

Neurocognitive Status in Long-Term Survivors of Childhood CNS Malignancies: A Report From the Childhood Cancer Survivor Study

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To assess neurocognitive functioning in adult survivors of childhood Central Nervous System (CNS) malignancy, a large group of CNS malignancy survivors were compared to survivors of non-CNS malignancy and siblings without cancer on a self-report instrument (CCSS-NCQ) assessing four factors, Task Efficiency, Emotional Regulation, Organization and Memory. Additional multiple linear regressions were used to assess the contribution of demographic, illness, and treatment variables to reported neurocognitive functioning in CNS malignancy survivors and the relationship of reported neurocognitive functioning to socioeconomic indicators. Survivors of CNS malignancy reported significantly greater neurocognitive impairment on all CCSS-NCQ factors than non-CNS cancer survivors or siblings ($p < .01$). Within the CNS malignancy group, medical complications (hearing deficits, paralysis and cerebrovascular incidents) resulted in a greater likelihood of reported deficits on all CCSS-NCQ factors. Total or partial brain irradiation and ventriculoperitoneal (VP) shunt placement was associated with greater impairment on Task Efficiency and Memory. Female gender was associated with a greater likelihood of impaired scores on Task Efficiency and Emotional Regulation, while diagnosis before age 2 years resulted in less likelihood of reported impairment on the Memory factor. CNS malignancy survivors with more impaired CCSS-NCQ scores demonstrated significantly lower educational attainment ($p < .01$), less household income ($p < .001$), less full time employment ($p < .001$), and fewer marriages ($p < .001$). Survivors of childhood CNS malignancy were found to be at significant risk for neurocognitive impairment that continues to adulthood and is correlated with lower socioeconomic achievement.

Keywords: neurocognitive functioning, brain tumors, CNS malignancies, Childhood Cancer Survivor Study

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Cancers of the central nervous system (CNS), the most common solid malignancies in childhood, are associated with a number of sequelae including dysfunction in neurologic, endocrine, social, psychological, and neurocognitive areas (Anderson et al., 2001; Packer et al., 2003; Schultz et al., 2007). In the neurocognitive domain, reduced global IQ compared with controls and normative samples has been reported (Ellenberg et al., 1987; Palmer et al., 2003), as have deficits in specific cognitive functions including verbal skills, visual spatial skills, attention, memory, psychomotor speed, and learning (Kiehna et al., 2006; Mabbott et al., 2008; Mulhern et al., 2004; Nagel et al., 2006). In particular, recent research has focused on attention, processing speed and working memory as domains of significant dysfunction in survivors of childhood CNS cancer, perhaps because of the sensitivity of these functions to white matter damage resulting from cranial irradiation (Ris, 2005).

Factors within the population of pediatric CNS malignancy patients that have been associated with neurocognitive outcome include tumor site (Mulhern et al., 1992), age at diagnosis (Sands et al., 2001), and radiation treatment (Reamers et al., 2003). Cortical tumors have been reported to result in more cognitive late effects than 3rd or 4th ventricle tumors (Ellenberg et al., 1987; Mulhern et al., 1992). However, pediatric posterior fossa tumors have also been associated with neurocognitive sequelae including deficits in attention, planning, sequencing, executive functioning, memory, processing speed, visual-spatial organization, modulation of affect, and behavior (Beebe et al., 2005; Karatekin et al., 2000; Levisohn et al., 2000; Riva & Giorgi, 2000; Schmahmann & Sherman, 1998; Steinlin et al., 2003).

Radiation therapy is a well established risk factor for neurocognitive difficulties of CNS cancer patients as well as of children with leukemia treated with prophylactic cranial radiation (Smibert et al., 1996; Spiegler et al., 2004). Correlation between the amount of radiation received and IQ declines have been demonstrated (Grill et al., 1999; Kieffer-Renaux et al., 2000). MRI studies suggest that radiation may be associated with changes to white matter, including calcification and reduction in white matter volume that may contribute to these difficulties (Mulhern et al., 1999). Animal studies of the pathophysiology of late effects of cranial radiation therapy suggest primary apoptosis of endothelial and oligodendroglial cells as well as secondary cell injury and death mediated by hypoxia/ischemia and neuro-inflammation that results in a cascade of events that alter the microenvironment, leading to further endothelial dysfunction, disruption of the blood-brain barrier, inhibition of neurogenesis, demyelination, and tissue necrosis (Wong & Van der Kogel, 2004).

CNS malignancy survivors treated with radiation therapy at younger ages have frequently been reported to show greater neurocognitive impairment (Radcliffe et al., 1994; Ris et al., 2001). For example, Palmer et al. (2001), in a longitudinal study of intellectual development in medulloblastoma patients, found patients treated at ≤ 8.02 years of age had significantly greater declines in IQ, knowledge and nonverbal abstract thinking than older patients. Mulhern and Palmer (2003) suggest that the greater cognitive decline may be because of the differential effect of cranial irradiation on greater cognitive decline white matter, which continues to develop until age 20, but seems to be lost at a similar rate by younger and older patients. The younger patients, then, may have more white matter loss over time, and reduced white

matter volume in younger CNS malignancy patients has been associated with greater intellectual deficits (Mulhern et al., 1999). In a recent study, Mabbott et al. (2008) reported no effect of age of diagnosis on attention and working memory in children treated for posterior fossa tumors with radiation therapy, although the authors caution that their sample was small and within a narrow age range, which may have skewed their results.

Most of the available literature on neuropsychological outcomes in pediatric CNS malignancy survivors followed patients for a limited period after treatment. The Childhood Cancer Survivors Study (CCSS) was designed to assess adults who survived childhood cancers. Based on CCSS data, adolescent and adult survivors of CNS malignancy, compared with other cancer survivors, show increased neurological deficits (Packer et al., 2003), problems with depression (Zebrack et al., 2004), anxiety, attention, social behavior (Schultz et al., 2007), and reduced reported quality of life (Zeltzer et al., 2008).

The main goal of the present study was to examine and quantify neurocognitive functioning and adaptive outcome in adult survivors of childhood CNS malignancies who are 16–34 years from their original diagnosis. We evaluated a large group of CCSS enrolled CNS malignancy survivors to determine their degree of reported neurocognitive dysfunction compared with survivors of non-CNS malignancy and a sibling cohort. Within the group of CNS malignancy survivors, we assessed factors related to treatment [cranial radiation, surgery, ventriculoperitoneal (VP) shunt], illness or therapy residuals (sensory and/or motor deficits, stroke), and demographic variables (gender, age at diagnosis) that might be associated with greater neurocognitive dysfunction. Moreover, we evaluated the degree of correlation between neurocognitive dysfunction and the adult socioeconomic outcomes of educational attainment, employment status and household income. We hypothesized the following:

Hypothesis 1: Survivors of CNS malignancies will report greater neurocognitive dysfunction than survivors of non-CNS malignancies and siblings.

Hypothesis 2: The greatest reported neurocognitive dysfunction will be in processing speed, memory, planning, and organization, aspects of task efficiency and executive functioning.

Hypothesis 3: There will be greater reported neurocognitive deficits in CNS malignancy survivors who had significant motor or sensory residuals, cranial radiation, cortical tumors, or were younger at diagnosis.

Hypothesis 4: Reported neurocognitive impairment will be associated with poorer adaptive outcome in adulthood as assessed by lower achievement in education, full time employment and income, and less likelihood of being married.

Method

Participants

The methodology for the CCSS and the characteristics of the study population has been published previously (Robison et al.,

2002). The CCSS is a retrospective cohort of children and adolescents treated for cancer at 26 collaborating institutions in the US and Canada (see Appendix A). Individuals below the age of 21 diagnosed between 1970 and 1985 with leukemia, CNS malignancy, Hodgkin's disease, non-Hodgkin's lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, or malignant bone tumor who survived over 5 years were recruited. Respective institutional review boards of participating centers reviewed and approved the CCSS protocol. Of the 20,691 eligible individuals, 17,568 were located and 14,363 survivors (81.8%) and 3,899 siblings were enrolled. Of the survivors and siblings, who participated in the baseline survey, mostly tested between 1992 and 1998, 9,308 survivors (64.8%) and 2,951 siblings (75.7%) participated in the 2003 follow-up survey (2002–2005).

The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ), described below, was included in the 2003 Follow-up Survey and sent to all survivors and a selected subsample of 500 siblings, chosen using simple random sampling from those siblings who completed the baseline survey, were not lost to follow-up and had not refused further participation. The CCSS-NCQ was fully completed with no missing data for 802 (68.1%) of the 1,177 survivors of CNS cancer who participated in the follow-up survey as well as 5,937 (73.0%) of the 8,130 survivors of non-CNS cancers and 382 (76.4%) of the selected group of 500 siblings. Comparison of the 802 CNS participants to the 375 CNS nonparticipants demonstrated that nonparticipants were more likely to be from ethnic or racial minority backgrounds (13.9% vs. 7.1%; $p < .001$). In addition, nonparticipants were more likely to be younger at time of CNS diagnosis (6.9 years vs. 8.5 years; $p < .001$). No statistically significant differences were detected between participants and nonparticipants in gender, treatment with cranial radiation therapy or time since diagnosis (16.1–34.6 years). The diagnoses of the survivors of non-CNS childhood cancers were as follows: Leukemia (37.6%), Hodgkin's disease (15.3%), non-Hodgkin's lymphoma (8.6%), neuroblastoma (7.3%), soft tissue sarcoma (10.3%), osteosarcoma (6.4%), Ewings and other bone tumors (3.6%), and Wilm's tumor (10.9%).

The survey forms were sent directly to any participant 18 years or older and to the parents of individuals under 18 years of age. Parents completed the forms for all participants <18 years of age. Otherwise, forms were completed by the subject or by someone else who was familiar with the subject's neurocognitive functioning (proxy), with a box on the survey form to indicate whether the form was completed by self or proxy. Not all completed forms were appropriately marked. Data were available for 785 of the CNS malignancy survivors, and it was indicated that 136 of the CCSS-NCQs were completed by proxy (spouse: 3, friend: 1, sibling: 2, in-law: 4, legal guardian: 1, caseworker: 1, parent or not otherwise specified: 124). For the non-CNS cancer survivors, 243 of 5,870 for whom data were available were completed by proxy (spouse: 33, friend: 4, sibling: 1, in-law: 1, legal guardian: 3, grandparent: 1, parent or not otherwise specified: 200) and for the sibling group, 3 of 379 for whom data were available were completed by proxy (spouse: 1, parent or not otherwise specified: 2). Although there was no code for the reason forms were completed by proxy, many of the proxy respondents for CNS survivors indicated by writing on the form that they completed it because of cognitive problems of the participant. Other reasons informally

provided by proxy respondents for all groups included mental health or drug abuse issues, participant away at school or military and participant not interested.

Instrument

To assess self-reported neurocognitive functioning, an instrument was developed for the CCSS population based on the Behavior Rating Inventory of Executive Functioning (BRIEF), a multidimensional standardized behavior rating inventory for children, adolescents, and adults with scales labeled Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor (Gioia, Isquith, & Guy, 2000; Guy, Isquith, & Gioia, 2004; Roth, Isquith, & Gioia, 2005). The two items of each BRIEF scale with the highest item-total correlation were combined with independently derived items designed to assess the neurocognitive domains of processing speed, memory, and academic functioning. The resulting 25 items were factor analyzed in a group of 382 siblings of CCSS survivors (Krull et al., 2008). Four reliable and valid factors were found based on 19 of the original 25 items, labeled Task Efficiency, Emotional Regulation, Organization, and Memory, and these 19 items constitute the resulting instrument, the CCSS-NCQ, presented in Appendix B.

Although the 25 item questionnaire was also given to a group of 900 individuals as part of the standardization of the adult version of the BRIEF, the 382 siblings were used as the normative group for ultimate development of the CCSS-NCQ because they were demographically more similar to the cancer survivors in terms of ethnic group and education (compared to the non-CNS malignancy survivors). The sums of item endorsements by the siblings (i.e., "Never a problem" [scored 1], "Sometimes a problem" [scored 2], "Often a problem" [scored 3]) on each factor were converted to *T* scores, such that the sibling group had a mean of 50 and a standard deviation of 10 on each of the four factors, with higher scores indicative of greater reported neurocognitive impairment.

Treatment and Radiation Exposure

Medical records were abstracted for treatment-related information including chemotherapy, surgery, and radiation therapy. To quantify radiation exposure, the brain was partitioned into four segments, posterior fossa (Field 1), temporal lobe (Field 2), frontal cortex (Field 3), and parietal or occipital lobe (Field 4) and maximum radiation dosages were assigned for each field utilizing radiation oncology records from the treating institutions. A segment was said to be included in a radiation field if at least 50% of the segment was in the primary radiation volume. Nearly all CNS malignancy survivors who received cranial radiation therapy received high doses, at or above 40 gray (the Standard International Unit for absorbed ionizing radiation, abbreviated Gy), with only 2% receiving a lower dose.

Data Analysis

The first set of analyses compared survivors of CNS malignancy with survivors of non-CNS malignancy and the sibling group. Descriptive statistics for gender, age, ethnicity, education, household income, and employment status were generated for the three groups. The groups were compared on each of the four CCSS-NCQ factor

scores via multiple linear regression, adjusting for age at the time of the study, gender, and ethnicity. When survivors and siblings were compared, the modification of linear regression by Generalized Estimating Equations was used to account for potential within-family correlation (Zeger & Liang, 1986).

The remaining analyses involved only survivors of CNS malignancy. Within the CNS malignancy patient group, multiple linear regression was used to assess the effects of the following potential independent variables on each of the four CCSS-NCQ factor scores, adjusted for race: age at survey; age at diagnosis; VP shunt; gender; sensory/motor complications [hearing loss (reduced hearing, deafness in one or both ears), visual difficulty (blindness, cataracts), paralysis, cerebrovascular incident]; surgery (yes/no); cranial radiation therapy [whole brain, partial (less than all 4 dosimetry fields), none]; and chemotherapy (yes/no). Only treatments provided within the first 5 years from the original diagnosis of cancer were considered. We also adjusted for whether or not the questionnaire was completed by proxy.

To assess the contribution of more specific factors to outcome, multiple linear regressions adjusted for age at the time of the study, gender, and ethnicity were used for individual comparisons. CCSS-NCQ scores of CNS malignancy survivors with and without paralysis, hearing and/or visual difficulties, and stroke were examined. Because gender was significantly associated with CCSS-NCQ factor scores in CNS malignancy survivors, gender was examined in the sibling group to assess whether the effects were specific to CNS malignancy survivors or a more general gender effect. To assess the effect of tumor site in radiated CNS malignancy survivors, those with cortical versus subcortical radiation boosts were compared. To assess the effect of radiation dose on neurocognitive outcome, CNS malignancy survivors who received cortical radiation without a cortical tumor were compared to leukemia survivors who received 24 Gy of cranial radiation and nonirradiated leukemia patients. Finally, to assess the relationship between neurocognitive outcome and socioeconomic variables in adulthood, individual multiple linear regressions were used to examine the association between age, gender, and ethnicity adjusted CCSS-NCQ scores of CNS malignancy survivors and educational attainment (<high school degree, high school graduate, college graduate), household income (<\$20,000; \$20,000–\$39,999; \$40,000–\$59,999; and ≥\$60,000), employment status (<full time, full time), and marital status (ever married/never married). All statistical analyses were performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC) and 2-sided statistical inferences were employed throughout the analyses.

Results

Characteristics of the Study Population

Demographic characteristics of survivors of CNS malignancy, non-CNS cancers and the sibling group are presented in Table 1. Compared to survivors of CNS malignancy, the sibling group was older ($p = .002$), better educated ($p = .003$), more likely to be employed ($p < .001$), had higher family income ($p < .001$), and were more likely to have been married ($p < .001$). Siblings were also older ($p < .001$), had higher household incomes ($p < .001$), and were more likely to have been married ($p < .001$) than survivors of non-CNS cancers. Compared to survivors of non-CNS malignancies, survivors of CNS malignancy were more likely to be male ($p = .04$), less educated ($p < .001$), less fully employed

($p < .001$), and have lower household incomes ($p < .001$). With age at diagnosis divided into developmentally based categories (infancy, early and middle childhood, early and late adolescence), more non-CNS malignancy survivors than CNS malignancy survivors were observed in the 0–2 and 16–20-year-old age categories. In terms of treatment, CNS malignancy survivors were more likely to have received surgery ($p < .001$) and less likely to have received chemotherapy ($p < .001$) than were survivors of non-CNS cancers.

Neurocognitive Outcomes in Survivors of Childhood CNS Malignancies, Non-CNS Malignancies, and Siblings

As presented in Table 2, CNS malignancy survivors reported significantly greater neurocognitive dysfunction than the sibling cohort or non-CNS malignancy survivors on all CCSS-NCQ factors. Effect sizes for the differences between CNS cancer survivors and siblings as well as between CNS and non-CNS cancer survivors were small for Organization (CNS vs. sibs = .22, CNS vs. non-CNS = .23) and Emotional Regulation (CNS vs. sibs = .29, CNS vs. non-CNS = .11), medium for Memory (CNS vs. sibs = .68, CNS vs. non-CNS = .53), and large for Task Efficiency (CNS vs. sibs = 1.16, CNS vs. non-CNS = .90). Non-CNS malignancy survivors scored closer to the sibling cohort; while they showed more impaired scores on three of the four CCSS-NCQ scales, the effect sizes were small (Task Efficiency = .26, Emotional Control = .18, Memory = .15).

Factors Predicting Neurocognitive Dysfunction in CNS Cancer Survivors

Factors that predicted self and/or proxy reported neurocognitive dysfunction in survivors of CNS malignancy are presented in Table 3. Medical complications, including visual and hearing difficulties, paralysis, and stroke, were associated with greater reported deficits on all of the CCSS-NCQ factors, with generally small effect sizes (.22–.50). Cranial radiation was correlated with greater impairment on Task Efficiency and Memory, with medium effect sizes for total brain irradiation (.65 and .63, respectively), and smaller effect sizes for partial brain irradiation (.49 and .43, respectively). VP shunt predicted more impaired Task Efficiency and Memory scores, as well, but to a lesser degree (Effect sizes: Task Efficiency .26, Memory .32). Female gender predicted more impaired scores on the Task Efficiency and Emotional Regulation scales, with small effect sizes (Task Efficiency .38, Emotional Regulation .45), whereas diagnosis before age 2 predicted less impairment on the Memory scale with a moderate effect size (.64). Completion of the form by proxy was associated with more impairment on all CCSS-NCQ scales. The effect size was very large for the Task Efficiency scale (1.39), medium for Organization (.51) and Memory (.57), and small for Emotional Regulation (.34).

Specific Predictor Variables

Complications. Table 4 provides results of multivariate analysis investigating selected medical complications and domain-specific scores. CNS malignancy survivors with concomitant hearing and visual complications scored significantly poorer on each of the four CCSS-NCQ scales than other CNS survivors, with me-

Table 1

Comparison of Demographic Variables Between CNS Malignancy Survivors, Non-CNS Malignancy Survivors and Siblings

Characteristics ^{a,b}	CNS survivors (n = 802)	Non-CNS survivors (n = 5,937)	Siblings (n = 382)	p (CNS vs. non-CNS)	p (CNS vs. sibs)	p (non-CNS vs. sibs)
Sex				0.04	0.14	0.78
Male	419 (52.2%)	2,876 (48.4%)	182 (47.6%)			
Female	383 (47.8%)	3,061 (51.6%)	200 (52.4%)			
Age at time of study				0.01	0.002	<.001
Mean (SD)	31.5 (7.1)	32.2 (7.6)	34.1 (8.4)			
Range	17.4–51.8	17.0–54.1	17.8–58.4			
Median	31.2	31.9	33.7			
Ethnicity				0.36	0.99	0.65
White	745 (93.2%)	5,397 (91.2%)	336 (93.9%)			
Black	17 (2.1%)	147 (2.5%)	8 (2.2%)			
Hispanic/Latino	20 (2.5%)	222 (3.8%)	9 (2.5%)			
Other	17 (2.1%)	152 (2.6%)	5 (1.4%)			
Education				<.001	0.003	0.37
<12 years	43 (5.4%)	219 (3.7%)	9 (2.4%)			
High school grad.	455 (56.8%)	2886 (48.6%)	181 (47.5%)			
College grad.	303 (37.8%)	2,831 (47.7%)	191 (50.1%)			
Employment				<.001	<.001	0.13
Full time	353 (44.0%)	3,931 (66.2%)	267 (69.9%)			
Other	449 (56.0%)	2,006 (33.8%)	115 (30.1%)			
Household income				<.001	<.001	<.001
<\$19,999	163 (21.2%)	663 (11.4%)	26 (6.9%)			
\$20,000–39,999	199 (25.9%)	1,335 (22.9%)	62 (16.5%)			
\$40,000–59,999	165 (21.5%)	1,232 (21.1%)	82 (21.8%)			
Over 60,000	241 (31.4%)	2,604 (44.6%)	206 (54.8%)			
Ever married				<.001	<.001	<.001
Yes	277 (34.8%)	3,489 (59.3%)	271 (71.7%)			
No	518 (65.2%)	2,391 (40.7%)	107 (28.3%)			
Age at diagnosis				<.001		
0–2	136 (17.0%)	1,355 (22.8%)				
3–5	165 (20.6%)	1,325 (22.3%)				
6–10	232 (28.9%)	1,101 (18.5%)				
11–15	201 (25.1%)	1,302 (21.9%)				
16–20	68 (8.5%)	854 (14.4%)				
Treatment				<.001		
Surgery only	225 (30.1%)	280 (5.0%)				
Chemotherapy only	0 (0.0%)	499 (9.0%)				
Radiation only	13 (1.7%)	11 (0.2%)				
Chemo. + radiation	3 (0.4%)	850 (15.3%)				
Chemo. + surgery	12 (1.6%)	1,164 (20.9%)				
Radiation + surgery	344 (46.1%)	441 (7.9%)				
Chemo. + rad + surgery	150 (20.1%)	2,322 (41.7%)				
Cranial radiation ^c				<.001		
None	268 (37.1%)	3,910 (71.5%)				
Whole brain	218 (30.2%)	1,436 (26.3%)				
Partial brain	236 (32.7%)	124 (2.2%)				
Cranial radiation dose				<.001		
None	268 (37.1%)	3,910 (71.5%)				
0.1–19 Gy	2 (0.3%)	674 (12.3%)				
20–39 Gy	7 (1.0%)	762 (13.9%)				
40–59 Gy	423 (58.6%)	112 (2.0%)				
≥60 Gy	22 (3.0%)	12 (0.2%)				
Tumor Type	495 (61.7%)					
Astrocytoma						
Medulloblastoma, PNET	172 (21.5%)					
Other CNS	135 (16.8%)					

Note. Percentages are based on the total with available data for each variable.

^a For categorical characteristics, bootstrap of the families was used to account for the family effect when the *p*-values were obtained. ^b For continuous characteristics GEE was used to account for the family effect when the *p*-values were obtained. ^c Does not include patients for whom radiation status was unknown.

dium effect sizes for Task Efficiency (.86) and Memory (.69) and smaller effect sizes for Emotional Regulation (.43) and Organization (.47), although those with hearing deficits alone scored worse on all scales except Emotional Regulation (Effect sizes: Task

Efficiency .80, Memory .50, Organization .32). Visual complications alone were not significantly associated with poorer scores. History of stroke was significantly associated with poorer mean scores in Task Efficiency (Effect size .78), Emotional Regulation (Effect size

Table 2
 CCSS-NCQ Scores of Childhood Cancer Survivors and Siblings

Characteristics	CNS survivors (n = 802)	Non-CNS survivors (n = 5,937)	Siblings (n = 382)	p-values*		
				CNS vs. non-CNS	CNS vs. sibs	Non-CNS vs. sibs
Task efficiency				<.001	<.001	<.001
Mean (SD)	61.6 (16.0)	52.6 (12.6)	50.0 (10.0)			
Effect size	1.16	0.26				
Emotional regulation				0.004	<.001	0.002
Mean (SD)	52.9 (11.1)	51.8 (10.9)	50.0 (10.0)			
Effect size	0.29	0.18				
Organization				<.001	0.007	0.82
Mean (SD)	52.2 (10.8)	49.9 (10.0)	50.0 (10.0)			
Effect size	0.22	-0.01				
Memory				<.001	<.001	0.002
Mean (SD)	56.8 (13.5)	51.5 (11.8)	50.0 (10.0)			
Effect size	0.68	0.15				

* p-values are age, gender, and race adjusted.

.39), and Memory (Effect size .45) and reported paralysis was associated with significantly more impairment in Task Efficiency (Effect size .45) and Organization (Effect size .30).

Cranial radiation dose/tumor location. Precise site of CNS tumor was not available for the CCSS cohort. However, many CNS malignancy survivors who had radiation therapy had a "boost" field, a smaller field inside a region already treated with a larger field, used to treat the specific tumor site with additional irradiation. Patients with cortical radiation focus (Boosts to Fields 2, 3, and/or 4; $n = 119$) were compared to patients with subcortical radiation focus (Boost to posterior fossa Field 1; $n = 102$) on CCSS-NCQ scale scores. The groups were not significantly different.

To assess the association of cranial radiation dose with neurocognitive impairment, CCSS-NCQ scores of 65 CNS malignancy patients who received whole brain radiation (mean dose = 36.3 Gy, $SD = 5.97$ Gy), with the highest dose (boost) to Field 1, indicating a subcortical tumor, were compared to scores of 510 leukemia survivors who received 24 Gy of cranial radiation and 744 nonradiated leukemics. The CNS survivors reported significantly more impairment ($p < .001$) on the Task Efficiency factor than leukemia survivors who received 24 Gy of cranial radiation (Effect size .64), who in turn reported significantly more impairment than nonradiated leukemia survivors (Effect size .45). On the Memory factor, the CNS malignancy group and the radiated leukemics did not differ from each other, but both showed significantly more impairment ($p < .001$) than the nonradiated leukemics (CNS malignancy effect size .71; radiated leukemics effect size .35).

Gender. In survivors of CNS malignancy, female gender predicted more impairment on Task Efficiency and Emotional Regulation in the multivariate analysis. To ascertain whether this was unique to CNS survivors, males and females in the sibling cohort were compared on CCSS-NCQ scale scores via univariate analysis. Female siblings had higher CCSS-NCQ scores than their male counterparts on the Emotional Regulation scale ($p < .001$), with similarly small effect size (CNS survivors: .45, sibling group: .34), suggesting that females, in general, may report slightly more difficulty with Emotional Regulation than males.

CCSS-NCQ scores and indicators of adaptive outcome. Within the group of CNS malignancy survivors, CCSS-NCQ scores were highly correlated with variables predictive of success

in the achievement of adult tasks (see Table 5). Lower educational attainment was associated with more impairment on CCSS-NCQ Task Efficiency, Emotional Regulation and Memory scales. Less than full time employment was associated with greater impairment on all CCSS-NCQ scales and household income under \$20,000 per year was associated with more impaired CCSS-NCQ scores on all scales compared to household income over \$60,000. Never having been married correlated with poorer Task Efficiency, Memory and Organization scores.

Discussion

Survivors of childhood CNS malignancies are at known risk for deficits in neuropsychological functioning. The current study was the first to follow a large cohort of CNS malignancy survivors to adulthood, using large non-CNS malignancy and sibling control groups, to quantify the degree and assess the nature of the neurocognitive dysfunction in these survivors, determine associated risk factors and evaluate the impact of neurocognitive impairment in adulthood. Among CNS malignancy survivors in the CCSS cohort, risk of neurocognitive dysfunction was significantly associated with treatment involving cranial irradiation or placement of a VP shunt, as well as a history of stroke, paralysis, or auditory difficulties.

Of the factors identified on the CCSS-NCQ in the present study, CNS malignancy survivors with cognitive impairment were most likely to report dysfunction on the Task Efficiency scale, which contains items related to speed of performance, self initiation and multitasking, as well as on the Memory scale, which assesses both long term and working memory. The two scales are highly correlated with each other (.71), whereas correlations between the other scales are less robust (.36 to .57). In contrast to some studies of selected subgroups of CNS cancer patients (Mabbot et al., 2008; Reddick et al., 2003; Schatz et al., 2000), our results suggest that the combined CNS malignancy survivor group is left with deficits in both information processing speed and working memory, rather than showing impairment in only one of the two variables.

The complications of paralysis, stroke, or hearing impairment were found to be highly predictive of neuropsychological dysfunction in survivors of CNS malignancy. The mean scores for Task Efficiency of CNS survivors in each of these groups was in the

Table 3
Multiple Linear Regression Analysis of Factors Predicting CCSS-NCQ Scores For CNS Malignancy Survivors^a

Variables	Task efficiency		Emotional regulation		Organization		Memory	
	Mean diff ^b (95% CI)	<i>p</i>	Mean diff ^b (95% CI)	<i>p</i>	Mean diff ^b (95% CI)	<i>p</i>	Mean diff ^b (95% CI)	<i>p</i>
Age at dx								
0–2	1.1 (–4.8, 7.0)	0.72	0.5 (–4.1, 5.1)	0.84	–1.1 (–5.5, 3.3)	0.63	–6.4 (–11.7, –1.0)	0.02
3–5	0.6 (–5.0, 6.1)	0.84	0.2 (–4.0, 4.5)	0.91	1.3 (–2.8, 5.4)	0.54	–4.8 (–9.7, 0.2)	0.06
6–10	–0.1 (–5.2, 4.9)	0.96	0.3 (–3.6, 4.2)	0.89	2.0 (–1.7, 5.8)	0.29	–3.2 (–7.7, 1.4)	0.17
11–15	–0.7 (–5.4, 4.0)	0.78	0.8 (–2.9, 4.4)	0.67	2.0 (–1.5, 5.5)	0.25	–1.7 (–5.9, 2.5)	0.43
16–20	Ref		Ref		Ref		Ref	
VP shunt								
Yes	2.6 (0.2, 5.0)	0.03	0.7 (–1.2, 2.6)	0.46	0.7 (–1.0, 2.5)	0.41	3.2 (1.1, 5.4)	0.003
No	Ref		Ref		Ref		Ref	
Brain RT								
Whole brain	6.5 (3.7, 9.4)	<.001	1.6 (–0.6, 3.8)	0.16	0.5 (–1.6, 2.6)	0.64	6.3 (3.8, 8.9)	<.001
Partial brain	4.9 (2.3, 7.4)	<.001	0.8 (–1.2, 2.8)	0.45	1.5 (–0.4, 3.4)	0.13	4.3 (2.0, 6.6)	<.001
None	Ref		Ref		Ref		Ref	
Surgery								
Yes	1.9 (–3.9, 7.8)	0.51	2.4 (–2.2, 6.9)	0.31	–2.4 (–6.7, 2.0)	0.29	2.7 (–2.6, 7.9)	0.32
No	Ref		Ref		Ref		Ref	
Chemotherapy								
Yes	2.1 (–0.6, 4.9)	0.13	0.4 (–1.8, 2.5)	0.73	0.4 (–1.6, 2.5)	0.69	1.4 (–1.1, 3.9)	0.27
No	Ref		Ref		Ref		Ref	
Complications								
Yes	5.0 (2.8, 7.2)	<.001	2.2 (0.5, 3.9)	0.01	2.4 (0.8, 4.0)	0.004	3.9 (2.0, 5.9)	<.001
No	Ref		Ref		Ref		Ref	
Gender								
Female	3.8 (1.7, 5.9)	<.001	4.5 (2.8, 6.1)	<.001	1.0 (–0.6, 2.6)	0.22	1.8 (–0.1, 3.8)	0.06
Male	Ref		Ref		Ref		Ref	
Completed by self								
No	13.9 (10.9, 16.8)	<.001	3.4 (1.1, 5.6)	0.004	5.1 (2.9, 7.2)	<.001	5.7 (3.1, 8.3)	<.001
Yes	Ref		Ref		Ref		Ref	
Age at study								
17–24	2.0 (–3.1, 7.1)	0.43	2.6 (–1.4, 6.5)	0.20	2.3 (–1.5, 6.1)	0.24	2.0 (–2.6, 6.6)	0.39
25–29	0.1 (–4.4, 4.7)	0.95	2.1 (–1.4, 5.6)	0.25	–1.0 (–4.3, 2.4)	0.57	–0.4 (–4.5, 3.7)	0.84
30–34	1.0 (–3.1, 5.1)	0.63	1.1 (–2.1, 4.3)	0.52	0.3 (–2.8, 3.4)	0.85	–0.6 (–4.3, 3.1)	0.74
35–39	0.4 (–3.7, 4.5)	0.84	1.4 (–1.7, 4.6)	0.37	0.3 (–2.7, 3.4)	0.84	–0.4 (–4.1, 3.3)	0.84
40+	Ref		Ref		Ref		Ref	
Race								
Other	3.1 (–1.3, 7.5)	0.17	0.4 (–3.0, 3.8)	0.82	2.8 (–0.5, 6.1)	0.09	3.8 (–0.2, 7.8)	0.06
White	Ref		Ref		Ref		Ref	

^a Ref = Reference group. ^b effect size = the mean difference divided by 10.

impaired range compared to the normative sibling group (>1.5 *SD* from the mean). The high degree of neurocognitive impairment among CNS malignancy survivors with hearing difficulties, but not visual deficits, is surprising. Compared with other CNS cancer survivors, those with hearing problems did not have significantly different diagnoses. However, they were more likely than other CNS survivors to have received cranial radiation (93% vs. 64%) or chemotherapy (40% vs. 20%), and to have been treated with Cisplatin, which is known to affect hearing (13% vs. 4%), although in our multiple regression model, hearing difficulties emerged as an independent contributor to reported neurocognitive dysfunction when controlling for treatment variables. To our knowledge, this association has not been previously reported. Our study did not consider tumor site as a variable. It may be that hearing loss is associated with CNS malignancies in areas of the brain where irradiation produces significant neurocognitive deficits. This possibility can be investigated using the current CCSS cohort, since data regarding tumor site will be available.

Because of the general uniformity of whole brain radiation dose in CNS malignancy patients, a relationship between radiation dose and degree of neuropsychological impairment could not be established using the CNS group alone in the current study. Comparison with a group of leukemia patients who received 24 Gy of cranial radiation, however, yielded data suggestive of a dose/response relationship between amount of cranial irradiation and neurocognitive impairment. Although CNS tumor and leukemia patients differ in many other ways, these data are in agreement with a number of previous studies correlating dose of cranial irradiation with neurocognitive outcome in survivors of ALL (Halberg et al., 1992) and medulloblastoma (Grill et al., 1999; Kieffer-Renaux et al., 2000; Mulhern et al., 1998).

Contrary to previous studies (Ellenberg et al., 1987; Sands et al., 2001), younger age at diagnosis was not correlated with greater reported neurocognitive dysfunction in the current large sample of adult CNS malignancy survivors. The present study assessed individuals who were significantly older and farther from the age at which they were diagnosed with and treated for cancer than other studies. It

Table 4
CCSS-NCQ Scores of CNS Malignancy Survivors With and Without Individual Medical Complications^a

	Task efficiency				Emotional regulation			Organization			Memory		
	Freq	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values
Sensory Deficits													
Hearing + visual	27	68.6 (16.3)	0.88	0.004	57.0 (11.1)	0.46	0.03	56.2 (10.7)	0.47	0.03	63.0 (12.9)	0.69	0.008
Hearing	89	68.0 (15.5)	0.86	<.001	53.7 (11.0)	0.17	0.17	54.7 (10.7)	0.34	0.006	61.1 (14.1)	0.54	<.001
Visual	101	63.4 (15.7)	0.26	0.12	52.4 (10.3)	-0.07	0.52	53.3 (10.7)	0.16	0.16	55.6 (12.9)	-0.06	0.66
Neither	573	60.0 (15.8)		Ref	52.7 (11.2)		Ref	51.5 (10.9)		Ref	56.1 (13.3)		Ref
Stroke													
Yes	35	70.0 (17.5)	0.87	0.001	56.6 (12.0)	0.37	0.05	53.8 (10.4)	0.17	0.37	61.1 (14.7)	0.47	0.04
No	763	61.2 (15.8)		Ref	52.7 (11.0)		Ref	52.0 (10.8)		Ref	56.6 (13.4)		Ref
Paralysis													
Yes	114	65.5 (17.4)	0.40	0.01	54.5 (12.2)	0.14	0.19	54.7 (11.1)	0.28	0.01	58.3 (13.2)	0.16	0.25
No	686	61.0 (15.7)		Ref	52.7 (10.8)		Ref	51.7 (10.7)		Ref	56.6 (13.5)		Ref

^a Sensory deficits, stroke, and paralysis were analyzed separately adjusting for age, gender and race, or ethnic group. Mean and *SD* were given for descriptive purposes and unadjusted, while effect sizes were estimated with the adjustment. Ref = Reference group.

is possible that children with CNS malignancies that are diagnosed and treated at younger ages show more difficulty with childhood outcome measures, such as academic achievement, than those diagnosed and tested when they are older. However, both groups appear to report similar difficulties with neurocognitive functioning in adulthood. As maturity demands more complex neurocognitive skills, including executive functions and the management of multiple simultaneous tasks, childhood CNS malignancy survivors may “grow into” neurocognitive deficits that carry a greater impact in adult life. It may be that the white matter abnormalities, including calcifications, other lesions and smaller white matter volumes, which have been implicated in the neurotoxicity of cranial radiation therapy (Fouladi et al.,

2004; Reddick et al., 2006), result in deficits in integrative neurocognitive functions that lead to greater impairment in complex adult tasks compared to those assessed in survivors during childhood. In addition, previous studies have relied on test data, whereas the current study used a self-report measure. It is possible that individuals experience neurocognitive deficits even when objective tests do not show commensurate impairment.

Mabbott et al. (2008) failed to find an age effect in information processing speed among childhood medulloblastoma survivors, in a recent small study. Most studies in the past have used more general measures of neuropsychological dysfunction (e.g., IQ). It may be that certain deficits, such as processing speed, are robust

Table 5
CCSS-NCQ Scores of CNS Malignancy Survivors by Categories of Education, Household Income, Ad Employment and Marital Status^a

	Task efficiency				Emotional regulation			Organization			Memory		
	Freq	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values	Mean (SD)	Effect size	<i>p</i> values
Education													
Not high school grad	43	75.8 (14.4)	1.87	<.001	57.9 (12.7)	0.68	<.001	54.6 (12.7)	0.26	0.15	63.7 (12.1)	1.09	<.001
High school grad	455	64.0 (16.3)	0.73	<.001	53.7 (10.9)	0.28	<.001	52.5 (10.9)	0.09	0.29	58.7 (13.6)	0.57	<.001
College grad	303	56.1 (13.6)		Ref	51.0 (10.6)		Ref	51.3 (10.4)		Ref	53.1 (12.4)		Ref
Income													
<\$20,000	163	66.3 (16.9)	0.85	<.001	55.7 (11.2)	0.52	<.001	53.8 (11.6)	0.27	0.014	60.1 (13.3)	0.54	<.001
20,000–39,999	199	61.8 (15.8)	0.40	0.007	52.9 (11.7)	0.27	0.008	52.0 (11.4)	0.09	0.401	57.0 (13.6)	0.22	0.084
40,000–59,999	165	60.5 (15.0)	0.20	0.208	52.4 (11.3)	0.18	0.098	51.9 (9.7)	0.06	0.576	55.9 (13.1)	0.10	0.439
Over 60,000	241	58.8 (15.8)		Ref	51.0 (9.8)		Ref	51.5 (10.8)		Ref	55.1 (13.4)		Ref
Employment													
Full time	353	54.7 (12.7)	-1.18	<.001	50.5 (10.3)	-0.34	<.001	49.9 (9.7)	-0.37	<.001	53.0 (12.4)	-0.69	<.001
Other ^b	449	67.1 (16.3)		Ref	54.7 (11.3)		Ref	53.9 (11.4)		Ref	59.9 (13.5)		Ref
Ever married													
Yes	277	56.0 (14.1)	-.82	<.001	52.4 (10.9)	-0.05	0.54	51.0 (10.2)	-0.17	0.053	54.7 (12.9)	-0.33	0.003
No	518	64.7 (16.3)		Ref	53.2 (11.1)		Ref	52.8 (11.2)		Ref	57.8 (13.6)		Ref

^a Education, income, employment, and marital status were analyzed separately adjusting for age, gender and race or ethnic group. Mean and *SD* were given for descriptive purposes and unadjusted, while effect sizes were estimated with the adjustment. Ref = Reference group. ^b Other includes: Part time (141); Unemployed, looking for a job (62); Retired (only one person), care for home and/or unable to work because of illness or disabilities and/or student (216); Other (29, such as Volunteer, nonprofit; Self employed, NOS; Leave of absence, maternity; Unemployed; Seasonal lay-off).

determinants of neurocognitive impairments in adulthood, so that even though older survivors do not show lower IQ scores for the first few years after diagnosis/treatment, deficits in key neurocognitive functions predict significant impairment in CNS malignancy survivors as adults. Finally, CNS malignancy survivors within the CCSS cohort who responded to the CCSS-NCQ were significantly older at diagnosis than those who declined to participate. It is possible that those survivors diagnosed younger who were more impaired refused more often to continue with CCSS participation, thereby skewing the results.

In the current study, CNS survivors diagnosed at the youngest ages (0–2) actually reported less memory impairment than other groups. This youngest age group did not differ from other patient groups in diagnosis or type of treatment. However, when analyzed by diagnosis, only patients diagnosed at ages 0–2 with astrocytomas had lower (less impaired) Memory scale scores, not those with medulloblastoma/PNET or other CNS tumors. Because our study design did not permit comparison of site or grade of tumor, these variables may have contributed to the better outcome in the youngest group. In addition, while the proportion of patients receiving cranial radiation did not differ by age group, patients diagnosed between birth and age 2 who underwent cranial irradiation received lower average doses than other patients (ages 0–2 $M = 48.1$ Gy, ages 3–20 $M = 52.3$ Gy; $p < .001$), which may have resulted in less residual memory impairment.

Compared with control groups of siblings and survivors of non-CNS childhood cancers, adult survivors of childhood CNS malignancy have been reported to show deficits in IQ, educational attainment, income, employment, and marital status (Mostow et al., 1991; Zebrack et al., 2004). The current study indicates that adverse outcomes in indicators of successful adult adaptation (educational attainment, income, employment, marital status) were most likely in survivors who report neurocognitive dysfunction on the CCSS-NCQ.

It is worth noting that significantly more CCSS-NCQ questionnaires were completed by proxy for CNS malignancy survivors than other study participants, and completion by proxy was highly correlated with reported impairment. The group for whom reports were by proxy was much more likely to have received radiation therapy, chemotherapy, or VP shunt placement, suffered hearing and/or visual impairments, paralysis, or stroke and to have been younger at diagnosis ($p < .001$). They were also more likely than other CNS survivors to have had an astrocytoma rather than a medulloblastoma/PNET ($p = .02$). Groups with these risk factors require careful early monitoring and intervention, because without it, they may have severe neurocognitive deficits as adults, to the point that they cannot independently complete a self-report questionnaire.

Although the current study has many strengths, including the large and well-characterized patient population who is a decade or more from their cancer diagnosis, the findings may be limited by the fact that neurocognitive dysfunction was evaluated by report rather than direct assessment. Self-reported and other-reported deficits in an important domain of cognition, executive functioning, have been shown to be well correlated with outcome measures (Rabin et al., 2006), and the current findings likely provide extremely useful information about everyday functioning. However, direct neuropsychological evaluation of at risk subgroups of CNS malignancy survivors is important to gain insight into the mech-

anisms underlying observed neurocognitive impairments, providing further direction for the development of treatment strategies. In addition, a significantly larger percentage of the CCSS-NCQs were completed by proxy for the CNS malignancy survivors than for the other groups. Although this is no doubt a reflection of the higher level of neurocognitive impairment in this group, specific items endorsed may differ in a systematic way depending on whether the questionnaire was completed by self or proxy. Furthermore, compared with CCSS study nonparticipants, participants were less likely to be from ethnic minorities, which may limit generalization to minority group survivors. Another study limitation was the absence of information about precise location of CNS malignancy. Using radiation dosimetry to infer tumor site helped correct for this lack to a certain extent, but precluded more detailed analysis of radiation and surgical factors within study subgroups. Finally, because study participants were diagnosed between 1970 and 1985, it is not possible in this study to evaluate the effects of improved treatments on neuropsychological outcome in CNS malignancy survivors. A new cohort is currently being recruited by CCSS that will provide data to address this question.

Survivors of CNS malignancy have consistently been shown to be at great risk for residual neurocognitive impairment in a large number of previous studies. The current study indicates that deficits extend to adulthood in many patients. Over 50% of survivors of childhood CNS malignancy reported significant impairment on at least one CCSS-NCQ Task Efficiency item, more than three times as many as in the sibling cohort. This underscores the need for continued attention to mitigating the long-term negative effects of CNS malignancies and their treatment. Cognitive rehabilitation aimed at improving attention and working memory in irradiated survivors of CNS cancer has shown some success in terms of outcome variables, with small to medium effect sizes, but little improvement on measures of neurocognitive functioning (Butler et al., 2008). Because neurocognitive skills are difficult to improve directly, it will be important to investigate the benefits of early and consistent use of compensatory strategies, including assistive technology, transitional facilities to promote independent living, and job placement and coaching, to enhance functional outcomes in at risk CNS malignancy survivors.

Also of interest is the study of resilience in CNS malignancy survivors, and exploration of protective factors among survivors in high risk groups who had good neurocognitive outcomes. A recent study in survivors of childhood ALL, for example, suggested that folate pathway genetic polymorphisms may be related to attentional disorders (Krull et al., 2008). In survivors of childhood traumatic brain injury, social advantage and low family stress may be associated with better neurocognitive outcome (Taylor et al., 2002). Better prediction of outcome could lead to more focused treatments.

References

- Anderson, D. M., Rennie, K. M., Ziegler, R. S., Neglia, J. P., Robison, L. R., & Gurney, J. G. (2001). Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. *Cancer*, *92*, 2709–2719.
- Beebe, D. W., Ris, M. D., Armstrong, F. D., Fontanesi, J., Mulhern, R., Holmes, E., & Wisoff, J. H. (2005). Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: Evidence of diminished

- cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). *Journal of Clinical Oncology*, 23, 5198–5204.
- Butler, R. W., Copeland, D. R., Fairclough, D. L., Mulhern, R. K., Katz, E. R., Kazak, A. E., et al. (2008). A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. *Journal of Consulting and Clinical Psychology*, 76, 367–378.
- Ellenberg, L., McComb, J. G., Siegel, S. E., & Stowe, S. (1987). Factors affecting intellectual outcome in pediatric brain tumor patients. *Neurosurgery*, 21, 638–644.
- Fouladi, M., Chintagumpala, M., Laningham, F. A., Ashley, D., Kellie, S. J., Langston, J. W., et al. (2004). White matter lesions detected by magnetic resonance imaging after radiotherapy and high-dose chemotherapy in children with medulloblastoma or primitive neuroectodermal tumor. *Journal of Clinical Oncology*, 22, 4451–4460.
- Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *Behavior Rating Inventory of Executive Function*. Odessa, FL: Psychological Assessment Resources, Inc.
- Grill, J., Renaux, V. K., Bulteau, C., Viguier, D., Levy-Piebois, C., Sainte-Rose, C., et al. (1999). Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. *International Journal of Radiation Oncology Biology Physics*, 45, 137–145.
- Guy, S. C., Isquith, P. K., & Gioia, G. A. (2004). *Behavior Rating Inventory of Executive Function: Self report version*. Odessa, FL: Psychological Assessment Resources, Inc.
- Halberg, F. E., Kramer, J. H., Moore, I. M., Wara, W. M., Matthay, K. K., & Ablin, A. R. (1992). Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. *International Journal of Radiation Oncology Biology Physics*, 22, 13–16.
- Karatekin, C., Lazareff, J. A., & Asarnow, R. F. (2000). Relevance of the cerebellar hemispheres for executive functions. *Pediatric Neurology*, 22, 106–112.
- Kieffer-Renaux, V., Bulteau, C., Grill, J., Kalifa, C., Viguier, D., & Jambaque, I. (2000). Patterns of neuropsychological deficits in children with medulloblastoma according to craniospinal irradiation doses. *Developmental Medicine and Child Neurology*, 42, 741–745.
- Kiehna, E. N., Mulhern, R. K., Li, C., Xiong, X., & Merchant, T. E. (2006). Changes in attentional performance of children and young adults with localized primary brain tumors after conformal radiation therapy. *Journal of Clinical Oncology*, 24, 5283–5290.
- Krull, K. R., Gioia, G., Ness, K. K., Ellenberg, L., Recklitis, C., Leisenring, W., et al. (2008). Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. *Cancer*, Sep 12.
- Krull, K. R., Brouwers, P., Jain, N., Zhang, L., Bomgaars, L., Dreyer, Z., et al. (2008). Folate pathway genetic polymorphisms are related to attention disorders in childhood leukemia survivors. *The Journal of Pediatrics*, 152, 101–105.
- Levisohn, L., Cronin-Golomb, A., & Schmahmann, J. D. (2000). Neuropsychological consequences of cerebellar tumour resection in a paediatric population. *Brain*, 123, 1041–1050.
- Mabbott, D. J., Penkman, L., Witol, A., Strother, D., & Bouffet, E. (2008). Core neurocognitive functions in children treated for posterior fossa tumors. *Neuropsychology*, 22, 159–168.
- Mostow, E. N., Byrne, J., Connelly, R. R., & Mulvihill, J. J. (1991). Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *Journal of Clinical Oncology*, 9, 592–599.
- Mulhern, R. K., Hancock, J., Fairclough, D., & Kun, L. (1992). Neuropsychological status of children treated for brain tumors: A critical review and integrative analysis. *Medical and Pediatric Oncology*, 20, 181–191.
- Mulhern, R. K., Kepner, J. L., Thomas, P. R., Armstrong, F. D., Friedman, H. S., & Kun, L. E. (1998). Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: A Pediatric Oncology Group study. *Journal of Clinical Oncology*, 16, 1723–1728.
- Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E., & Kun, L. E. (2004). Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncology*, 5, 399–408.
- Mulhern, R. K., & Palmer, S. L. (2003). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer*, 4, 177–197.
- Mulhern, R. K., Reddick, W. E., Palmer, S. L., Glass, J. O., Elkin, T. D., Kun, L. E., et al. (1999). Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Annals of Neurology*, 46, 834–841.
- Nagel, B. J., Delis, D. C., Palmer, S. L., Reeves, C., Gajjar, A., & Mulhern, R. K. (2006). Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology*, 20, 105–112.
- Packer, R. J., Gurner, J. G., Punyko, J. A., Donaldson, S. S., Inskip, P. D., Stovall, M., et al. (2003). Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood cancer survivor study. *Journal of Clinical Oncology*, 21, 3255–3261.
- Palmer, S. L., Gajjar, A., Reddick, W. E., Glass, J. O., Kun, L. E., Wu, S., et al. (2003). Predicting intellectual outcome among children treated with 35–40 Gy craniospinal irradiation for medulloblastoma. *Neuro-psychology*, 17, 35–40.
- Palmer, S. L., Goloubeva, O., Reddick, W. E., Palmer, S. L., Glass, J. O., Gajjar, A., et al. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *Journal of Clinical Oncology*, 19, 2302–2308.
- Rabin, L. A., Roth, R. M., Isquith, P. K., Wishart, H. A., Nutter-Upham, K. E., Pare, N., et al. (2006). Self- and informant reports of executive function on the BRIEF-A in MCI and older adults with cognitive complaints. *Archives of Clinical Neuropsychology*, 21, 721–732.
- Radcliffe, J., Bunin, G. R., Sutton, L. N., Goldwein, J. W., & Phillips, P. C. (1994). Cognitive deficits in long-term survivors of childhood medulloblastoma and other noncortical tumors: Age-dependent effects of whole brain radiation. *International Journal of Developmental Neuroscience*, 12, 327–334.
- Reamers, T. S., Ehrenfels, S., Mortensen, E. L., Schmiegelow, M., Sonderkaer, S., Carstensen, H., et al. (2003). Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Medical and Pediatric Oncology*, 40, 26–34.
- Reddick, W. E., White, H. A., Glass, J. O., Wheeler, G. C., Thompson, S. J., Gajjar, A., et al. (2003). Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. *Cancer*, 97, 2512–2519.
- Reddick, W. E., Shan, Z. Y., Glass, J. O., Helton, S., Xiong, X., Wu, S., et al. (2006). Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. *Cancer*, 106, 941–949.
- Ris, M. D., Packer, R., Goldwein, J., Jones-Wallace, D., & Boyett, J. M. (2001). Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: A Children's Cancer Group study. *Journal of Clinical Oncology*, 19, 3470–3476.
- Ris, M. D., Ryan, P. M., Lamba, M., Brenemen, J., Cecill, K., Succop, P., & Ball, W. (2005). *Pediatric Blood Cancer*, 44, 487–493.
- Riva, D., & Giorgi, C. (2000). The cerebellum contributes to higher functions during development: Evidence from a series of children surgically treated for posterior fossa tumours. *Brain*, 123, 1051–1061.
- Robison, L. L., Mertens, A. C., Boice, J. D., Breslow, N. E., Donaldson, S. S., Green, D. M., et al. (2002). Study design and cohort characteristics of the Childhood Cancer Survivor Study: A multi-institutional collaborative project. *Medical and Pediatric Oncology*, 38, 229–239.
- Roth, R. M., Isquith, P. K., & Gioia, G. A. (2005). *Behavior Rating Inventory of Executive Function: Adult version*. Odessa, FL: Psychological Assessment Resources, Inc.

- Sands, S. A., Kellie, S. J., Davidow, A. L., Diez, B., Villablanca, J., Weiner, H. L., et al. (2001). Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: From the First International CNS Germ-Cell Tumor Study. *Neuro-Oncology*, 3, 175–183.
- Schatz, J., Kramer, J. H., Ablin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: A developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology*, 14, 189–200.
- Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain*, 121, 561–579.
- Schultz, K. A., Ness, K. K., Whitton, J., Recklitis, C., Zebrack, B., Robison, L. L., et al. (2007). Behavioral and social outcomes in adolescent survivors of childhood cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology*, 25, 3649–3656.
- Smibert, E., Anderson, V., Godber, T., & Ekert, H. (1996). Risk factors for intellectual and educational sequelae of cranial irradiation in childhood acute lymphoblastic leukemia. *British Journal of Cancer*, 73, 825–830.
- Spiegler, B. J., Bouffet, E., Greenberg, M. L., Rutka, J. T., & Mabbott, D. J. (2004). Change in neurocognitive functioning after treatment with cranial radiation in childhood. *Journal of Clinical Oncology*, 22, 706–713.
- Steinlin, M., Imfeld, S., Zulauf, P., Boltshauser, E., Lovblad, K., Luthy, A. R., et al. (2003). Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. *Brain*, 126, 1998–2008.
- Taylor, G., Yeates, K. O., Wade, S. L., Drotar, D., Stancin, T., & Minich, N. (2002). A prospective study of short- and long-term outcomes after traumatic brain injury in children: Behavior and achievement. *Neuropsychology*, 16, 15–27.
- Wong, C. S., & Van der Kogel, A. J. (2004). Mechanisms of radiation injury to the central nervous system: Implications for neuroprotection. *Molecular Interventions*, 4, 273–284.
- Zebrack, B. J., Gurney, J. G., Oeffinger, K., Whitton, J., Packer, R. J., Mertens, A., et al. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology*, 22, 999–1006.
- Zeger, S. L., & Liang, K. Y. (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, 42, 121–130.
- Zeltzer, L. K., Lu, Q., Leisenring, W., Tsao, J. C. I., Recklitis, C., Armstrong, G., et al. (2008). Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: A report from the childhood cancer survivor study. *Cancer Epidemiology Biomarkers & Prevention*, 17, 435–446.

(Appendixes follow)

Appendix A

The Childhood Cancer Survivor Study (CCSS) is a collaborative, multi-institutional project, funded as a resource by the National Cancer Institute, of individuals who survived five or more years after diagnosis of childhood cancer.

CCSS is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed before age 21 between 1970 and 1986 and approximately 4,000 siblings of survivors, who serve as a control group. The cohort was assembled through the efforts

of 26 participating clinical research centers in the United States and Canada. The study is currently funded by a U24 resource grant (NCI grant # U24 CA55727) awarded to St. Jude Children's Research Hospital. Currently, we are in the process of expanding the cohort to include an additional 14,000 childhood cancer survivors diagnosed before age 21 between 1987 and 1999. For information on how to access and utilize the CCSS resource, visit www.stjude.org/ccss

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Appendix B

Factors and Items of the Childhood Cancer Survivors Study Neurocognitive
Questionnaire (CCSS-NCQ)

Task Efficiency

1. It takes me longer to complete my work
2. I have problems completing my work
3. I have problems getting started on my own
4. I am easily overwhelmed
5. I have trouble doing more than one thing at a time
6. I have trouble prioritizing my activities
7. I read slowly
8. I am slower than others when completing my work
9. I don't work well under pressure

Emotional Regulation

1. I get upset easily
2. I get frustrated easily
3. My mood changes frequently

Organization

1. I am disorganized
2. I have trouble finding things in my bedroom, closet or desk
3. My desk/workspace is a mess

Memory

1. I forget instructions easily
 2. I have difficulty recalling things I learned before
 3. I forget what I am doing in the middle of things
 4. I have trouble remembering things, even for a few minutes
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