping						
Step 1: Group	Group	−0.46	−2.82**	.22	.22	7.92**
Step 2: DLPFC BOLD Signal Change	Group	−0.47	−2.99**	.30	.09	3.48
	DLPFC	0.30	1.87			
Step 3: Secondary Control Coping	Group	−0.46	−2.95**	.34	.04	1.60
	DLPFC	0.22	1.34			
	SCC	0.21	1.27			

Note. SFG = Superior frontal gyrus; DLPFC = Dorsolateral prefrontal cortex; SCC = Secondary control coping.
**$p < .01$. *$p < .05$.

Table 7 Hierarchical Linear Regressions: Predictors of Social Problems.

Step	Predictors	β	*t*(*p*)	R^2	ΔR^2	ΔF
SFG and Secondary Control Coping						
Step 1: Group	Group	0.45	2.76*	.20	.20	7.63*
Step 2: SFG BOLD Signal Change	Group	0.44	2.85**	.32	.11	4.81*
	SFG	−0.34	−2.19*			
Step 3: Secondary Control Coping	Group	0.42	3.47**	.59	.27	18.47**
	SFG	−0.03	−0.23			
	SCC	−0.60	−4.30**			

Note. SFG = Superior frontal gyrus; SCC = Secondary control coping.
**$p < .01$. *$p < .05$.

Table 8 Hierarchical Linear Regressions: Predictors of Attention Problems.

Step	Predictors	β	*t*(*p*)	R^2	ΔR^2	ΔF
SFG and Secondary Control Coping						
Step 1: Group	Group	0.38	2.23*	.14	.14	4.96*
Step 2: SFG BOLD Signal Change	Group	0.37	2.25*	.24	.10	3.72
	SFG	−0.31	−1.93			
Step 3: Secondary Control Coping	Group	0.35	2.37*	.38	.14	6.21*
	SFG	−0.10	−0.55			
	SCC	−0.43	−2.49*			
DLPFC and Secondary Control Coping						
Step 1: Group	Group	0.38	2.23*	.14	.14	4.96*
Step 2: DLPFC BOLD Signal Change	Group	0.38	2.36*	.25	.11	4.25*
	DLPFC	−0.33	−2.06*			
Step 3: Secondary Control Coping	Group	0.36	2.46*	.40	.15	7.05*
	DLPFC	−0.19	−1.21			
	SCC	−0.41	−2.66*			

Note. SFG = Superior frontal gyrus; DLPFC = Dorsolateral prefrontal cortex; SCC = Secondary control coping.
**$p < .01$. *$p < .05$.

remained significant. When secondary control coping was added in the third step, both coping and group significantly predicted attention problems. In the second regression, both group and brain activation in the DLPFC (BA9) were significant predictors of attention problems in the second step. When secondary control coping was added in the third step of the model, group and coping were significant predictors of attention problems, but the association between brain activation in the DLPFC (BA9) was no longer significant.

DISCUSSION

The treatment of brain and central nervous system (CNS) malignancies reflects a double-edged sword (Rosoff, 2006). On one hand, significant advances in treatment have led to dramatically improved rates of survival. On the other hand, these aggressive

treatment methods are associated with significant long-term adverse effects, including deficits in neurocognitive and psychosocial functioning. Consistent with previous research, the current results indicate that survivors of pediatric brain tumors report elevated symptoms of anxiety and depression, attention problems, and social difficulties, with mean scores approximately a full standard deviation above the normative mean. However, because not all survivors experience these deficits, exploration of underlying neuroanatomical processes may be helpful in determining mechanisms of risk. The current study is among the first to use functional neuroimaging methods to better understand the nature of these deficits in childhood survivors of brain tumors.

Similar to previous research on the associations among coping and emotional problems (Compas et al., 2012), use of secondary control coping was associated with better social and emotional functioning for both brain tumor survivors and healthy controls. Use of primary control coping was associated with fewer symptoms of anxiety and depression, whereas use of disengagement coping was associated with greater symptoms of anxiety and depression. Within the sample of brain tumor survivors, strong correlations were also found between secondary control coping and symptoms of anxiety and depression, social problems, and attention problems. Because survivors of pediatric brain tumors are at risk for social and emotional difficulties, monitoring of how survivors cope with stress and exploration of whether their coping strategies are limited by other late effects (e.g., neurocognitive deficits) are imperative.

Analyses of BOLD signal activation during the *N*-back task indicated that, as task difficulty increased, brain tumor survivors recruited frontal and parietal regions observed in other studies to activate during completion of an *N*-back task (Owen, McMillan, Laird, & Bullmore, 2005). Although the activation patterns found in healthy controls did not quite exceed the conservative threshold of significance, they did show some increase in BOLD signal in these regions as well. This suggests that participants in both groups were actively engaged during the *N*-back task completion. These brain regions are associated with higher level organization of information, simultaneous processing of multiple cognitive tasks, maintenance of information in working memory, retention of temporal information, visuospatial attention, and complex problem solving. Survivors' recruitment of significantly greater resources to the DLPFC (BA9) during task completion may provide further evidence to support the theory of compensatory activation in children at risk for neurocognitive deficits, as was found in survivors of pediatric leukemia (Robinson et al., 2010).

Patterns of brain activation during a working memory task were associated with levels of emotional, social cognitive, and interpersonal functioning. Specifically, use of secondary control coping was associated with greater activation in the SFG (BA8), whereas use of disengagement coping was associated with reduced activation in the SFG (BA8) and DLPFC (BA9). These findings are consistent with those reported by McRae et al. (2010), who examined the neurobiological underpinnings of reappraisal and distraction, two types of secondary control coping responses, and found evidence of increased activation in the prefrontal and cingulate regions. These two particular regions underlie functions such as the processing of complex, multilevel information as well as the maintenance of visual attention and holding information in working memory over a delay (Owen et al., 2005; Smith & Jonides, 1997). Each of these skills may enable a person to engage in secondary control coping responses by fostering their ability to focus attention on a stressor for a necessary period of time and to generate and examine possible alternatives with the end goal of adjusting reactions to a stressor. These skills rely heavily

on functions tied to the prefrontal regions, and the observed pattern of activation indicates that participants who were able to recruit these cortical regions were more likely to engage in these coping responses. Notably, this process appears to be adaptive, as use of secondary control coping is associated with better overall psychosocial functioning, whereas use of disengagement coping is associated with poorer emotional and social functioning.

In contrast, participants' use of disengagement coping was negatively associated with activation in the DLPFC (BA9) and SFG (BA8). Those who tended to use disengagement forms of coping when faced with stress were less likely to recruit oxygenated blood to regions responsible for complex problem solving, sustained attention, and higher level processing and organization of information. Disengagement coping responses (e.g., denial, avoidance) require little cognitive "effort." Survivors showing lesser activation in these important regions at a neurobiological level may be unable to utilize engagement coping responses and, therefore, resort to disengagement responses. Animal models have found that stress impairs the functioning of the PFC, and researchers have suggested that this may occur through hyperdopaminergic mechanisms that reduce activation of the PFC in favor of more habitual responses mediated by more primitive subcortical structures (e.g., Arnsten & Goldman-Rakic, 1998). Because the temporal development of cognitive deficits and coping responses was not directly assessed, nor was stress level directly assessed during neuroimaging, this interpretation is quite speculative but worthy of future consideration.

Although psychosocial deficits have been well documented in survivors of pediatric brain tumors, the relationships among these deficits and underlying neurobiological processes has not been explored. In the current study, increases in activation in the SFG (BA8), DLPFC (BA9), and APFC (BA10) were negatively associated with symptoms of anxiety and depression across both groups and within only the group of survivors. Participants who showed increased activity of regions associated with complex problem solving, sustained attention, and higher level executive function in response to a working memory task were less likely to report elevated internalizing symptoms. Overall, this pattern reaffirms that activation in these brain regions is adaptive. Notably, although survivors did show significant activation in this specific cluster in the SFG (BA8), between-group analysis of the SFG indicated that healthy controls showed significantly more activation in this region overall than did survivors (Robinson et al., in press).

Using hierarchical regression, we further explored the possibility that the use of adaptive coping accounts for significant variance in the associations among brain activation and psychosocial and attention problems. Within the pooled sample of survivors of pediatric brain tumors and healthy children, secondary control coping did indeed account for significant variance in attention problems and social problems. Although temporal progression could not be examined in this cross-sectional study, these findings suggest an indirect impact of differences in brain activation on symptoms via the limits the activation imposes on the use of adaptive coping responses. In contrast, only group was a significant predictor of social competence. The measure of social competence used in this study includes items that are more related to social contact/exposure (e.g., number of times seeing friends outside of school) as opposed to the quality of peer interactions and frequency of social difficulties. It may be that use of secondary control coping is unrelated to social competence in this sense, whereas it is more relevant to the social problems index, which includes the more interpersonal aspects of social difficulties.

The current study has several strengths that provide unique contributions to this area of research. This is one of few studies to use fMRI to examine the working memory in survivors of pediatric brain tumors and is the first known study to examine associations among brain activation, social and emotional outcomes, and coping. This contributes 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 empirically validated questionnaires and a well-established verbal working memory task conducted during functional neuroimaging.

Despite these strengths, several limitations need to be considered. Given the cross-sectional nature of this study, we are unable to comment on the time course of social and emotional difficulties, as well as the adoption of adaptive versus maladaptive coping styles. Further longitudinal studies will be necessary to explore these issues. Although ratings of coping and psychosocial and emotional functioning were collected from multiple informants, it is possible that by creating statistical composites, shared method variance may contribute to the predictive strength of coping. Our use of two standard deviations from the mean in identifying outliers may have resulted in underidentification due to the impact of outliers on both mean and standard deviation. Additionally, although parallel analyses were conducted with a sample of healthy children and are reported here, direct comparison between groups may provide unique additional information on whether compensatory versus reduced activation is occurring in survivors; these analyses are reported elsewhere (see Robinson et al., in press). We also conceptualized brain activation during the working memory task as a proxy for general neurocognitive functioning, but inclusion of objective measures of neurocognitive functioning may be useful to determine how closely task performance during fMRI mirrors other indicators of this domain. Although the sample sizes reported in this study are adequate for fMRI analysis, limited sample sizes restricted our ability to explore significant associations among questionnaire and assessment measures. The relatively small sample of survivors from one geographic region also may not be not representative of the broader population of survivors of childhood brain tumors. Furthermore, this small sample size limited our ability to include treatment-related variables in analyses. Although subgroup analyses indicated that children who received chemotherapy and/or radiation did not differ on the included measures from children who underwent surgery only, these analyses were markedly underpowered and should be interpreted with caution. Replication of the findings in a larger, multisite sample would be beneficial.

Several avenues of further research would contribute greatly to our understanding of the associations explored in this study. First, although survivors of pediatric brain tumors reported more social problems and lower social competence than both healthy controls and normative expectation, no significant associations among these deficits and neurobiological substrates were identified. Additional analyses may be useful in determining whether difficulties in these areas are uniquely associated with differences in activation in social brain networks (e.g., the "mentalizing network") as opposed to networks more specifically associated with nonsocial working executive function (Lieberman, 2010; Meyer & Lieberman, 2012; Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012). Second, considerable research has indicated that the emergence of neurocognitive and psychosocial functioning deficits is dependent on characteristics of survivors, their diagnosis, and treatment. Future analyses exploring differences in these associations within a

larger, likely multisite, sample of survivors would allow for the consideration of subgroups identified by demographic, diagnostic, or treatment-related variables and would contribute to the broader understanding of moderators of risk and resilience in this population. Additionally, although some longitudinal studies document the emergence of neurocognitive deficits in survivors of pediatric brain tumor (e.g., Copeland, deMoor, Moore, & Ater, 1999; Stargatt, Rosenfeld, Maixner, & Ashley, 2007), the temporal development of difficulties in executive and psychosocial function in survivors remains to be determined. Finally, a better understanding of the underlying processes associated with executive function, psychosocial functioning, and coping in survivors will provide useful information for the development of intervention strategies targeting one or more of these domains. Researchers have begun to examine models of executive function training and cognitive rehabilitation within similar populations, and it is possible that interventions directly targeting the development of adaptive coping responses may be effective as well. This may include, for example, developing coping-related age-appropriate neuroimaging paradigms and examining whether changes in coping following behavioral intervention are evident at a neurobiological level.

This study replicates prior research documenting neurocognitive and psychosocial deficits 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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