Published in final edited form as:

J Neurooncol. 2014 August ; 119(1): 197–205. doi:10.1007/s11060-014-1476-4.

The relationship between working memory and cerebral white matter volume in survivors of childhood brain tumors treated with conformal radiation therapy

Lisa M. Jacola, Ph.D.¹, Jason M. Ashford, M.S.¹, Wilburn E. Reddick, Ph.D.², John O. Glass, M.S.², Robert J. Ogg, Ph.D.², Thomas M. Merchant, D.O., Ph.D.³, and Heather M. Conklin, Ph.D.¹

¹Department of Psychology, St. Jude Children's Research Hospital

²Division of Translational Imaging, St. Jude Children's Research Hospital

³Division of Radiation Oncology, St. Jude Children's Research Hospital

Abstract

Background—Survivors of childhood brain tumors (BTs) treated with CNS-directed therapy show changes in cerebral white matter that are related to neurocognitive late effects. We examined the association between white matter volume and working memory ability in survivors treated with conformal radiation therapy (CRT).

Methods—Fifty survivors (25 males, age at assessment=13.14±2.88, age at CRT=7.41±3.41 years) completed Digit Span from the Wechsler Intelligence Scales for Children, 4th Edition and experimental Self-Ordered Search tasks as measures of working memory. Caregiver ratings were obtained using the Behavior Rating Inventory of Executive Function (BRIEF). MRI exams were acquired on a 1.5 Tesla scanner. Volumes of normal appearing white matter (NAWM) were quantified using a well-validated automated segmentation and classification program.

Results—Correlational analyses demonstrated that NAWM volumes were significantly larger in males and participants with tumors located in the infratentorial space. Correlations between NAWM volume and Digit Span Backward were distributed across anterior and posterior regions, with evidence for greater right hemisphere involvement ($r=32-34$, $p < .05$). Correlations between NAWM volume with Digit Span Backward ($r=.44-.52$; $p < .05$) and NAWM volume with SOS-O Total ($r=.45-.52$, $p < .05$) were of greater magnitude in females. No relationship was found between NAWM volume and caregiver report.

Conclusion—Working memory performance in survivors of pediatric BTs treated with CRT are related to regionally specific NAWM volume. Developmental differences in cerebral myelination may explain findings of greater risk for neurocognitive late effects in female survivors. Future

Corresponding Author: Heather M. Conklin, Ph.D. Department of Psychology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop # 740, Memphis, Tennessee, 38105, Telephone: 901-595-3585, Fax: 901-595-4701, heather.conklin@stjude.org.

This study was conducted in accordance with laws and regulations of the United States of America.

The authors declare that they have no conflict of interest.

studies are needed to better isolate vulnerable white matter pathways, thus facilitating the development of neuroprotective interventions.

Keywords

neuroimaging; working memory; white matter; brain tumors; childhood

Introduction

Survivors of pediatric brain tumors (BTs) treated with CNS-directed therapy are at significant risk for neurocognitive deficits that impact functional outcomes [1-2]. These deficits reflect difficulty acquiring skills at an age appropriate rate [3]. Specific deficits in attention, processing speed, and working memory have been identified in survivors of childhood BTs [4-6]. Working memory is a limited capacity system used to store and manipulate information in support of goal-directed behavior [7]. Working memory accounts for a substantial portion of developmental variance in global intelligence in healthy children [8] and in childhood cancer survivors [9]. Performance on working memory tasks improves throughout adolescence [10]. The dorsolateral prefrontal cortex and parietal lobes are frequently implicated in functional imaging studies of working memory [11]. Structural neuroimaging studies document protracted development maturation of white matter connections between these regions, including the cerebellar-thalamo-cerebral and fronto-subcortical circuitry [12-13].

The goal of contemporary treatment protocols for childhood BTs is to maintain survival rates while improving neurocognitive outcomes. Conformal radiation therapy (CRT) uses three-dimensional imaging to closely target the volume of brain to be treated, thus reducing the amount of normal brain tissue in the radiation field. CRT has been used successfully to treat focal neoplasms in children without compromising disease control [14-15].

Longitudinal studies of survivors document relative sparing of performance on measures of global intelligence [16] and adaptive functioning [17]. Despite these promising findings, survivors treated with CRT continue to be at risk for problems with reading [18], functional communication [19], and visual-auditory learning [20]. Parent ratings completed for survivors of childhood BTs who were five years post-treatment with CRT documented increased risk for working memory problems when compared with healthy age-matched peers [21]. This cohort performed significantly below age expectations on performance-based measures of working memory when compared to age-matched peers and to survivors of childhood cancer treated without CNS-directed therapy [6].

Multiple demographic and clinical factors are associated with neurobehavioral outcomes in survivors of pediatric BTs treated with CRT. Younger age at treatment, increased intensity of treatment, and additional treatment with chemotherapy are most frequently linked to increased risk [4, 16, 18, 20, 22-24]. Other factors include severity of clinical presentation (e.g., hydrocephalus at diagnosis) [25] and supratentorial tumor location [16, 18-20, 26]. The number and extent of surgical resections have been associated with poorer baseline neurocognitive performance [19-20].

Findings regarding gender differences in survivors of pediatric BTs treated with CRT are mixed. Male gender was predictive of significant improvement over time in verbal auditory learning in survivors of localized ependymoma treated with CRT [16]. Female gender predicted lower scores on a verbal auditory learning measure for survivors of pediatric craniopharyngioma; however, a gender effect was not seen in children treated for low grade glioma [20]. There was no effect of gender on a decline in functional communication skills over a five-year period in survivors treated for localized ependymoma with CRT [19]. Caregiver ratings of working memory problems were significantly elevated in male survivors of pediatric BTs treated with CRT [21]; however, no gender effect was found on performance-based measures [6]. Clarification of risk and resiliency factors associated with neurobehavioral outcomes in survivors will inform the development and implementation of interventions and facilitate decision-making for families.

The impact of CNS-directed treatment on cerebral white matter has been most consistently investigated in survivors of pediatric medulloblastoma, who are treated with maximal surgical resection and whole-brain craniospinal irradiation (CSI) [26-32]. Using an automated segmentation and classification program, subtle reductions of normal appearing white matter (NAWM) volume have been identified in survivors of childhood medulloblastoma following treatment with CSI as compared to children treated for pilocytic astrocytoma with surgery alone [28]. A longitudinal study of 26 medulloblastoma survivors found decreased white matter maturation was more pronounced in survivors treated with 36 Gy CSI versus those treated with 23.4 CSI [33]. In contrast, one study has examined the impact of CRT on white and grey matter T1 signal in children treated for BTs [34].

The relationship between cerebral white matter and cognitive development is well established in healthy children [e.g., 35]. This association has been studied in survivors of pediatric BTs treated with whole-brain CSI [28, 30-31, 36-41]. Using data from a heterogeneous cohort of BT survivors, Reddick and colleagues found that 60 to 80% of the variance in academic achievement was accounted for by NAWM volume, attention, and global intelligence (IQ) [31]. Diffusion tensor imaging (DTI) studies have found associations between reduced white matter diffusivity and global IQ [37], processing speed [38], working memory [39-40], and reading ability [41] in survivors treated with CSI.

To our knowledge, no study has explored the relationship between white matter and neurocognitive abilities in pediatric BT survivors treated with CRT. Exploring the impact of treatment modifications on neurodevelopmental outcomes post-therapy for childhood BTs will provide information that is crucial for understanding neurodevelopmental outcomes and interventions. Accordingly, this study aimed to investigate the association between cerebral white matter and working memory in survivors of pediatric BTs treated with CRT. Drawing from behavioral findings [6, 21], we hypothesized that NAWM volume as measured on structural MRI exams completed in the context of protocol treatment would significantly and positively correlate with working memory. We also explored the impact of demographic (age and gender) and clinical factors (time since treatment, hydrocephalus with or without shunting, and tumor characteristics) on NAWM volume. We expected female gender, younger age at treatment, and tumor location to negatively impact NAWM volume.

Methods

All participants had been treated for a primary CNS tumor with CRT on an institutional phase II trial (RT-1; NCT00187226). CRT was administered over a six to seven week course to a totaling dose of 59.4 Gy. The target treatment volume included the tumor or tumor bed, a 10-mm margin surrounding the tumor to treat microscopic disease. A 3 to 5 mm planning volume was included to account for uncertainty in patient positioning and image registration. MRI exams were obtained as per the clinical treatment protocol.

Fifty survivors were recruited for the current study. Recruitment was stratified by gender, age at neuropsychological assessment (8-12 years old; 13-18 years old), and tumor location (supratentorial; infratentorial). Participants initiated CRT at least two years prior to enrollment and had no evidence of recurrent disease at the time of participation. All participants were primary English speakers. Individuals with global intellectual impairment (IQ < 70) were not considered for participation. Participants were also excluded for a history of CNS injury or attention deficit hyperactivity disorder predating cancer diagnosis, the use of psychotropic medications within two weeks of study participation, and sensory or motor impairment that would impact assessment validity. The study was approved by the Institutional Review Board. Written informed consent was obtained prior to participation.

Procedure

Demographic information was obtained by caregiver questionnaire. Tumor location was categorized based on initial diagnostic neuroimaging. Clinical variables including tumor type, number and extent of surgical resection, hydrocephalus with or without shunting, and prior treatment with chemotherapy were extracted via chart review.

Participants completed two subtests from the Wechsler Abbreviate Scale of Intelligence (WASI) as a measure of abbreviated IQ (ABIQ) [42]. Scores on the WASI are age-standardized ($M=100$, $SD=15$).

Working memory was assessed using the Digit Span subtest from the WISC-IV, Integrated [43] or the Wechsler Adult Intelligence Scale, 3rd Edition [44]. This subtest includes Digit Span Forward and Digit Span Backward tasks. Digit Span Forward is a measure of auditory attention and recall and requires individuals to repeat verbatim number sequences read by the examiner. Digit Span Backward requires participants to repeat number sequences backward and is a measure of verbal working memory [45]. Z-scores were computed for the longest digit span forward (LDSF) and longest digit span backward (LDSB) using data provided in the WAIS-III and WISC-III manuals in order to combine performance scores across Wechsler scales.

Participants completed two computerized working memory measures: the Self-Ordered Search Verbal (SOS-V) and Object (SOS-O) tasks that have been previously described [6]. Briefly, participants were presented with stimulus arrays (words or objects) of increasing size. For SOS-O, the most recently selected object location is covered with a black square. Participants are instructed to select a stimulus only once. After each response, the stimuli are rearranged randomly, cuing the next response. The goal is to complete each trial in as few

responses as possible. The task ends when the participant either selects all target stimuli in an array or after 3N responses, in which N is the number of stimuli in a trial. Error scores (E) are calculated for each array size in both the Verbal and Object conditions using the following formula: $E = (R - N) / N$ where R is the number of responses.

Caregivers completed the Behavior Rating Inventory of Executive Function (BRIEF) to provide information regarding executive function problems in daily life [46]. The BRIEF is comprised of clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials and Self-Monitoring), from which two index scores (Metacognition and Behavioral Regulation) and one composite score (Global Executive Composite) are derived. Scores are standardized by age and gender ($M=50$, $SD=10$). T-Scores $\geq 1.5 SD$ above the mean ($T \geq 65$) indicate clinically significant problems. T-scores $\geq 1 SD$ above the mean ($T \geq 60$) indicate at-risk elevations.

Imaging Acquisition

Data were acquired on 1.5 T whole-body MR systems using a standard polarized volume head coil (Avanto, Siemens Medical Systems, Inselin, NJ). Each series consisted of 27 contiguous 5-mm thick axial images. T1-weighted images were acquired with a gradient echo sequence, T2/PD-weighted with a dual spin-echo sequence, and fluid-attenuated inversion recovery (FLAIR) images were acquired with a multi-echo inversion recovery sequence. All MRI sets within an individual examination were registered, intensity inhomogeneity corrected, and tissues were segmented using an automated hybrid neural network segmentation and classification method [47]. Robust reliability and validity have been demonstrated for the segmentation method, with a predicted variance of approximately 2% in the repeated measure of grey and white matter [48]. All regional NAWM volumes were assessed across a seven slice volume at the level of the basal ganglia and normalized to intracranial volume (Figure 1).

Statistical Analyses

Distributions were examined for normality in order to determine whether the use of parametric statistics was appropriate. Descriptive analyses were conducted to characterize the participants with respect to demographic and clinical variables. Univariate analyses were conducted to examine whether total NAWM volumes differed by demographic or clinical variables. Post-hoc analyses were conducted using regional NAWM volumes for significant findings. Correlational analyses were used to examine the association between regional NAWM volumes and measures of working memory. Correlational analyses were conducted separately by gender and on the group as a whole. All reported p-values are 2-tailed unless otherwise specified.

Results

Demographic and clinical characteristics

Twenty-five males and 25 females between the ages of 8 and 18 participated in this study (Table 1). The majority of the cohort self-identified as Caucasian and non-Hispanic. Age at neuropsychological assessment and MRI examination were not significantly different

($t_{(1,49)}=0.34, p=.74$). As such, all further analyses make use of the age at neuropsychological assessment. On average, participants were 6 years old at diagnosis and 7 years old at the initiation of CRT. Participants with infratentorial tumor location were significantly younger at diagnosis ($t_{(2,48)}=3.14, p=.00$) and at initiation of CRT ($t_{(37,45)}=3.86, p=.00$). The group was balanced with respect to clinical characteristics including tumor diagnosis and location, extent of surgical resection, hydrocephalus, and shunt placement. Males and females were balanced with regard to tumor diagnosis ($\chi^2=0.00, p=1.00$), tumor location ($\chi^2=0.33, p=.60$), surgical resection ($\chi^2=0.08, p=.78$), hydrocephalus ($\chi^2=2.05, p=.15$), and shunt placement ($\chi^2=2.05, p=.15$), and treatment with chemotherapy ($\chi^2=0.76, p=.38$).

Summary of assessment findings

Performance and rater-based working memory data in Table 2 have been previously reported and are summarized here for ease of interpretation [6, 21]. Performance was within age expectations for the group as a whole on measures of intelligence and working memory. Two participants were excluded from data analyses for the SOS-V due to inadequate reading ability. There was a significant main effect for stimulus array size on SOS-V and SOS-O performance, demonstrating success in parametrically manipulating task difficulty. There were no significant demographic or clinical predictors of performance on Digit Span, SOS-V, or SOS-O.

BRIEF parent ratings were excluded for one participant due to an elevated validity scale (Negativity). Participants were categorized as elevated on BRIEF scales if T-scores were 61 (84th percentile). Caregivers rated participants as elevated more frequently than expected based on the rate in the normative sample on several scales.

Impact of demographic and clinical variables on volumes NAWM

There was no impact of tumor diagnosis, extent of surgical resection, hydrocephalus, shunt placement, or chemotherapy on NAWM volume. No significant associations were seen between NAWM volume and age at diagnosis or assessment or time since treatment. Mean total NAWM was significantly greater for males ($t_{(2,48)}=2.04, p=.05, d=0.58$) and in participants with tumors in the infratentorial space ($t_{(2,48)}=2.14, p=.04, d=0.61$). NAWM volume in the left posterior region was significantly greater for males than females ($t_{(2,48)}=2.13, p=.04, d=.60$). Participants with infratentorial tumors demonstrated significantly greater mean NAWM volume than those with supratentorial tumors in the right ($t_{(2,48)}=2.56, p=.01, d=0.74$) and left frontal quadrants ($t_{(2,48)}=2.93, p=.01, d=0.83$).

Association between NAWM volumes and working memory

Significant correlations were distributed across regions for the whole group and suggest that greater NAWM volume is related to higher LDSF and LDSB (Table 3). There were no significant relationships between NAWM volume and performance on SOS-Verbal or Object tasks or between NAWM volume and elevated BRIEF scales. In females, significant correlations were present between NAWM volume and performance on LDSB and SOS-Object (Table 4). These correlations were of stronger magnitude but did not significantly

differ from males. There were no significant associations between caregiver report and NAWM volume.

Discussion

This study examined NAWM volume and working memory in survivors of pediatric BTs treated with CRT. As expected, significant associations were seen between regional NAWM volume and performance on working memory tasks. For the group as a whole, better performance on LDSB was positively related to right frontal and right and left posterior NAWM volumes. Frontal and parietal involvement during working memory tasks is consistent with data from functional neuroimaging studies of healthy controls [11]. Findings of greater right hemisphere white matter involvement are consistent with those from acquired brain injury populations (e.g., TBI) and suggest that visualization is employed as a task strategy [45]. Findings underscore the importance of cerebello-thalamo-cerebral connections in the development of working memory [39].

Contrary to our hypothesis, there was no relationship between NAWM volume and parent ratings. These results are consistent with findings from studies of adult survivors of childhood medulloblastoma [40] and studies in healthy children, although caregiver-reported executive function was significantly associated with frontal volumes of grey matter [49]. Investigators should carefully consider the clinical and research utility of working memory measurements when designing studies. Performance-based measures appear to have greater neuroanatomical specificity, and thus may facilitate the identification of neural processes associated with cognition. Rater-based measures provide information regarding daily behavior that is challenging to elicit during structured clinical assessment.

Hypotheses regarding the impact of demographic and clinical factors on neurobehavioral outcomes were partially supported. There was no significant effect of age at diagnosis, treatment, or assessment on NAWM volume, despite findings of performance deficits in comparison with healthy controls and children treated without CNS-directed therapy [6]. It is possible that our segmentation method lacked anatomical specificity (e.g., DTI). Participants with infratentorial tumors evidenced larger total NAWM volumes. This finding is not surprising when one considers the impact of posterior fossa tumors on the development of cerebello-thalamo-cortical white matter connections. The finding that NAWM was not impacted by hydrocephalus is consistent with studies suggesting the initial impact of hydrocephalus and related surgery on white matter may lessen over time [50].

Our study found significant relationships between working memory performance and NAWM volume in females. This finding is challenging to interpret, given that performance on working memory tasks did not differ by gender [6], although caregivers rated boys as at significantly greater risk for working memory problems [21]. Nonetheless, it is possible that increased vulnerability to treatment-related brain changes may explain findings of increased risk for neurocognitive late effects in female survivors, given findings of gender-based differences in white matter development, including greater increase and later peak volume in healthy males [35]. Finally, more females had hydrocephalus than males. It is possible that differential effects of tumor size may be responsible, as females often have smaller heads

than males. Studies exploring the impact of tumor size on neurocognitive outcomes would be useful to explore this hypothesis.

Limitations and Future Directions

To our knowledge, this was the first study to identify an association between working memory and NAWM volume in survivors of pediatric BTs treated with CRT. Our work is not without limitations. Recent clinical research studies make use of advanced imaging techniques, such as DTI, in scan acquisition; however, not all institutions have the capacity to integrate advanced techniques into routine clinical scanning. Our findings may be generalizable to a wider variety of treatment settings. Nonetheless, studies employing DTI are necessary in order to more specifically identify targets for interventions. Our rudimentary approach to segmentation resulted in a lack of specificity in brain behavior relationships. Despite this limitation, our findings are consistent with expectations based on functional neuroimaging studies of working memory.

Acknowledgments

Support for this work was provided by the following sources: the National Cancer Institute (St. Jude Cancer Center Support [CORE] Grant [P30 CA21765]; H.C., Working Memory Performance among Childhood Brain Tumor Survivors [R21 CA131616]); the International Neuropsychological Society (H.C., Rita G. Rudel Award); and the American Lebanese Syrian Associated Charities (ALSAC).

References

1. Mulhern RK, Butler RW. Neurocognitive sequelae of childhood cancers and their treatment. *Ped Rehab*. 2004; 7:1–14.
2. Moore BD. Neurocognitive outcomes in survivors of childhood cancer. *J Ped Psych*. 2005; 30:51–63.
3. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *J Clin Oncol*. 2001; 19:2302–2308. [PubMed: 11304784]
4. Palmer SL, Reddick WE, Gajjar A. Understanding the cognitive impact on children who are treated for medulloblastoma. *J Ped Psych*. 2007; 32:1040–1049.
5. Kahalley LS, Conklin HM, Tyc VL, et al. Slower processing speed after treatment for pediatric brain tumor and acute lymphoblastic lymphoma. *Psycho-Oncology*. 2013
6. Conklin HC, Ashford JM, Howarth RA, et al. Working memory performance among childhood brain tumor survivors. *J Int Neuropsychol Soc*. 2012; 18:996–1005. [PubMed: 22691544]
7. Baddeley A. Working memory. *Comptes Rendus de l'Academie des Sciences - Series iii, Sciences de la Vie* 1998. 1998; 321:167–173.
8. Fry AS, Hale S. Processing speed, working memory, and fluid intelligence: evidence for a developmental cascade. *Psychol Sci*. 1996; 4:237–241.
9. Schatz J, Kramer JH, Ablin A, et al. Processing speed, working memory, and IQ: A developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychol*. 2000; 14:189–200.
10. Conklin HM, Luciana M, Hooper CJ, Yarger RS. Working memory performance in typically developing children and adolescents: Behavioral evidence of protracted frontal lobe development. *Dev Neuropsychol*. 2007; 31:103–128. [PubMed: 17305440]
11. Nee DE, Brown JW, Askren MK, et al. A meta-analysis of executive components of working memory. *Cereb Cortex*. 2013; 2:266–82.
12. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences*. 2004; 1021:105–109. [PubMed: 15251879]

13. Otsby Y, Tamnes CK, Fjell AM, Walhovd KB. Morphometry and connectivity of the fronto-parietal verbal working memory network in development. *Neuropsychologia*. 2011; 49:3854–3862. [PubMed: 22001853]
14. Merchant TE, Kun LE, Wu S, et al. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. *J Clin Oncol*. 2009; 27:3598–604. [PubMed: 19581536]
15. Merchant TE, Kun LE, Hua Ch, et al. Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 2013; 85:187–92.
16. Di Pinto M, Conklin HM, Li C, et al. Investigating verbal and visual auditory learning after conformal radiation therapy for childhood ependymoma. *Int J Radiat Oncol Biol Phys*. 2010; 77:1002–8. [PubMed: 19783376]
17. Netson KL, Conklin HM, Wu S, et al. Longitudinal investigation of adaptive functioning following conformal irradiation for pediatric craniopharyngioma and low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2010; 5:1301–6.
18. Conklin HM, Li C, Xiong X, et al. Predicting change in academic abilities after conformal radiation therapy for localized ependymoma. *J Clin Oncol*. 2008; 26:3965–70. [PubMed: 18711186]
19. Netson KL, Conklin HM, Wu S, et al. A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma. *Int J Radiat Oncol Biol Phys*. 2012; 84:217–233. [PubMed: 22541967]
20. Di Pinto M, Conklin HM, Li C, et al. Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2012; 84:e363–9. [PubMed: 22867897]
21. Howarth RA, Ashford JM, Merchant TE, et al. The utility of parent report in the assessment of working memory among childhood brain tumor survivors. *J Int Neuropsychol Soc*. 2013; 19:380–389. [PubMed: 23351399]
22. Merchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. *J Neurosurg*. 2006; 104:94–102. [PubMed: 16506496]
23. Dennis M, Spiegler BJ, Obonsawin MC, et al. Brain tumors in children and adolescents-III. Effects of radiation and hormone status on intelligence and on working, associative and serial-order memory. *Neuropsychologia*. 1992; 30:257–275. [PubMed: 1574161]
24. Grill J, Renaux VK, Bultau C, et al. Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. *Int J Rad Oncol Biol Phys*. 1999; 45:137–45.
25. Reddick WE, Mulhern RK, Elkin TD, et al. A hybrid neural network analysis of subtle brain volume differences in children surviving brain tumors. *Magnetic Resonance Imaging*. 1998; 16:413–421. [PubMed: 9665552]
26. Rueckriegel SM, Driever PH, Blankenburg F, et al. Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and without adjuvant treatment as detected by magnetic resonance imaging. *Int J Rad Oncol Biol Phys*. 2010; 76:859–866.
27. Mulhern RK, Reddick WE, Palmer SL, et al. Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Annals of Neurology*. 1999; 46:834–841. [PubMed: 10589535]
28. Mulhern RK, Palmer SL, Reddick WE, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. *J Clin Oncol*. 2001; 19:472–479. [PubMed: 11208841]
29. Palmer SL, Reddick WE, Glass JO, et al. Decline in corpus callosum volume among pediatric patients with medulloblastoma: longitudinal MR imaging study. *Am J Neuroradiol*. 2002; 7:1088–94. [PubMed: 12169462]
30. Reddick RE, White HA, Glass JO, et al. Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. *Cancer*. 2003; 97:2512–2519. [PubMed: 12733151]
31. Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk adapted therapy for childhood medulloblastoma. *Magn Reson Imaging*. 2005; 24:1015–22.

32. Shan ZY, Liu JZ, Glass JO, et al. Quantitative morphologic evaluation of white matter survivors of childhood medulloblastoma. *Magn Reson Imaging*. 2006; 24:1015–22. [PubMed: 16997071]
33. Reddick WE, Russel JM, Glass JO, et al. Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. *Magn Reson Imaging*. 2000; 7:787–93. [PubMed: 11027871]
34. Steen RG, Koury M, Granja CI, et al. Effect of Ionizing Radiation on the human brain: white matter and grey matter T1 in pediatric brain tumor patients treated with conformal radiation therapy. *Int J Rad Oncol Biol Phys*. 2001; 49:79–91.
35. Mabbott DJ, Noseworthy MD, Bouffet E, et al. Diffusion tensor imaging of white matter after cranial radiation in children for medulloblastoma: Correlation with IQ. *Neuro-Oncology*. 2006 Jul.;245–252.
36. Schmithorst VJ, Holland SK, Dardinski BJ. Developmental differences in white matter architecture between boys and girls. *Hum Brain Mapp*. 2008; 6:696–710. [PubMed: 17598163]
37. Khong PL, Leung LH, Fung AS, et al. White matter anisotropy in post-treatment childhood cancer survivors: preliminary evidence of association with neurocognitive function. *J Clin Oncol*. 2006; 24:884–90. [PubMed: 16484697]
38. Aukema EJ, Caan MW, Oudhuis N, et al. White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. *Int J Rad Oncol Biol Phys*. 2009; 74:837–843.
39. Law N, Bouffet E, Laughlin S, et al. Cerebello-thalamo-cerebral connections in pediatric brain tumor patients: impact on working memory. *Neuroimage*. 2011; 56:2238–2248. [PubMed: 21473922]
40. Brinkman TM, Reddick WE, Luxton J, et al. Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma. *Neuro-Oncology*. 2012; 14:iv25–iv26. [PubMed: 23095827]
41. Palmer SL, Reddick WE, Glass JO, et al. Regional white matter anisotropy and reading ability in patients treated for embryonal tumors. *Brain Imaging Behav*. 2010; 4:132–140. [PubMed: 20502994]
42. Wechsler, D. Wechsler Abbreviated Scale of Intelligence. San Antonio, Texas: Harcourt Assessment; 1999.
43. Wechsler, D. Wechsler Intelligence Scale for Children- Fourth Edition, Integrated. San Antonio, TX: Psychological Corporation; 2003.
44. Wechsler, D. Wechsler Intelligence Scale for Children- Third Edition. San Antonio, TX: Psychological Corporation; 1991.
45. Lezak, MD. Neuropsychological Assessment. 3rd. New York: Oxford University Press; 1995.
46. Gioia, GA.; Isquith, PK.; Guy, SC.; Kenworthy, L. Behavior Rating Inventory of Executive Function. Lutz, Florida: Psychological Assessment Resources, Inc.; 2006.
47. Glass JO, Reddick WE, Li C, et al. Computer-aided detection of therapy-induced leukoencephalopathy in pediatric acute lymphoblastic leukemia patients treated with intravenous high-dose methotrexate. *Magn Reson Imaging*. 2006; 24:785–791. [PubMed: 16824973]
48. Reddick WE, Glass JO, Langston JW, Helton KJ. Quantitative MRI assessment of leukoencephalopathy. *Mag Reson Med*. 2002; 47:912–921.
49. Mahone ME, Martin R, Kates WR, et al. Neuroimaging correlates of parent ratings of working memory in typically developing children. *J Int Neuropsychol Soc*. 2009; 15:31–41. [PubMed: 19128526]
50. Reddick WE, Glass JO, Palmer SL, et al. Atypical white matter volume development in children following craniospinal irradiation. *Neuro-Oncology*. 2005; 7:12–19. [PubMed: 15701278]

Figure 1. Automated segmentation map. Grey matter is yellow, white matter is green, and cerebrospinal fluid is blue. Quadriant divisions are shown as white lines.

Table 1
Demographic and clinical characteristics of brain tumor survivors

	n (%)	M ± SD	Median	p ^c
Gender (Male)	25 (50)			
Race (Caucasian)	46 (92)			
SES ^a		37.61 ± 12.19	39.00	
Age at diagnosis		6.34 ± 3.43	6.50	
Age at MRI exam		13.13 ± 2.88	12.67	
Age at neuropsychological assessment		13.14 ± 2.88	12.67	
Age at initiation of CRT		7.41 ± 3.41	7.79	
Time since initiation of CRT		5.77 ± 2.27	5.75	
Tumor Diagnosis				
Ependymoma	22 (44)			0.15
Craniopharyngioma	16 (32)			
Low grade glioma	12 (24)			
Tumor Location				
Supratentorial	28 (56)			0.40
Infratentorial	22 (44)			
Extent of surgical resection ^b				
Near/gross total	25 (50)			1.00
Biopsy/subtotal	25 (50)			
Pre-CRT chemotherapy				
No	44 (88)			0.00
Yes	6 (12)			
Hydrocephalus				
No	21 (42)			0.26
Yes	29 (58)			
Shunt placement				
No	29 (58)			0.26
Yes	21 (42)			

^a SES is based on the Barratt Simplified Measure of Social Status which takes into account maternal and paternal education and occupation; scores can range from 8 to 66 with higher scores indicative of higher SES.

^b Extent of surgical resection was dichotomized: biopsy/subtotal resection (tumor sampling to determine pathology; incomplete resection with gross residual disease present on post-operative neuroimaging) or near/gross total resection (incomplete resection with minimal residual disease present on neuroimaging; the complete absence of residual disease observed by neurosurgeon or on post-operative neuroimaging).

^c p-value is from a Chi-Square test that indicates whether there is equal distribution across subcategories. N = 50.

Table 2
Group performance on measures of intelligence and working memory

	N	M ± SD	Median	% at-risk	p ^e
WASI ABIQ (Standard Score) ^d	50	98.20 ± 13.91	95.50		
Digit Span (Scaled Score) ^b	50	9.12 ± 3.50	9.00		
Digit Span Forward (Z score) ^c		- 0.22 ± 1.04	-0.28		
Digit Span Backward (Z score) ^c		-0.12 ± 1.08	-0.15		
SOS Verbal Mean Error Score	48	.43 ± .38	0.33		
SOS Object Mean Error Score	50	.50 ± .35	0.53		
BRIEF Parent Rating Scale (T score) ^d	49				
Behavior Regulation Index		49.47 ± 10.40	49.00	16	1.00
Inhibit		48.20 ± 9.29	44.00	10	.25
Shift		49.84 ± 10.46	47.00	20	.44
Emotional Regulation		50.53 ± 10.86	48.00	20	.44
Metacognitive Index		54.10 ± 11.56	52.00	32	<.01
Initiation		53.94 ± 10.15	53.00	24	.12
Working Memory		57.24 ± 14.33	53.00	40	<.01
Planning and Organization		53.96 ± 10.96	51.00	30	<.01
Organization of Materials		50.18 ± 9.50	50.00	20	.44
Monitor		51.16 ± 11.19	48.00	26	.05
Global Executive Composite		52.57 ± 11.05	50.00	26	.05

^a Standard scores have a mean of 100 and a standard deviation of 15.

^b Scaled scores have a mean of 10 and a standard deviation of 3.

^c Z scores have a mean of 0 and a standard deviation of 1.

^d T scores have a mean of 50 and a standard deviation of 10.

^e p-value is from a Chi-Square test. A significant result indicates that there is a greater than expected proportion of participants with elevated scores. Self-Ordered Search - Mean Error scores for SOS-V and SOS-O are presented for data reduction purposes.

Table 3
Correlations between regional volumes of NA WM and performance or rater-based measures of working memory

	R. frontal	L. frontal	R. posterior	L. posterior
Digit Span Forward (Z score) ^a	0.28*	0.09	0.23	0.23
Digit Span Backward (Z score)	0.32*	0.15	0.33*	0.34*
SOS-Verbal Mean Total Error Score	-0.15	0.00	-0.10	-0.01
SOS-Object Mean Total Error Score	-0.26	-0.21	-0.25	-0.27
BRIEF Global Executive Composite (T score) ^{b,c}	-0.01	-0.03	0.1	0.05
Metacognitive Index	0.04	-0.03	0.11	0.01
Initiation	0.05	-0.00	0.12	0.11
Working Memory	-0.05	-0.11	0.04	-0.04
Planning and Organization	0.06	-0.01	0.12	0.02
Organization of Materials	0.10	0.02	0.11	0.09
Monitor	0.05	0.03	0.08	0.07

Results are reported as R-values.

^aZ scores have a mean of 0 and a standard deviation of 1.

^bT scores have a mean of 50 and a standard deviation of 10.

^cN = 49.

* p-value .05.

Table 4
Correlations between regional volumes of NAWM and performance or rater-based measures of working memory reported by gender

	Males				Females			
	R. frontal	L. frontal	R. posterior	L. posterior	R. frontal	L. frontal	R. posterior	L. posterior
Digit Span Forward (Z)	0.29	0.09	0.23	0.25	0.28	0.08	0.23	0.20
Digit Span Backward (Z)	0.15	-0.05	0.18	0.14	0.45**	0.35	0.44**	0.52**
Self-Ordered Search Verbal (Total Error)	-0.18	-0.02	0.03	-0.09	-0.17	0.01	-0.27	-0.10
Self-Ordered Search Object (Total Error)	-0.20	-0.17	-0.13	-0.26	-0.45*	-0.36	-0.52**	-0.39
BRIEF Global Executive Composite (T) ^c	-0.04	-0.01	-0.10	-0.23	-0.08	-0.15	0.13	0.07
Metacognitive Index	0.06	-0.06	-0.04	-0.13	-0.10	-0.15	0.10	0.05
Initiation	-0.02	-0.08	-0.02	-0.06	0.02	-0.03	0.14	0.14
Working Memory	-0.04	-0.16	-0.08	-0.17	-0.24	-0.24	-0.12	-0.12
Planning and Organization	0.12	0.05	0.02	-0.11	-0.10	-0.22	0.08	-0.04
Organization of Materials	0.08	-0.06	-0.10	-0.18	-0.03	-0.07	0.11	0.14
Monitor	0.04	0.00	-0.06	-0.13	0.00	-0.17	0.13	0.18

Results are reported as R-values.

^a Z scores have a mean of 0 and a standard deviation of 1.

^b T scores have a mean of 50 and a standard deviation of 10.

^c N = 49.

* p-value .05;

** p-value .01