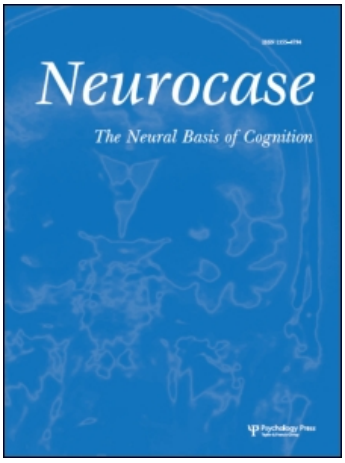

Neurocase
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713658146

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Online publication date: 03 February 2010

To cite this Article Schmidt, Adam T., Martin, Rebecca B., Ozturk, Arzu, Kates, Wendy R., Wharam, Moody D., Mahone, E. Mark and Horská, Alena(2010) 'Neuroimaging and neuropsychological follow-up study in a pediatric brain tumor patient treated with surgery and radiation', Neurocase, 16: 1, 74 — 90
To link to this Article: DOI: 10.1080/13554790903329133
URL: http://dx.doi.org/10.1080/13554790903329133

NEUROCASE
2010, 16 (1), 74–90

Psychology Press
Taylor & Francis Group

Neuroimaging and neuropsychological follow-up study in a pediatric brain tumor patient treated with surgery and radiation

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Intracranial tumors are the most common neoplasms of childhood, accounting for approximately 20% of all pediatric malignancies. Radiation therapy has led directly to significant increases in survival of children with certain types of intracranial tumors; however, given the aggressive nature of this therapy, children are at risk for exhibiting changes in brain structure, neuronal biochemistry, and neurocognitive functioning. In this case report, we present neuropsychological, magnetic resonance imaging, proton magnetic resonance spectroscopic imaging, and diffusion tensor imaging data for two adolescents (one patient with ependymal spinal cord tumor with intracranial metastases, and one healthy, typically developing control) from three time points as defined by the patient's radiation schedule (baseline before the patient's radiation therapy, 6 months following completion of the patient's radiation, and 27 months following the patient's radiation). In the patient, there were progressive decreases in gray and white matter volumes as well as early decreases in mean N-acetyl aspartate/choline (NAA/Cho) ratios and fractional anisotropy (FA) in regions with normal appearance on conventional MRI. At the last follow-up, NAA/Cho and FA tended to change in the direction to normal values in selected regions. At the same time, the patient had initial reduction in language and motor skills, followed by return to baseline, but later onset delay in visuospatial and visual perceptual skills. Results are discussed in terms of sensitivity of the four techniques to early and late effects of treatment, and avenues for future investigations.

Keywords: Neuroimaging; Neuropsychological; Neoplasm; Radiation; Diffusion; Magnetic resonance spectroscopy.

A portion of this study was presented at the 34th Annual International Neuropsychological Society Conference, Boston, Massachusetts, February 4, 2006. The authors wish to thank Melissa Matson, Ph.D., David Bonekamp, M.D., Trisha Hay, Jena Peebles, and Mahaveer Degonkar, Ph.D., for their contribution to an earlier version of this work.

Supported by R01 NS04285, HD-24061 (Developmental Disabilities Research Center), P30HD024061-16, and Johns Hopkins University School of Medicine Institute for Clinical and Translational Research, an NIH/NCRR CTSA Program, UL1-RR025005.

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http://www.psypress.com/neurocase DOI: 10.1080/13554790903329133

INTRODUCTION

Intracranial tumors are the most common neoplasms of childhood, with an incidence rate of approximately 3.7 cases per 100,000 children, accounting for approximately 20% of all pediatric malignancies (Butler & Haser, 2006; Pollock, 1999; Young, Ries, Silverberg, Horm, & Miller, 1986). Although some tumors such as low-grade astrocytomas can be treated with surgery alone with a high rate of event free survival (Beebe et al., 2005), other more aggressive tumor types require additional therapeutic intervention such as radiation.

Radiation therapy (RT) has led directly to significant increases in survival of children with certain types of intracranial tumors (Butler & Haser, 2006; Ris et al., 2005); however, given the aggressive nature of this therapy, children are at risk for exhibiting changes in brain structure, neuronal biochemistry, and neurocognitive functioning (Belka, Budach, Kortmann, & Bamberg, 2001; Duffner, 2004; Mulhern, Hancock, Fairclough, & Kun, 1992; Ris & Noll, 1994; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). Early detection of radiation injury is important in order to evaluate success of treatment, to assess the need for treatment of neurotoxic effects, and to evaluate effectiveness of neuroprotective drugs.

Neuronal injury secondary to radiation treatment has been classified according to the time symptoms develop following RT exposure (Ball, Prenger, & Ballard, 1992; New, 2001; Valk & Dillon, 1991). For example, a*cute injury* appears to be secondary to transient vasogenic edema and occurs within several weeks after treatment; it generally manifests as transient worsening of symptoms and has little prognostic significance. *Early delayed injury* occurs within 1–6 months following RT treatment and typically impacts deep gray and white matter; however, these effects are usually transient. Conversely, *late radiation injury*, which may occur months to years following treatment, is progressive, often irreversible, and potentially fatal (Duffner, 2004; Hoppe-Hirsch et al., 1990). Late radiation injury has been associated with leukoencephalopathy, brain atrophy, necrosis, endocrine dysfunction and neurocognitive deterioration (Anderson, 2003; Duffner, 2004; Monje & Palmer, 2003; Valk & Dillon, 1991). In each of the stages of radiation injury, there is an increase in free tissue water that may result from damaged endothelial cells or demyelination. These damages can potentially cause increased capillary permeability and vasogenic edema, or cause water to replace hydrophobic myelin (Valk & Dillon, 1991).

The development of increasingly sophisticated neuroimaging techniques has been invaluable for the characterization of structural and biochemical changes which may result from radiation injury (Vezina, 2008). For example, research using structural magnetic resonance imaging (MRI) indicates that radiation injury primarily involves deep white matter (subventricular zone) and hippocampal area, with early sparing of subcortical white matter and the adjacent cortex (Ball et al., 1992; Belka et al., 2001). However, despite extensive involvement of deep white matter, the corpus callosum, anterior commissure, and hippocampal commissure often appear spared.

MRI has been the imaging modality of choice for tumor detection, evaluation of tumor location, size and extent, and, in some cases, diagnosis (Vezina, 2008). However, the value of conventional MRI for detection of neurotoxic injury and the separation of neurotoxic injury from recurrent tumor is more limited (Armstrong et al., 2000; Ball et al., 1992; Constine, Konski, Ekholm, McDonald, & Rubin, 1988). In contrast, other imaging modalities based on magnetic resonance technology have the potential to provide valuable information regarding the possible neurotoxic impact of radiation. The contribution of advanced imaging methods including proton magnetic resonance spectroscopic imaging (MRSI) and diffusion tensor imaging (DTI) to evaluate diagnosis and treatment of brain tumors, including radiation therapy planning, has been reviewed recently (Lemort, Canizares-Perez, Van der Stappen, & Kampouridis, 2007).

Proton MRSI can map distribution of important brain metabolites including N-acetyl aspartate (NAA), total choline (Cho), and total creatine (Cr). NAA, located predominantly in neuronal cell bodies, dendrites, and axons, is considered a neuronal marker (Barker, 2001). MRSI may differentiate a tumor from radiation necrosis and could be applied to prognosticate overall survival (Vezina, 2008). In adult patients treated with radiation, proton MRSI detected a decrease in N-acetyl aspartate (NAA) levels 4 months after the start of radiation therapy; however, subsequent evaluation after another 4 months indicated restoration of normal levels (Esteve, Rubin, Grand, Kolodie, & Le Bas, 1998). Since brain irradiation may result in demyelination and neuronal loss, biochemical changes detected with *in vivo* MRSI may be used to reveal the presence, extent, and mechanism of brain tissue damage.

The DTI technique can measure diffusion of water molecules in white matter, thus providing unique information on tissue integrity. Diffusion anisotropy in white matter is affected both by presence of intact membranes and the degree of myelination (Beaulieu, 2002). DTI has been used to study effects of therapy (radiation, gene therapy) on tumors, including human brain tumors (Kauppinen, 2002). In addition to being able to localize the tumor, DTI can also assess global white matter injury in children treated with whole brain radiation (Khong et al., 2005). Using DTI and proton MR spectroscopy, Kitahara, Nakasu, Murata, Sho, and Ito (2005) found that the most prominent changes in fractional anisotropy (FA, a measure of white matter integrity) and NAA/Cr ratios occurred 3–5 months following radiation. However, no significant differences between patients and controls 10–12 months after treatment were detected. In contrast, in a more recent study that included 25 adult patients treated with radiation, a progressive decrease in FA in the genu and the splenium up to 45 weeks after commencement of radiation therapy was reported (Nagesh et al., 2008). The investigators argued their findings indicated demyelination and mild axonal disruption. Late-delayed effects of radiation detected by DTI were also reported in medulloblastoma survivors, in particular in the frontal lobe (Qiu, Kwong, Chan, Leung, & Khong, 2007). Furthermore, studies have associated abnormal FA in children treated with radiation therapy with poor intellectual outcomes and deterioration in school performance (Khong et al., 2003; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006).

Early research in children with brain tumors indicated that those treated with RT, as compared to those treated with surgery alone, exhibited greater decreases in overall intellectual abilities (Mulhern et al., 1992; Palmer et al., 2001; Ris & Noll, 1994; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004; Walter et al., 1999). These early studies attributed IQ declines to children failing to make expected developmental gains, rather than actual loss of skills. Nevertheless, more recent research demonstrates actual cognitive declines beginning as early as the first year post-treatment and continuing up to 10 years after the completion of radiation therapy (Spiegler et al., 2004; Yeo, Hill, Campbell, Vigil, & Brooks, 2000). Further, recent evidence posits greater IQ loss in the early post-treatment years, with losses stabilizing around 5–6 years after treatment (Mulhern et al., 1992; Palmer et al., 2001).

Additionally, recent research points to more specific, long-term neurocognitive effects of RT, including deficits in working memory, attention, visual perception, visual motor integration, visual memory, and aspects of executive functioning (Butler & Copeland, 2002; Butler & Haser, 2006; Lockwood, Bell, & Colegrove, 1999; Mulhern et al., 1998; Palmer, Reddick, & Gajjar, 2007; Reddick et al., 2003; Schatz, Kramer, Ablin, & Matthay, 2000; Spiegler et al., 2004). The extent of neurocognitive deficits appears to be due, in part, to factors such as dose and location of radiation (Fuss, Poljanc, & Hug, 2000; Silber et al., 1992), age at time of treatment, use of adjunct chemotherapy (Reimers et al., 2003; Ris & Noll, 1994) and neurological complications such as hydrocephalus (Butler & Haser, 2006; Duffner, 2004; Reimers, Mortensen, & Schmiegelow, 2007). Additionally, neurocognitive morbidities may exacerbate the already considerable emotional and psychosocial strain placed upon families who have to endure diagnosis and treatment of a childhood cancer, and they may also have additional implications for educational/vocational planning and quality of life for the child (Mabbott et al., 2005; Poggi et al., 2005a; Ris et al., 2005).

Some of the more consistent neuropsychological deficits seen in children treated with radiation appear to be correlated with findings on neuroimaging. For example, neuroimaging studies highlight the impact of RT on development of white matter (Khong et al., 2006; Reddick et al., 2003), particularly in the right hemisphere (Goldberg & Costa, 1981), and as such RT is frequently associated with deficits in processing speed, motor skills, attention, and nonverbal skills – all considered to be dependent on white matter structures (Butler & Haser, 2006; Palmer et al., 2007; Reddick et al., 2003). However, much of the research investigating late effects of RT has been conducted using older, less sophisticated RT protocols. Current RT protocols have been developed in an attempt to reduce the overall toxicity to the developing brain by manipulating factors such as dose, volume irradiated, beam orientation, and fractionation schedule (Schmiegelow et al., 2000). Thus, less is known about the long-term neurocognitive effects using the more recently developed RT treatment approaches designed to reduce neurodevelopmental morbidity.

In this case report, we present neuropsychological, magnetic resonance imaging (MRI), proton magnetic resonance spectroscopic imaging (MRSI), and diffusion tensor imaging (DTI) data for two individuals (one patient with spinal cord tumor,

one healthy control) from three time points: baseline (just before start of radiation therapy), 6 months following start of treatment, and 27 months following treatment. The control participant was matched in age at baseline, and followed at similar time points. Based upon previous research, we hypothesized that our patient would demonstrate decreased white matter volume over the course of the study, compared to the control participant, but that gray matter changes would be more subtle. Similarly, we hypothesized that the patient would manifest perturbations in measures of neuronal and white matter integrity (e.g., NAA/Cr ratios and FA values, respectively) across the course of the study. Finally, in terms of neuropsychological functioning, we hypothesized that the patient would manifest some initial deficits in language and right-side motor skills based upon the location of the tumor; however, in terms of late effects, we expected to see a relatively greater impact on those neuropsychological abilities thought to be more dependent on white matter integrity (e.g., attention, processing speed, and visuospatial skills).

This study is unique in several respects. First, it presents data using multiple imaging methods as well as neuropsychological assessment. Second, it compares a patient treated with RT to an age- and sex-matched healthy control (controlling for the impact of normal developmental variation). Third, it follows the patient and control participant over a 27-month time period, so that potential late effects of treatment can be observed. This report is an initial step in a larger study that aims to improve the precision of RT by helping to characterize the long-term effects of this treatment, and in doing so, contribute to the development of a less neurotoxic RT protocol.

CASE REPORT

Patient

The patient's course of illness and treatment are outlined in Figure 1. The patient is a 15-year 4-month-old (at baseline) male diagnosed with spinal myxopapillary ependymoma (MPE). He had a normal early developmental history, meeting all developmental, social, and behavioral milestones within normal limits and no report of medical problems until diagnosed with spinal cord tumor. The patient initially presented with a history of limping due to left hip pain, leading to a MRI which revealed a mass in the spinal canal from T12–L1 to L3–L4. At age 13 years, 9 months, the patient had a resection of lumbar MPE followed by external beam radiation therapy (50.4 Gy) to the operative site. He had recurrence in both left temporal lobe and cerebellum the following year at age 15. The left temporal lobe occurrence was accompanied by a major left temporal hemorrhage requiring emergent surgery. A grade 2 ependymoma in the temporal lobe was almost completely removed in a sub-total resection. In the following 2 months, the patient received whole-brain RT (36 Gy) and a boost to the left temporal region (54 Gy), followed by gamma knife radiosurgery (20 Gy) for bilateral cerebellar lesions. He was also treated with Decadron (2 mg twice a day) for 10 days after completion of RT, and with Dilantin for over 3 months following his surgery. More than a year later, at age 17 years, the patient developed thoracic spine epidural metastases (at T1, T5, and T7) and was treated with thoracic spine radiation (46.8 Gy). In his brain imaging follow-up there was a stable small post-treatment change in the left temporal tip without any

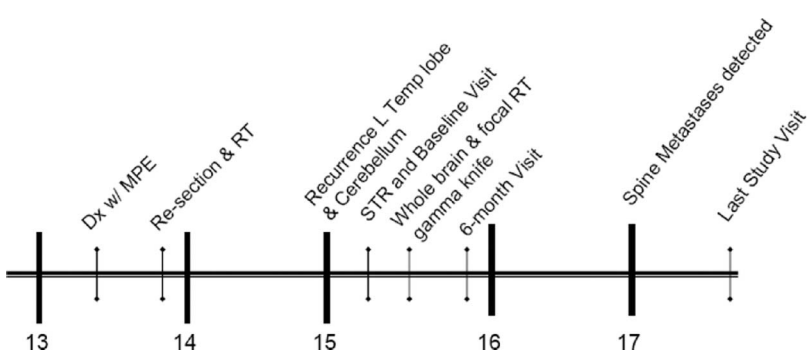

Figure 1. Timeline of illness and treatment for patient. *Note*: Dx, diagnosis; MPE, myxopapillary ependymoma; RT, radiation therapy; L Temp lobe, left temporal lobe; STR, sub-total resection.

evidence of tumor residual or recurrence. Although there were no abnormal neurological exam findings, he has been attending a vocational school due to a difficulty in English classes. At the patient's most recent evaluation (age 19 years and 3 months), he was stable showing no progression of disease (Figure 1).

Control participant

The control participant is a healthy, typically-developing, 15-year 6-month old (at baseline) male with no history of psychiatric disorder, neurological illness, or learning disability. He was on no medications during the course of the study.

PROCEDURES

Screening

All neuropsychological testing was completed by a trained master's level psychology associate or postdoctoral fellow, under the supervision of a licensed psychologist, in an outpatient neuropsychology clinic. At baseline, both participants were screened for psychiatric disorders using the structured Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV) (Reich, Welner, & Herjanic, 1997), which is based on the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 1994). This is a semi-structured interview that is designed for determining selected current and retrospective psychiatric diagnoses including Attention Deficit Hyperactivity Disorder, Conduct Disorder, Oppositional Defiant Disorder, Major Depressive Disorder, Bipolar Disorders, Dysthymia, Separation Anxiety Disorder, Panic Disorder, Generalized Anxiety Disorder, Specific Phobia, and Obsessive Compulsive Disorder. Both the patient and the control were free from psychiatric diagnoses at baseline, based on DICA-IV assessment. At follow-up assessments, parent reported no changes in psychiatric status. The patient and control participants were matched on socioeconomic status (SES) – estimated by the four-factor index (i.e., gender, marital status, education, and occupation (Hollingshead, 1975). Both families participating in the study signed a written informed consent form following the Institutional Review Board standards of the Johns Hopkins Medical Institution.

Neuroimaging

High-resolution 3D MRI, proton MRSI, and DTI were acquired at 1.5 Tesla using the standard bird-cage quadrature head coil.

MRI

Oblique-axial images were obtained with a 3D volumetric radiofrequency spoiled gradient echo (SPGR) series partitioned into 124, 1.5-mm contiguous slices. The following parameters were used: repetition time (TR) 17 ms, echo time (TE) 3.2 ms, inversion time 300 ms, field-of-view (FOV) 240 mm, phase FOV 0.75, acquisition matrix 256×128. Raw image data were imported into *BrainImage* (Reiss, 1999; http://spnl.stanford.edu/tools/brainimage.htm) for visualization, processing, and quantitation (Subramaniam, Naidu, & Reiss, 1997). To prepare the stacks for measurement, non-brain material (i.e., skull, scalp, and vasculature) was removed using a semi-automated edge detection routine that involves region growing as well as stepwise morphologic operations (Subramaniam et al., 1997). The 'skull-stripped' images were re-sliced so that the interpolated slice thickness (z-dimension) is the same as the x and y pixel dimensions thereby converting the image stacks into cubic voxel data sets. The cubic voxel data sets were opened into the multiplanar visualization mode of *BrainImage* so that three orthogonal representations of the data could be viewed simultaneously.

Isolated brain tissue was subdivided into cerebral lobes, subcortical regions, brainstem, and cerebellar regions using the revised Talairach (Talairach & Tournoux, 1988) stereotaxic grid atlas specific for measurement in pediatric study groups (Andreasen et al., 1993; Kaplan et al., 1997; Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Each region was then segmented to delineate and measure lobar volumes of gray, white, and ventricular compartments using a constrained fuzzy algorithm that assigns voxels to one or more tissue categories based on intensity values and tissue boundaries. The segmentation method used was determined reliable for all gray matter, white matter, and CSF volumes (Reiss et al., 1998). Gray and white matter volumes for frontal, temporal, parietal and occipital lobes, and for total intracranial volume were analyzed in the present case study.

Proton magnetic resonance spectroscopic imaging

Proton MRSI was performed using a spin-echo sequence with two-dimensional phase-encoding and outer-volume saturation pulses for lipid suppression (Duyn, Gillen, Sobering, van Zijl, & Moonen, 1993), with a 240-mm rectangular field-of-view and a reduced phase-encoding (Golay, Gillen, van Zijl, & Barker, 2002). Four 15-mm thick slices (2.5 mm slice gap) were recorded parallel to the anterior commissure – posterior commissure line with TR/TE = 2000 ms/140 ms. The full echo signal was digitized with 256 data points and a spectral width of 1000 Hz was used. The MRSI data sets were processed by 3D Fourier transformation, with cosine filters in the spatial (phase-encoding) domains after zero-filling to 32 × 32 matrix size, and exponential line broadening of 3 Hz, zero-filling to 8192 data points, and a high-pass convolution filter to remove the residual water signal (50 Hz stop-band) in the time-domain. No baseline correction was applied. Signals of Cho, Cr, and NAA were fitted to a Gaussian lineshape using a simplex routine using in-house software csx3 and imax3 (http://godzilla.kennedykrieger.org/csx/). NAA/Cho ratios were calculated for the Wernicke's area, splenium, temporal-occipital white matter, corona radiata, and dorsal parietal cortex (Figure 2). Prior to MRSI, T_1-weighted localizer images were recorded at the same slice location and thickness as MRSI for anatomical correlations.

Diffusion tensor imaging

DTI data were collected using a single-shot diffusion-weighted spin-echo echo-planar imaging sequence with the following parameters: TR = 8 s, TE = 93.7 ms, acquisition matrix 96 × 96, field-of-view 240 mm, two $b = 0$ s/mm^2 images, 15 different gradient directions, maximum $b = 1000$ s/mm^2, two acquisitions. Twenty-four axial slices parallel to the anterior commissure-posterior commissure plane were acquired with 5-mm slice thickness and no gap. Diffusion tensors were computed using the DTI Studio (H. Jiang and S. Mori, Johns Hopkins

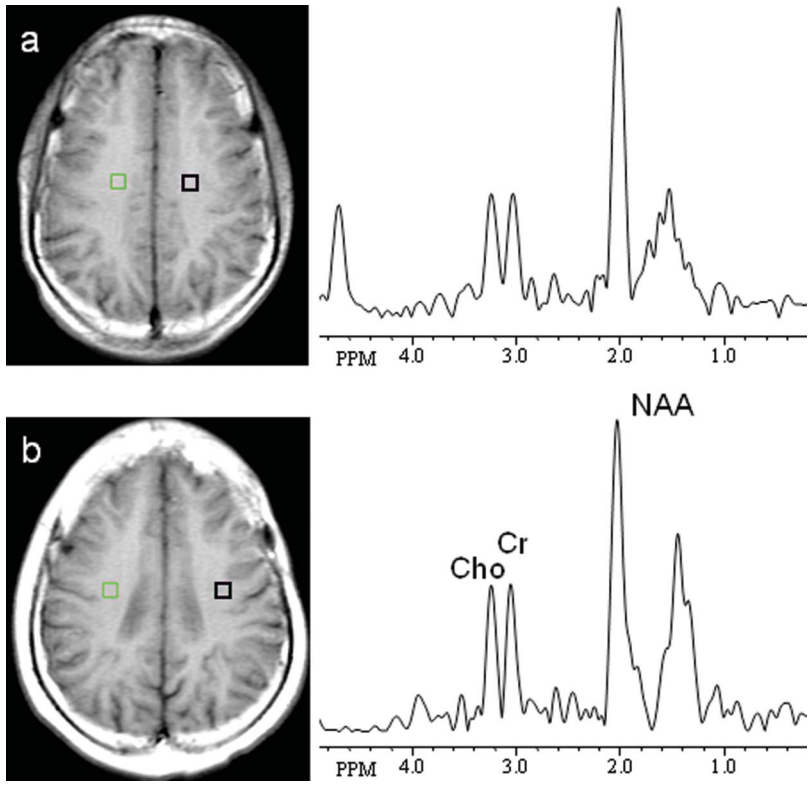

Figure 2. T_1-weighted localizer images and corresponding proton MR spectra acquired at T_{27} for control and patient. *Note*: T_1-weighted localizer images showing the region of interest in the left corona radiata and corresponding proton MR spectra acquired at the last follow-up examination in the control (a) and the patient (b). Signals of choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA) were detected. Both spectra also show presence of small lipid signals originating from the skull.

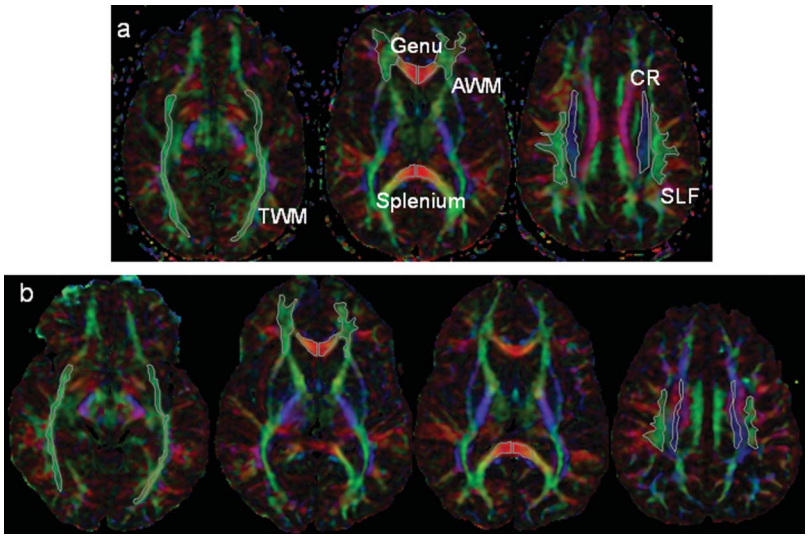

Figure 3. Regions of interest for diffusion tensor imaging. *Note*: DTI regions of interest in the temporal white matter (TWM), genu and splenium of the corpus callosum, anterior white matter (AWM), corona radiata (CR), and superior longitudinal fasciculus (SLF) in the control (a) and the patient (b). To view this figure in color, please visit the online version of this Journal.

University, cmrm.med.jhmi.edu). Drawing of regions of interest was performed on the color-coded maps, using the color information and intensity to identify fiber bundles and avoid gray matter. For the current study, FA values from the following regions of interest were analyzed: superior longitudinal fasciculus, corona radiata, temporal white matter, anterior white matter, genu and splenium of the corpus callosum (Figure 3).

Neuropsychological assessment

The measures chosen for the neuropsychological assessment were based on prior research which has emphasized localization of brain-behavior relationships based upon adult acquired lesion data. Some measures were also included due to their established relationship with neurobehavioral functions of interest, and the presumed emphasis of brain regions associated with each neurobehavioral function. Since this study has a unique design, four principles guided the selection of neuropsychological assessment measures. First, the protocol was designed to provide a broad sampling of the primary neurobehavioral domains. Second, the protocol was designed to utilize the same standardized instruments in the age range of interest. Third, the protocol was specifically designed to be repeatable, with minimal practice effect. Fourth, the protocol was designed to be completed in one morning (approximately 2 h of testing), in order to minimize potential effects of fatigue. Specific measures used for the case study are described below.

IQ screening

Peabody Picture Vocabulary Test, Third Edition (Dunn & Dunn, 1997)

The PPVT-III is a screening test of verbal ability and a measure of receptive (i.e., listening) single-word vocabulary attainment for standard English. The scale is reported to correlate at .90 with Wechsler Intelligence Scale, Third Edition Full Scale IQ (Dunn & Dunn, 1997), and as such, it was used as an estimate for IQ (Natale et al., 2000; Snitz, Bieliauskas, Crossland, Basso, & Roper, 2000). Participants were shown a page with four pictures and the examiner provided the participant with a vocabulary word. The participants were asked to identify the picture that best describes the word either by pointing or verbalizing the number of the picture.

Attention Tests

Visual Matching, Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001)

Participants were asked to locate and point to two matching shapes in a row of four to five shapes, under time constraints. This is a measure

of visual selective attention, and processing speed, and requires the capacity to stay on task in a vigilant manner. Similar tasks have been frequently used in neuroimaging studies of visual attention (see Downing, Liu, & Kanwisher, 2001).

Working Memory Tests

Auditory Working Memory, Woodcock Johnson-III (Woodcock et al., 2001)

This is a measure of short-term auditory memory span and auditory (verbal) working memory. The participant is asked to listen to a series that contains digits and words such as 'dog', '1', 'shoe', '8', and attempt to reorder the words, repeating the objects first and the numbers second. The task requires the individual to maintain the information in immediate awareness, and manipulate it by dividing the words into two groups, and has been shown to correlate with frontal lobe gray matter volumes in children (Mahone, Martin, Kates, Hay, & Horska, in press).

Bead Memory, Stanford Binet Intelligence Scale, Fourth Edition (Thorndike, Hagen, & Sattler, 1986)

This is a test of visuospatial working memory and visual span. The participant is asked to look at a picture of beads placed in a particular pattern, then (after a brief pause) to reproduce the pattern from memory. Among typically developing children, Bead Memory performance correlates with right frontal NAA/Cr ratios on MRSI (Ozturk et al., in press).

LANGUAGE AND VERBAL MEMORY TESTS

Language and Memory Tests

Retrieval Fluency, Woodcock Johnson-III (Woodcock et al., 2001)

The Retrieval Fluency Test is a measure of rapid lexical retrieval and executive functioning for children and adolescents. Participants were asked to produce as many words as possible beginning within a certain category (i.e., things to eat/drink, first names, animals). The number of correct items, repetitions, and rule breaks provide information about speed and efficiency of lexical retrieval and executive control. A similar task has been linked to activation within the left inferior frontal gyrus (Grabowski, Damasio, & Damasio, 1998).

Memory for Words, Woodcock Johnson-III (Woodcock et al., 2001)

This is a test of short-term auditory verbal memory. Participants were asked to repeat lists of unrelated words in the correct sequence. Verbal memory tasks have been associated with activation of left posterior temporal regions (Henson, Burgess, & Frith, 2000).

Sound Blending, Woodcock Johnson-III (Woodcock et al., 2001)

This is a measure of auditory processing and phonetic decoding. Participants were asked to listen to a series of syllables or phonemes and then blend the sounds into a word. Phonological processing has been associated with activation in left occipito-temporal and temporo-parietal regions (Shaywitz et al., 2002; Simos et al., 2000).

Visuospatial, Visuoperceptual, and Visual ConstructionTests

Spatial Relations, Woodcock Johnson-III (Woodcock, McGrew, & Mather, 2001)

The Spatial Relations test is an untimed multiple-choice test in which the participant is asked to mentally match fragments of shapes to a model. From an array of three to six choices, participants are asked to select the appropriate shapes (either two or three) that can be assembled to replicate the displayed model. This task taps the spatial perception of abstract forms, and does not require a motor response. Performance on visuospatial reasoning tasks have been associated with activation of right frontal and bilateral parietal brain regions (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997).

Block Design, Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003)

The Block Design subtest requires the participant to construct a design with 3D blocks based on a pictorial representation. It is considered a measure of visual construction. Recent research has shown that performance on the Block Design subtest is positively correlated with total frontal,

parietal, temporal, and occipital gray matter volumes (Colom, Jung, & Haier, 2006).

Beery Developmental Test of Visuomotor Integration (VMI; Beery & Beery, 2004)

The VMI is a developmental sequence of geometric forms to be copied with paper and pencil. It was designed to assess the extent to which individuals can integrate their visual and motor abilities. A recent study examining DTI correlates of motor dysfunction found that lower fractional anisotropy and higher transverse diffusivity in a patient group was related to relatively poorer performance on the VMI (Ludeman et al., 2008).

Beery Developmental Test of Visual Perception (VP; Beery & Beery, 2004)

On the Visual Perception test, the participant is shown one geometric form and is asked to choose the geometric form that is exactly the same from a group of forms within a 3-min time limit. Thus, the test is designed as a measure of motor-free visual-perceptual skills. Performance on this test is correlated with temporal lobe volumes in typically developing children (Wells et al., 2008).

Motor Tests

Purdue Pegboard (Tiffin, 1968)

The Purdue Pegboard test was used as a measure of manipulative dexterity. The board consists of 25 parallel holes. Pegs are located at the top of the board. The participant is asked to place pegs in the holes in a vertical manner, first with the dominant hand, then with the nondominant hand, and then using both hands. The examiner records the number of pegs placed in 30 s. Performance on the Purdue Pegboard has been associated with frontal NAA/Cr ratios in children (Ozturk et al., in press).

Data analyses

Data were analyzed at baseline/post-surgery (T_0), 6-month follow-up (T_6) and 27-month follow-up (T_{27}) for the patient and control. Raw neuropsychological test scores and imaging data from each visit were recorded. For each participant, change scores from T_0 to T_6, and from T_6 to T_{27} were calculated. In addition, the *difference* in T_6–T_{27} change between the patient and control was also calculated for each variable of interest.

RESULTS

Results of volumetric MRI are listed in Table 1. In general, the patient showed slightly larger baseline gray and white matter volumes across regions. At T_6, the patient had bilaterally decreased temporal and frontal white matter volumes, reduced total cranial white matter volume, but slight increases in gray matter volumes. At T_6, the control participant had more stable presentation, with most regions (except frontal white matter) showing slightly

TABLE 1
Volumetric MRI: lobar volumes (cm^3)

	Control			*Patient*		
	T_0	T_6	T_{27}	T_0	T_6	T_{27}
Tot Cranial G	638.66	658.71	692.22	687.49	720.39	677.4
Frontal G	199.42	205.39	216.8	200.87	215.00	206.57
Parietal G	124.88	130.75	139.79	137.63	137.42	132.34
Temporal G	114.94	126.55	128.13	128.61	135.41	131.8
Occipital G	60.81	65.24	63.35	75.89	73.71	65.29
Tot Cranial W	402.13	428.24	413.21	460.65	399.57	372
Frontal W	140.86	132.14	137.6	159.03	134.84	131.19
Parietal W	101.89	102.41	99.96	100.33	109.26	101.06
Temporal W	42.47	53.2	52.88	69.12	56.52	53.24
Occipital W	29.41	36.62	30.36	40.67	40.64	32.94
Total Volume	1040.78	1086.95	1105.44	1148.13	1119.95	1049.39

Note: G, gray matter; W, white matter; T_0, baseline visit; T_6, 6-month follow up visit; T_{27}, 27-month follow up visit.

increased volumes, compared to baseline. Between the T_6 and T_{27} visits, the patient showed decreased volume bilaterally across all regions, with most striking reductions observed in total white and gray matter volumes. The total volume loss observed in the patient did not appear to be primarily a function of normal maturation, as the control demonstrated more stable patterns of volume measurements between the T_6 and T_{27} visits. The notable exception in the control was a decrease in total left (but not right) cranial white matter volume to a level closer to baseline.

NAA/Cho ratios for the patient and control are listed in Table 2. At baseline, there was no difference in the mean NAA/Cho ratio between the patient and the control. While, in the control, the NAA/Cho ratio tended to increase over the examined period of time, a trend to decreasing NAA/Cho ratio was detected in the patient after completion of RT. The decline in NAA/Cho ratios was detected in most regions of interest in the patient, with temporal-occipital white matter (bilaterally), splenium, and corona radiata (left) showing the greatest decrease at T_6. Although, at the T_{27}, mean NAA/Cho ratio was lower by 24.5% in the patient, a trend to increases in NAA/Cho in the direction of normal values was observed in some regions (the right temporal-occipital white matter, splenium, and left corona radiata).

Fractional anisotropy (FA) values for the patient and control are listed in Table 3. At baseline, no difference in mean FA was detected between the patient and the control. Over the examined time, mean FA tended to increase in the control; however, in the patient, mean FA decreased by 8% at T_6. The patient demonstrated declines in FA across several fiber tracts (right superior longitudinal fasciculus, left corona radiata, genu, splenium, temporal white matter (bilateral) and anterior white matter (bilateral). At the T_{27} visit, the regional FA values in the patient tended to change in the direction to the baseline levels; however, the mean FA was 12.4% lower in the patient compared to the control.

Results of neuropsychological assessment are listed in Table 4. Compared to baseline, at the T_6 (early delay) visit, the patient showed skill loss (i.e., raw score declines) on neuropsychological measures of right-sided motor and language skills involving phonological awareness and oral fluency (perhaps indicative of acute effects of the left temporal surgery), but stability in all other neuropsychological domains. The control participant showed stable to improved neuropsychological function at T_6, with the exception of a slight reduction in motor speed. At T_{27} (late effects) assessment, the patient demonstrated raw score improvements in most neuropsychological measures, although generally at a slower pace than would be predicted for age, resulting in reduced standardized scores, particularly in visuospatial and visuoperceptual skills.

In summary, the patient showed decreases in temporal and frontal white matter volumes at T_6 and overall white and gray matter volumes at T_{27}, where as the control was more stable with slight increases in overall gray and white matter volumes over time. Similarly, NAA/Cho ratios generally decreased in the patient overtime, while they increased in the control. The patient also showed a

TABLE 2
Magnetic resonance spectroscopic imaging: NAA/Cho ratio

	Control			*Patient*		
ROI	T_0	T_6	T_{27}	T_0	T_6	T_{27}
Wernicke's	2.69	2.97	3.13	1.57	2.37	1.39
TOWM	1.91	2.01	2.23	2.97	1.46	1.98
Splenium	3.51	2.76	2.95	2.37	1.59	2.95
CR	2.59	2.29	2.74	2.26	1.64	2.43
DPC	2.86	2.29	3.58	2.68	2.83	2.09
Mean NAA/Cho	2.62	2.43	2.92	2.47	2.02	2.17

Note: TOWM, temporal-occipital white matter; CR, corona radiata; DPC, dorsal parietal cortex; T_0, baseline visit; T_6, 6-month follow up visit; T_{27}, 27-month follow up visit.

TABLE 3
Diffusion tensor imaging: fractional anisotropy (FA)

	Control			*Patient*		
ROI	T_0	T_6	T_{27}	T_0	T_6	T_{27}
SLF	0.47	0.54	0.47	0.42	0.40	0.42
CR	0.42	0.42	0.38	0.43	0.43	0.42
TWM	0.41	0.53	0.75	0.47	0.43	0.54
Genu	0.78	0.79	0.73	0.73	0.65	0.72
Splenium	0.74	0.79	0.81	0.69	0.62	0.80
AWM	0.47	0.51	0.68	0.47	0.41	0.46
Mean FA	0.55	0.60	0.63	0.54	0.49	0.56

Note: SLF, superior longitudinal fasciculus; CR, corona radiata; TWM, temporal white matter; AWM, anterior white matter. In the patient, NAA/Cho ratios in the Wernicke's area could be evaluated only in one hemisphere at T_0 and T_{27}, due to low quality of the spectra. T_0, baseline visit; T_6, 6-month follow up visit; T_{27}, 27-month follow up visit.

TABLE 4
Neuropsychological assessment

	Control			*Patient*		
Variable	T_0	T_6	T_{27}	T_0	T_6	T_{27}
PPVT-3	148	165	168	156	160	160
Spat Relations	58	63	64	78	77	75
Sound Blend	16	18	18	26	19	21
Visual Match	57	58	52	41	39	40
Aud Wor Mem	32	31	32	16	23	26
Retrieval Flu	62	66	58	55	40	51
Mem Words	17	18	17	17	18	17
Block Design	34	40	53	42	49	53
VMI	25	24	26	29	27	29
VP	20	24	26	27	28	27
Pegboard RH	12	10	11	14	10	13
Pegboard LH	14	10	12	12	15	13
Pegboard Both	9	4	9	6	8	10
Bead Memory	22	30	32	22	29	32

Note: All values represent raw scores. PPVT-3, Peabody Picture Vocabulary Test, Third Edition; Spat Relations, Spatial Relations; Sound Blend, Sound Blending; Aud Wor Mem, Auditory Working Memory; Retrieval Flu, Retrieval Fluency; Mem Words, Memory for Words; VMI, Beery Developmental Test of Visual Motor Integration; VP, Beery Developmental Test of Visual Perception; Pegboard, Purdue Pegboard; T_0, baseline visit; T_6, 6-month follow up visit; T_{27}, 27-month follow up visit.

decline in FA across fiber tracts, such as the right superior longitudinal fasciculus, while the control participant's mean FA values tended to increase. These patterns were consistent in the neuropsychological testing as well, where the patient showed a raw score decrease in phonological awareness and oral fluency at T_6 and a decrease in standard scores in visuospatial and visuoperceptual skills at T_{27}.

DISCUSSION

The current case study presents longitudinal data from neuropsychological, volumetric MRI, MRSI, and DTI evaluations of two individuals: a healthy, typically developing adolescent, and an age-matched patient who had recently undergone subtotal resection of a metastatic grade 2 left temporal ependymoma, with subsequent treatment with cranial radiation. Change from baseline was evaluated in order to assess early delayed effects (6 month) and late effects (27 month).

Consistent with our first hypothesis, the patient exhibited progressive volume losses in white matter across brain regions during the 27-month period. However, the patient also exhibited progressive losses in gray matter volume over the 27-month period (see Table 1). These findings were most striking when considering total gray and white matter volumes. Cerebral spinal fluid (CSF) volumes were also examined (not reported in Table) and found to be very similar in the patient and the control.

Consistent with our second hypothesis, the patient also had initially reduced NAA/Cho values on MRSI (particularly near the area of resection), with continued disruption in left Wernicke's area at 27 months (also near the site of the resection; Table 2), and modest, yet widespread, reductions in FA values on diffusion tensor imaging at 6 months, which also showed some 'rebound' by 27-month follow-up (Table 3). The MRSI and DTI abnormalities were present despite normal finding on conventional MRI in these regions of interest. Considering the time course and extent of the observed MRSI and DTI changes, our findings can be interpreted as neuronal injury, dysfunction or functional inactivity, rather than neuronal loss (Kaminaga & Shirai, 2005). Across imaging modalities, the control participant had more stable measurements, with overall slight increase across time in volume, NAA/Cho ratios, and FA values.

Again, generally consistent with our final hypothesis, neuropsychological dysfunction observed in the patient followed a parallel route, with early deficits observed in language and right-sided motor functions (consistent with the site of surgery, and with changes in NAA/Cho ratios), but later age-related (i.e., failure to keep pace) declines in visuospatial and visuoperceptual skills, more suggestive of late white matter injury.

None of the imaging modalities detected any apparent abnormalities in the evaluated brain regions at the baseline scan, suggesting minimal effects of tumor presence and treatment (surgery) at that time point. Conversely, findings from volumetric MRI, MRSI, DTI, and neuropsychological assessment appear sensitive to both early and late effects of surgical intervention and treatment with cranial radiation. Although volumetric MRI findings in the patient showed progressive decreases in regional gray and white matter volumes over the examined time, NAA/Cho and FA tended to 'recover' at the last follow-up in some regions. However, despite these changes in the direction to normal values, both mean NAA/Cho and FA values were still lower than in the control subject. Since the patient appeared to show decreases in

brain volume and 'lags' in NAA/Cr and FA increases, it may be possible that changes in FA and NAA/Cho or decreases in white matter volume may underlie the relative delay in visuospatial skill acquisition as observed in the 27-month neuropsychological data.

Since the baseline NAA/Cr levels were comparable between the patient and the control, there is no indication of impairment of neuronal integrity or function before the start of radiation. Rather, the decrease in NAA levels in the early-delayed phase post-treatment detected in the patient is consistent with previously published data in children and adults with brain tumors or metastases (Kaminaga & Shirai, 2005; Lee, Pirzkall, McKnight, & Nelson, 2004; Rutkowski, Tarnawski, Sokol, & Maciejewski, 2003). A trend to recovery of the NAA/Cho ratio observed in some regions is also in agreement with the literature (see Esteve et al., 1998). The incomplete recovery of NAA levels at the last follow-up may be explained by relatively high radiation doses (37–50 cGy). Previous studies demonstrated that in regions receiving high radiation doses, NAA levels may not fully recover within 6 months post-treatment (Lee et al., 2004; Szigety, Allen, Huyser-Wierenga, & Urtasun, 1993). Thus, the decreases in the NAA/Cho ratio, in particular at the 6-month follow-up, may be explained by adverse effects of radiation therapy rather than by a direct result of the surgical intervention (e.g., edema). However, an effect of surgery still should be considered, since, at the 27-month visit, the patient's earlier reductions in verbal skills and motor speed were no longer observed.

No apparent abnormalities were revealed by DTI at the baseline scan. The direction of time-related changes in mean FA (a decrease at T_6 followed by an increase at T_{27}) was similar to changes in NAA/Cho. These findings are in agreement with the results of Kitahara et al. (2005) who showed that the most prominent changes in FA (and NAA/Cr ratios) were detected 3–5 months after radiation; whereas these investigators found no differences between patients and controls 10–12 months after completion of radiation. Importantly, our findings do not rule out the possibility of additional late effects occurring past the 27-month follow-up period used in the current investigation (see Khong et al., 2003; Mabbott et al., 2006; Nagesh et al., 2008; Qiu et al., 2007).

Previous studies have shown that radiation therapy induces predominantly white matter loss while gray matter volume is unaffected (Dellani et al., 2008; Mulhern et al., 1999, 2001; Reddick et al., 1998, 2000). In the patient evaluated in our study, a progressive white matter volume loss was observed with volumetric MRI. White matter volume loss was accompanied by impairment of axonal integrity as detected with DTI and MRSI only at the 6-month follow-up visit. In the patient, there was also lack of increase in the total volume of gray matter, which was noted in the control subject. Interestingly, in childhood leukemia survivors, combined radiation and chemotherapy was associated with lower gray matter density in the caudate (Porto et al., 2008) and low FA in the hippocampus (Dellani et al., 2008). Given the importance of these structures to cognition and specific neuropsychological functions, a focus of future investigations may be to examine the relationship between white and gray matter disruption in specific brain regions with respect to cognitive/neuropsychological outcomes.

Of the four assessment methods used, the late effects (observed behaviorally in the patient) were least corroborated by DTI. Although the increase in mean FA at the 27-month follow-up was interpreted as a change towards normal values, it has to be noted that an increase in FA may also be associated with pathological conditions, for example, in Williams syndrome (Hoeft et al., 2007). Considering the patient's decreased white matter volume, decreased branching of white matter tracts, a reduced number of crossing association or commissural fibers, which may result in increased directionality of water diffusion within the white matter, could also explain increase in FA in the patient and the last visit.

Limitations and future directions

The current study has several important limitations that need to be emphasized. First, as with any case study, our evaluation and subsequent analysis is mainly qualitative and descriptive and merely provides an initial step upon which to base future (larger scale) investigations. It will be important to conduct a larger scale study with individuals with different types and locations of tumors to determine if the obtained results are indicative of a general trend in terms of the initial and late effects of RT or if other factors such as age and/or tumor characteristics better explain the current pattern of findings. A shortcoming of the case study design as it relates to neuroimaging investigations is the potential for measurement error and

artifact. Imaging results for both participants were within normal limits and fairly consistent between assessments, thereby reducing the likelihood of systematic errors; however, the possibility of random perturbations occurring and partly explaining some of the noted variations cannot be entirely discounted.

Although the patient and control participant were carefully matched on variables such as age, SES, and sex the obtained results cannot be generalized to the population of brain tumor survivors treated with radiation. Given the age of the two individuals participating in this case study (i.e., early adolescence) and the dynamic nature of this age in terms of brain development, it would not be at all surprising if individuals treated with radiation at older or younger ages would have a different pattern of findings. For example, younger children exposed to RT are at a greater risk for impairment in intellectual abilities relative to older children who undergo RT (Mulhern et al., 1998; Palmer et al., 2001). More specifically, younger children are at an increased risk for reading difficulties (Mulhern et al., 2005), attention problems (Butler & Haser, 2006; Mulhern et al., 1998), and behavioral difficulties especially internalizing behavior problems (e.g., anxiety and depression; Poggi et al., 2005b). Therefore, it is conceivable we may have observed more notable deficits if our patient was younger at the time that treatment was initiated. Moreover, children exposed to RT have a greater probability of exhibiting cognitive dysfunction the more time that elapses after RT (Butler & Haser, 2006; Duffner, 2004; Poggi et al., 2005b); thus, assessments conducted beyond the 27-month follow-up period may reveal further declines in neuropsychological functioning. The current neuropsychological protocol did not assess a broad range of executive functions and social skills. Thus, it is possible that more extensive neuropsychological and behavioral/emotional testing, including use of caregiver rating scales (Mahone et al., 2009), may have revealed subtle, later onset, deficits in cognitive control, planning, organization, or working memory.

CONCLUSIONS

In summary, the current longitudinal, case study of the early and late effects of treatment for brain tumor in an adolescent suggest that multiple imaging and behavioral methods may be required to detect the trajectory and range of neurological and cognitive dysfunction, as each may uncover different elements of dysfunction. The results of this case study are promising as they show differences that are already apparent between two age- and sex-matched individuals, indicating the potential for additional findings when group analyses are conducted. Future research investigating late effects of treatment in pediatric brain tumor in larger groups, using multiple imaging and assessment methods can serve to expand on these initial findings. Nevertheless, the current investigation has demonstrated some interesting avenues for future investigations. For example, more thorough investigations of other neuropsychological domains such as executive abilities, emotional functioning, prospective memory, and social cognition is important to provide additional information on long-term outcomes (e.g., social/adaptive and academic functioning). In addition, utilization of functional MRI techniques would help to understand if the structural changes observed in the current study alter the interaction between brain circuits involved in cognitive tasks. Finally, given the various changes in brain maturation occurring during adolescence, longer-term follow-up is critical to assess the impact of RT on this dynamic process. These types of studies will not only help to shape a less pernicious RT protocol, but can contribute to our understanding of the process of typical and atypical cognitive development by further elucidating how the developing brain deals with insults that pose a substantial risk to remaining on a normal trajectory.

Original manuscript received 18 December 2008
Revised manuscript accepted 25 June 2009

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