12-18-2013

Hippocampal Volume and its Association with Verbal Memory in Adult Survivors of Pediatric Brain Tumor

Reema Jayakar
Georgia State University

HIPPOCAMPAL VOLUME AND ITS ASSOCIATION WITH VERBAL MEMORY IN ADULT SURVIVORS OF PEDIATRIC BRAIN TUMOR

by

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Under the Direction of Dr. Tricia Z. King

ABSTRACT

Verbal memory (VM) has been shown to be impacted in brain tumor (BT) survivors, but the nature of VM problems and underlying neuropathology are poorly understood and a long-term outlook is lacking. Our study examined hippocampus volume (HV) and VM in adult survivors of pediatric BT (n=32) and controls (n=48). Results indicate that disruption to a maturing brain in childhood is detectable 17 years (mean) after diagnosis, as HV is significantly lower in survivors compared to controls. Analysis of the VM scores shows that survivors have significantly lower overall immediate recall compared to controls, but learning slope, retention, and recognition are not different across the groups. Survivors' memory profile indicates that auditory attention and retrieval difficulties could be contributing to their lower immediate recall. For survivors, HV is significantly correlated with delayed free recall but not with other VM indices. Implications of these findings are discussed.

INDEX WORDS: Hippocampus, Verbal memory, Pediatric brain tumor, Survivorship, Long-term outcomes, Neuroimaging

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

in the College of Arts and Sciences

Georgia State University

2013

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REEMA JAYAKAR

Committee Chair: Tricia Z. King

Committee: Robin Morris

Christopher Henrich

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

December 2013

ACKNOWLEDGMENTS

I would like to express my gratitude to the individuals who have provided me with assistance, advice, and supervision on all aspects of my Master's thesis: Dr. Tricia Z. King (Committee Chair); Dr. Christopher Henrich and Dr. Robin Morris (Committee Members). First and foremost, I would like to thank my advisor Dr. Tricia King – for her careful guidance throughout the entire project, specifically, helping me think about theories and concepts in a different way; challenging me to do better work; for supporting me in all aspects of my M.A. degree training. For helpful consultations on methodological and statistical concepts, a thank you to Dr. Christopher Henrich. I am also grateful for the assistance of Dr. Robin Morris, who shared his neuropsychological expertise with me.

I am deeply grateful to all individuals who participated in this study and generously contributed their time and effort to research. For their support, a special thanks to Kristen Smith and Ryan Brewster. My gratitude also goes out to all current and former members of the King Developmental Neuropsychology Laboratory, who helped with data acquisition and management. Many other important individuals have provided guidance throughout my thesis research, including staff at the GSU-GA Tech Joint Center for Advanced Brain Imaging (CABI).

Lastly, I would like to express my heartfelt gratitude to my family and friends for their unwavering support and enthusiastic presence throughout my education.

This work was supported in part by a Research Scholar Grant, American Cancer Society (#RSGPB-CPPB-114044) awarded to Dr. Tricia Z. King and a GSU Brains & Behavior Fellowship awarded to Reema Jayakar.

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1. INTRODUCTION

Quality of survival has become a justifiable concern for adult survivors of childhood brain tumor because of the high survival rate that has been achieved (Ris, 2007). The survival rate for childhood brain tumors is estimated to be 70% at 5 years post diagnosis and 4 new cases are diagnosed per 100,000 every year (Bleyer, 1999; Legler, Ries, Smith, Warren, Heineman, Kaplan, & Linet, 1999). While treatment related advances have led to promising survival rates, neurocognitive dysfunction has been shown to be one of the sequelae of childhood central nervous system (CNS) cancer. Deficits in a wide range of neuropsychological domains have been reported for survivors of childhood brain tumors (Maddrey, Bergeron, Lombardo, McDonald, Mulne, Barenberg, & Bowers, 2005; Reimers, Ehrenfels, Mortensen et al., 2003). In the past, neurobehavioral late effects in brain tumor patients were assumed to be less prevalent than what the evidence currently shows (Ris, 2007).

1.1 Cognitive Outcomes

IQ tests have been the most common method used to report the neurocognitive effects of brain tumors and their treatment, as IQ tests are well normed and standardized on a large sample from the general population (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). IQ declines of up to 25-30 points have been observed in pediatric brain tumor survivors (Reimers, Ehrenfels, Mortensen et al., 2003; Ris, 2007). This finding has been quite consistent in longitudinal studies, especially those in which patients were treated with radiotherapy. These declines, however, reflect scaled scores. Examination of raw scores reveals significant increase over time, which suggests that pediatric survivors are continuing to acquire new information

and skills over time, but at a slower rate compared to a neurotypical population (Palmer, Goloubeva, Reddick et al., 2001).

It has been suggested that these declines in IQ scaled scores could be due to deficits in underlying memory abilities as learning efficiently and retaining information are critical for acquiring new information (Mulhern & Palmer, 2003; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). Some researchers have shown that pediatric brain tumor survivors have decreased verbal memory (Dennis, Spiegler, Hoffman, Hendrick, Humphreys, & Becker, 1991; Ellenberg, Liu, Gioia et al. 2009; Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001). Researchers have also shown that memory impairment could be contributing to learning disabilities during schooling (Gimenez, Junque, Naberhaus et al., 2004). As underlying memory abilities could be responsible for rate of information acquisition in survivors, we need to further our understanding of verbal memory in adult survivors of pediatric brain tumor.

Verbal memory is defined as the ability to learn, retain, and recall verbal items or words. One study involving survivors of adult brain tumors (Age at testing, *M* = 36 years) reported that free recall of a word list is negatively affected in adults with low grade supratentorial tumors treated with radiotherapy (Armstrong, Stern, & Corn, 2001). Another study showed list learning and delayed list recall impairment in child survivors of third ventricle tumors, some of whom were treated with and some of whom were not treated with radiotherapy (King, Fennell, Williams, Algina, Boggs, Crosson, & Leonard, 2004). The authors, however, acknowledged that it was unclear whether these impairments were due to poor encoding or poor retrieval. Another study involving children with third ventricle tumors (including radiotherapy and non-radiotherapy patients) reported a retrieval deficit (Micklewright, King, Morris, & Morris, 2007).

Specifically, these children were unable to encode new words at the same rate as healthy peers and also showed impaired performance on delayed recall. They showed adequate performance on delayed recognition and attentional abilities. The same study revealed that children with cerebellar tumors, in contrast to third ventricle tumors, had significant auditory attentional impairments. Rate of encoding new words for the cerebellar tumor group was similar to healthy peers and adequate retrieval was noted. Thus, findings on the nature of verbal memory problems that may be faced by brain tumor survivors are mixed and complicated by developmental stage and tumor location. Therefore, one of the goals of the current study was to clarify the nature of verbal memory deficits in adult survivors of pediatric brain tumor.

As most research on survivors takes place in the first 5 years following treatment, a long-term outlook on memory is lacking. Many previous studies have demonstrated that there is a high risk for neurocognitive impairment in survivors of CNS malignancy during childhood. Very few studies, however, have examined long-term cognitive sequelae. In two studies of pediatric brain tumor survivors, one with a heterogeneous sample of tumors and another with only posterior fossa tumors, cognitive dysfunction and significant memory problems were reported on average 8-10 years after diagnosis (Lannering, Marky, Lundberg & Olsson, 1990; Steinlin, Imfeld, Zulauf, et al., 2003). The dysfunction was present in those treated with and without radiotherapy. A review paper on neurobehavioral outcome in pediatric brain tumor patients discussed several studies which showed an IQ<80 on average 10 years after diagnosis (Ris & Noll, 2004). There were, however, several limitations to the research included in this review. Firstly, most of the studies did not objectively test memory and used self-report measures. Secondly, the studies discussed were short-term (i.e. survivors were on average 4

years or less post-diagnosis) and thus were not able to fully explore long-term sequelae. Only one study included in the review showed that neurocognitive impairment extends into adulthood (for radiotherapy and non-radiotherapy pediatric survivors). This finding, however, was based solely on self-report measures (Ellenberg, Liu, Gioia et al., 2009). Thus, long-term memory sequelae in pediatric brain tumor survivors remain largely unexamined in the literature.

When brain tumors occur during childhood the brain maturation is incomplete. Therefore, short-term outcomes may not be good indicators of cognitive function during adulthood. Moreover, studies examining longer term survivors only investigate IQ or self-reported cognitive outcomes. Thus, it is unclear how memory develops as survivors of childhood brain tumors mature into adulthood. Therefore, studies examining memory outcomes in the time period after the first 5 years of diagnosis are needed, with a special emphasis on a developmental perspective. A developmental perspective acknowledges that the brain and memory systems are still maturing during childhood, at the time when the tumor is diagnosed and treated. As such, the diagnosis and treatment of the tumor may be impacting the systems that are already in place, as well as the systems that are yet to develop. Therefore, in our study we set out to investigate whether pediatric brain tumor survivors experience memory impairments as adults using standardized testing methods. This allowed us to address the extent and type of deficits that persist in the long-term.

1.2 Memory and Hippocampus

Declarative memory is highly dependent on the integrity of the hippocampus and other anatomically related structures (Squire, 1992; Nagel, Palmer, Reddick et al., 2004). Verbal memory is a type of declarative memory. A few studies of brain tumor survivors have reported memory problems. Thus, it is possible that hippocampal pathology underlies some of the memory impairment. Furthermore, recent neuroimaging studies have reported structural changes in hippocampal regions, as well as reduced white matter integrity, in childhood brain tumor survivors (Dennis, Spiegler, Fitz, & Hoffman, 1991; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Nagel, Palmer, Reddick et al., 2004; Van Petten, Plante, Davidson, Kuo, Bajuscak, & Glisky, 2004). Even so, the neuropathology underlying cognitive deficits in adult survivors of childhood brain tumor is poorly understood. It is unclear whether structural hippocampus and white matter changes persist into adulthood, or if they resolve over the course of brain development. Thus, extant research begs the question of whether decreased verbal memory in survivors is the result of a damaged hippocampus.

Hippocampal-dependent behavioural tasks are negatively impacted by apoptosis and decreased neurogenesis in this region (Nagel et al., 2004). It is well known that the hippocampus is primarily responsible for encoding declarative memories (which includes verbal memory). Hippocampal pathology in early Alzheimer's disease has been associated with an encoding deficit profile: deficits in both free recall and recognition memory, indicating impairment at the level of encoding (Carlesimo & Oscar-Berman, 1992; Fernandez, Weyerts, Schrader-Bolsche et al., 1998). In contrast, when memory declines are observed in the context of non-hippocampal related pathology (e.g. white matter disease), recognition abilities remain

relatively intact but retrieval abilities are damaged (Libon, Bogdanoff, Cloud, Skalina, Giovannetti, Gitlin, & Bonavita, 1998; Tierney, Black, Szalai, Snow, Fisher, Nadon, & Chui, 2001). This is known as a retrieval deficit profile and is typically seen in older adults in the presence of subcortical white matter hyperintensities (Van Petten, Plante, Davidson, Kuo, Bajuscack, & Glisky, 2004).

It follows then that hippocampal abnormalities in adults would lead to a memory profile primarily consisting of encoding deficits. In other words, lower hippocampal volume would be predictive of impairments on initial learning, recall, and recognition. One study of 30 patients with Alzheimer's disease and ischemic vascular dementia has shown that the size of the hippocampus is significantly correlated with the California Verbal Learning Test - II (CVLT-II) recognition discriminability index (Libon, Bogdanoff, Cloud, et al., 1998). This study reported that higher scores on the CVLT-II recognition discriminability index were associated with a larger size of the hippocampal body. Another study involving adolescents with a history of premature birth has reported positive correlations between hippocampal gray matter and verbal learning and memory (Gimenez, Junque, Narberhaus, et al., 2004). Stereological analysis revealed that lower volume of the left posterior hippocampus was associated with a lower level of learning. All of these findings indicate that the hippocampus is one of the key structures involved in verbal memory, specifically encoding.

Most of these findings linking the hippocampus to verbal memory, however, emerged from research where the hippocampus faced insults during adulthood. The relationship between memory functioning and hippocampal volume is controversial among developing children (Nagel, Palmer, Reddick et al., 2004). As such, examining the association between

hippocampal volume and memory functioning in pediatric brain tumor survivors during adulthood (when hippocampal development is complete) should make it possible to understand long-term outcomes in the face of early hippocampal insult. Currently, there is scant research within the population of adult pediatric brain tumor survivors on the hippocampus and its role in verbal memory. It is unclear what deficit patterns emerge in adulthood due to disruption of a developing memory system.

In a population of adult brain tumor survivors, for whom insults to the brain and possibly the hippocampus occurred during childhood, one would predict an encoding deficit profile. However, there is no current research that tests this prediction. The aforementioned research findings, from short-term studies with children and those from adult brain tumors, cannot be mapped on to adult survivors of pediatric brain tumors because damage to a maturing memory system could lead to different long-term outcomes than damage to an already mature system. Therefore, it is important to evaluate whether the prediction of an encoding deficit profile in adult survivors of childhood brain tumor holds true.

1.3 Hippocampal Development

Structural development of the cortex rather than sub-cortical regions is the focus of most imaging investigations of the developing brain (Giedd et all, 1999; Gogtay et al., 2004). Temporal cortex white matter integrity has been shown to increase across age groups in a study of healthy older children and adolescents (Mabbot, Rovet, Noseworthy, Lou Smith, & Rockel, 2009). Likewise, the hippocampus and other medial temporal lobe gray matter structures have been shown to increase in volume during childhood and adolescence. One

study has shown that the volume of the hippocampal formation increases sharply in typically developing children until they reach the age of 2, after which point the volume increase becomes much slower (Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). Normal hippocampal development, however, continues into early adulthood (Benes, Turtle, Khan, & Farol, 1994). Thus, some of the aforementioned memory impairments in childhood brain tumor survivors could be the consequence of a hippocampus that is not maturing as expected, due to injury during early developmental stages. Therefore, in our study we set out to extend previous neuroimaging investigations by specifically examining the long-term developmental outcomes of hippocampal structure and function.

With regard to structure, function, and the potential for plasticity, the hippocampus is unique (Williamson & Bilbo, 2013). However, the same reasons that make the hippocampus unique also make it particularly vulnerable to insult. Studies have shown that the hippocampus is rendered more vulnerable to damage due to brain-derived neurotropic factor (BDNF) plasticity in the hippocampal formation (Murray & Holmes, 2011). Neuron survival and apoptosis is modulated by BDNF-associated signalling, implicating it in developmental processes. Another underlying mechanism for the coexistence of plasticity and vulnerability within the hippocampus are immune signalling molecules such as chemokines (Williamson & Bilbo, 2013). Consistent with these findings, injuries and CNS disorders such as ischemia and Alzheimer's disease have been shown to have a remarkable negative impact on the hippocampus (Franklin et al., 2003; Araujo & Lapchak, 1994). Given these unique vulnerabilities of the hippocampus, it is important to examine how it is impacted in adult survivors of childhood brain tumor.

Atypical hippocampal development, as measured by neuroimaging, has been evidenced in at least one brain tumor research study. In a longitudinal study of 25 children newly diagnosed with medulloblastoma, the researchers examined hippocampal development for up to 5 years after diagnosis (Nagel, Palmer, Reddick et al., 2004). The children were on average 8.27 years old at the time of diagnosis and the time between diagnosis and initial examination was 0.31 years (mean). The study showed, over the course of 6 magnetic resonance imaging scans, that hippocampal volume declined in these children until 2 years post-diagnosis, after which the normal positive growth pattern resumed. These findings, however, should be interpreted with caution due to a number of limitations. Firstly, as study tracked development for 5 years it cannot address the question of whether initial declines in hippocampal volume were ultimately compensated for by return to normal growth in later life. Secondly, the study did not have a control group to compare how the hippocampal volume changed over a 2-year time span in healthy children of the same age. Furthermore, the study did not include any brain tumor patients who had not received radiation therapy. This makes it difficult to conclude whether atypical hippocampal development is associated with brain tumor and surgical factors or treatment factors.

In a study reporting atypical hippocampal development in pediatric brain tumor (Nagel, Palmer, Reddick et al., 2004), volume loss occurred predominantly in the posterior regions of the hippocampus. Examination of radiation dosimetry mapping for a sample case showed that posterior hippocampal regions were closer to higher-dose radiation fields. This finding is important in the context of verbal memory impairment because a study using functional magnetic resonance imaging has shown that the posterior part of the hippocampus is engaged

in verbal encoding (Fernandez, Weyerts, Schrader-Botsche et al., 1998). In this study, thirteen healthy volunteers performed a word list learning paradigm. For eleven of these volunteers, there was a significant correlation between voxel clusters in the posterior part of the hippocampus (images acquired during encoding) and subsequently recalled words. Together these studies indicate that a linkage between hippocampus volume (especially in the posterior part of the hippocampus) and encoding of verbal material potentially exists.

1.4 Current Study

In the current study, hippocampal volume was measured and verbal memory processes were tested in a large sample (*n*=38) of long-term survivors. The sample of survivors, who are now adults, were diagnosed and treated for brain tumors when they were children. We used FMRIB's Integrated Registration and Segmentation Tool (FIRST) (Patenaude, Smith, Kennedy, & Jenkinson, 2011) and the California Verbal Learning Test – Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). FIRST has been successfully used to obtain total hippocampal volume by other published empirical studies. In addition, the CVLT-II is a well validated measure widely used in clinical and research based neuropsychological assessments (Delis, Kramer, Kaplan, & Ober, 2000; Hubley, 2004). The CVLT-II is a short, word-list based, individually administered assessment tool that allows for the measurement of multiple components of memory: learning, retention, retrieval and recognition. The CVLT-II has been shown to predict residual brain damage in various psychiatric and neurological populations (Alexander, Stuss, & Fansabedian, 2003; Delis, Kramer, Kaplan, & Ober, 2000). Thus, it would serve our study well. The current study is the first analysis of hippocampus volume and verbal memory processes in a

unique sample of brain tumor survivors, who are many years past their diagnosis and treatment. This unique data set allowed us to interpret results from a developmental perspective.

We chose to combine the group of survivors who had received radiation therapy with the group of survivors who had not for three reasons: (1) it is possible to have memory deficits even in the absence of radiation therapy, as shown by some of the literature (see Ellenberg, Liu, Gioia, et al., 2009; King, Fennell, Williams, et al., 2004; Lannering, Marky, Lundberg, & Olsson, 1990; Micklewright, King, Morris, & Morris, 2007; Steinlin, Imfeld, Zulauf, et al., 2003); (2) it is important to examine non-radiotherapy survivors as hippocampus development could also be affected by the tumor or by brain surgery; (3) the sample size of the sub-sample of survivors who had not received radiation was small (*n*=13).

1.5 Radiation

There is evidence for radiation leading to pathological processes in the hippocampus from animal models. This further necessitates the study of this structure in brain tumor survivors. A review paper on radiation-induced brain injury notes several hippocampal changes, including neuro-inflammation and ablation of neurogenesis, in pediatric and young adult rodent brains that have been irradiated (Greene-Schloesser, Robbins, Peiffer, Shaw, Wheeler, & Chan, 2012). In studies of molecular pathways, alterations in neuronal function of the hippocampus have also been noted after radiation (Greene-Schloesser, Moore, & Robbins, 2013). One mechanism by which radiation therapy leads to these pathological processes is through alterations in cerebrovasculature (Monje, Mizumatsu, Fike, & Palmer, 2002; Monje & Palmer,

2003). Ischemic injury in hippocampal regions and white matter is also linked to radiation therapy (Tsuruda, Kortman, Bradley, Wheeler, Van Dalsem, & Bradley, 1987; Abayomi, 1996). Moreover, hippocampal volume has been linked to cranial radiation for medulloblastoma survivors in a dose-dependent way (Riggs, Schoenhoff, Liu, Wang, Dockstader, Bouffet, Mabbott, 2013). Riggs et al. found significant group differences when comparing children treated with standard dose radiation to those treated with reduced dose and healthy controls. As 59% of the adult pediatric brain tumor survivors in our study had received radiation therapy, there was a potential for radiation induced pathological processes in the hippocampus of those survivors. The absence of detailed radiation therapy specific information for our sample (i.e., whole brain vs. focal, dosage, posterior fossa boost, dosimetry) precluded precise examination of radiation effects. However, we did explore the role of radiation therapy by examining effect sizes for sample sub-groups.

1.6 Specific Aims and Hypotheses

1.6.1 Aim 1

Structural changes in the hippocampus have been reported in child survivors of brain tumor. Therefore, the first aim of our study was to compare the hippocampal volume of survivors to controls. Also, as the whole brain is subjected to many of the diagnostic and treatment related aspects of having a brain tumor we examined a control structure to help us determine if the hippocampus is structurally special or if there is a global impact to the brain.

Hypothesis 1. Survivors will show lower hippocampal volume compared to healthy controls.

1.6.2 Aim 2

Adult survivors of childhood brain tumor may have received insults to hippocampal regions and white matter development. Thus, it was likely that they would demonstrate verbal memory problems with regard to both encoding and retrieval. The second aim was to evaluate whether survivors differ from healthy controls on various verbal memory indices.

Hypothesis 2a. Survivors' immediate free recall performance compared to healthy controls will be lower. Evaluation of their learning characteristics will reveal lower auditory attention compared to controls but their learning slope will be comparable to controls.

Hypothesis 2b. Survivors will show lower delayed free recall compared to controls. Evaluation of their delayed free recall in the context of other memory performance scores will show problems with initial learning and with retention.

Hypothesis 2c. Delayed recognition memory will be lower compared to controls, due to problems with initial learning.

1.6.3 Aim 3

Another aim was to examine the correlation of hippocampus size and verbal memory indices for survivors. The size of the hippocampus has been reported to be correlated with various verbal memory indices in other patient populations. However, in neurologically intact adults the "bigger is better" account of regional structure-function relationships may be too simplistic (Van Petten et al., 2004). Therefore, we chose to examine the hippocampus – verbal memory association in the survivor group alone. Furthermore, we decided a priori that we

would proceed with Aim 3 only if the findings of Aim 1 were significant. In order to increase model specificity, we also examined the associations between a control region and verbal memory and the hippocampus and a control task.

2. METHODS

2.1 Participants

The sample of participants (*N*=80) consisted of long-term survivors of childhood brain tumors (*n*=32) and healthy controls (*n*=48). All data emerged from an American Cancer Society study (grant # RSGPB-CPPB-114044, PI: Tricia Z. King) of adult survivors of pediatric brain tumor. Survivors were recruited through large mailings: (1) to individuals who participated, as children, in a longitudinal study at the time of diagnosis, (2) through the Brain Tumor Foundation of Georgia, (3) to survivors treated at local hospitals over 10 years ago. Survivors were on average 17.04 years past their diagnosis. Healthy controls in the existing data set were recruited through the undergraduate Psychology participant pool at Georgia State University (GSU), the Joint GSU/GA Tech Center for Advanced Brain Imaging (CABI), friends of survivors, and community fliers.

Participants were considered ineligible and excluded from the current study if they did not indicate fluency in English, met diagnostic criteria for a pervasive developmental disorder, or had experienced any other significant neurological insult (e.g. traumatic brain injury). They were also considered ineligible if they did not pass the hearing screening. For healthy controls, there were additional exclusion criteria based on a Structured Clinical Interview of the DSM-IV

Axis I Disorders (SCID). Participants were excluded for current Major Depressive Disorder, substance use, or psychotic disorder.

All participants signed informed consent forms and the study protocol was approved by Georgia State University (GSU IRB # H03177) and Joint GSU/GA Tech Center for Advanced Brain Imaging (CABI) (IRB # H09157) Institutional Review Boards. All participants responded to a demographic questionnaire and were administered a hearing test, a structured clinical interview, a verbal memory test, and a fine-motor test among other measures. Survivors in the study were also interviewed to gather information about medical variables such as age at diagnosis and presence of radiation. The entire sample of participants also underwent neuroimaging.

2.2 Measures

2.2.1 Hearing screening

The hearing screening administered was a standard tone task using an audiometer. Participants wore earphones and tones with varying levels of frequency and wavelength were played. As the verbal memory task that was administered was auditory in nature it was important to ensure that participants were able to hear within the normal range of sounds. This was especially important for the brain tumor survivors as many individuals in this population endure damage to their hearing as a side-effect of treatments. Participants were excluded if they evidenced difficulties on screening and understanding conversational interactions during testing.

2.2.2 Psychiatric screening

In order to screen for psychiatric disorders, trained psychology graduate students administered the Structured Clinical Interview of DSM-IV Axis I Disorders (SCID) - Research Version. The SCID is a semi-structured interview designed to assess major psychiatric disorders based on DSM-IV criteria. This allowed researchers to diagnose psychiatric disorders that were part of the study's exclusion criteria for the healthy comparison group. Survivors were never excluded, except in the case of pervasive developmental disorders (*n*=1). Of the survivors included, two met criteria for Dysthymia, of which one also met criteria for Generalized Anxiety Disorder. One survivor met criteria for Alcohol Abuse and Dependence in Full Remission.

2.2.3 California Verbal Learning Test – Second Edition (CVLT-II)

The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) assesses various aspects of verbal memory. The CVLT-II has adequate reliability and validity overall, with internal consistency estimates usually in the range of .80 or higher (Delis et al., 2000; Hubley 2004). During the test, the experimenter verbally presents a list of 16 words and asks the participant to immediately recall as many items as they can. This is done for 5 consecutive trials. The CVLT-II generates multiple memory performance indices, a few of which were selected for the current study:

(1) The **Trials 1-5 Total Correct** score is a global measure of immediate free recall performance and consists of the total number of items recalled during the initial learning trials.

(2) The **Trial 1** score is the number of items learned and recalled after the first presentation of the word list and is thought to indicate auditory attention.

(3) The **Trial 5** score is the number of items learned and recalled after repeated presentation of the word list.

(4) The CVLT-II also assesses **Learning Slope**, which reflects the average number of new words acquired and recalled per trial.

(5) Following a delay period of 20 minutes after the initial learning trials, participants are again asked to recall as many items as possible. The **Long Delay Free Recall (LDFR)** score indicates the total number of items recalled after this 20 minute delay. LDFR provides an estimate of the amount of verbal information a person is able to retain and retrieve.

(6) The CVLT-II also assesses delayed recognition memory through correctly identified items (recognition hits) in a forced-choice yes or no test, presented at the end of the test. This forced-choice test consists of all 16 target words from the original list, in addition to other semantically related and unrelated words. Comparing the recognition hits to false positives (intrusions) yields the **Recognition Discriminability** index.

2.2.4 Grooved Pegboard Test

The Grooved Pegboard is a test of fine motor speed and manipulative dexterity. It is a commonly used measure of skilled motor speed in several neuropsychological batteries (Ruff & Parker, 1993). The task requires the participant to insert keyhole-shaped pegs into similarly shaped holes in a pegboard, using one hand at a time. The pegs, which have an edge along one side, must be matched to the holes. Participants are asked to perform this task as quickly as possible without making mistakes. The score obtained is the time required to complete the task

with the dominant hand. The norms used for the scores in studies were from Ruff & Parker (1993).

2.2.5 Neuroimaging parameters

A Siemens Trio 3T scanner with a standard head coil for radiofrequency transmission was used to collect all images. Participants were outfitted with protective earplugs to reduce scanner noise. We acquired high-resolution (1.0 mm x 1.0 mm x 1.0 mm) T1-weighted structural images of the brain by collecting 176 contiguous (i.e. no gap and sharing a common border) sagittal slices. A 3D magnetization prepared rapid gradient echo imaging (3D MPRAGE) sequence was used with the following parameters: acquisition matrix = 256 x 256, repetition time (TR) = 2250ms, echo time (TE) = 3.98ms, field of view (FOV) = 256 mm, slice thickness = 1.0 mm, flip angle = 9o.

2.2.6 Hippocampal volume

Segmentation and volumetric analysis of the hippocampus was performed with FMRIB's Integrated Registration and Segmentation Tool (FIRST) (Patenaude, Smith, Kennedy, & Jenkinson, 2011). FIRST is a model-based registration and segmentation tool in FSL 4.0 (Smith, Jenkinson, Woolrich, et al., 2004). The shape and appearance models used in FIRST are constructed from manually segmented images provided by the Center for Morphometric Analysis (CMA), MGH, Boston. During registration, the input 3D T1 image data were transformed to the MNI 152 standard space by means of affine transformations based on 12 degrees of freedom. After registration, a sub-cortical mask was applied to locate the hippocampus, followed by segmentation based on shape models and voxel intensities. The

hippocampus included the dentate gyrus, the ammonic subfields (CA1–4), the prosubiculum, and the subiculum and did not include the fimbria / fornix behind the posterior commissure. Hippocampal segmentations were visually checked for errors, and no errors were noted. The volume of each participant's left and right hippocampus was measured in mm3, and the sum of these two values yielded Total Hippocampal Volume values to be used in all subsequent analyses. See Figures 2.1 & 2.2 for a sample FIRST segmentation of the left and right hippocampus.

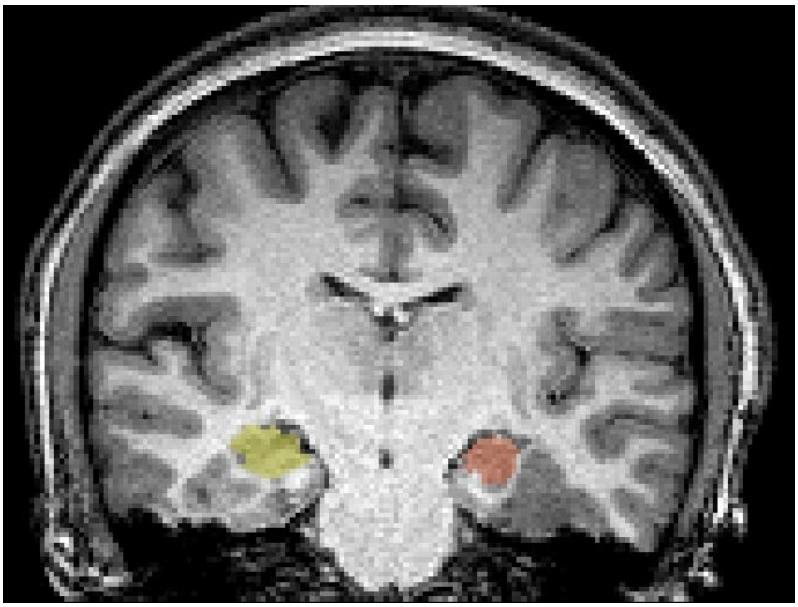

Figure 2.1 Sample FIRST segmentation of the hippocampus

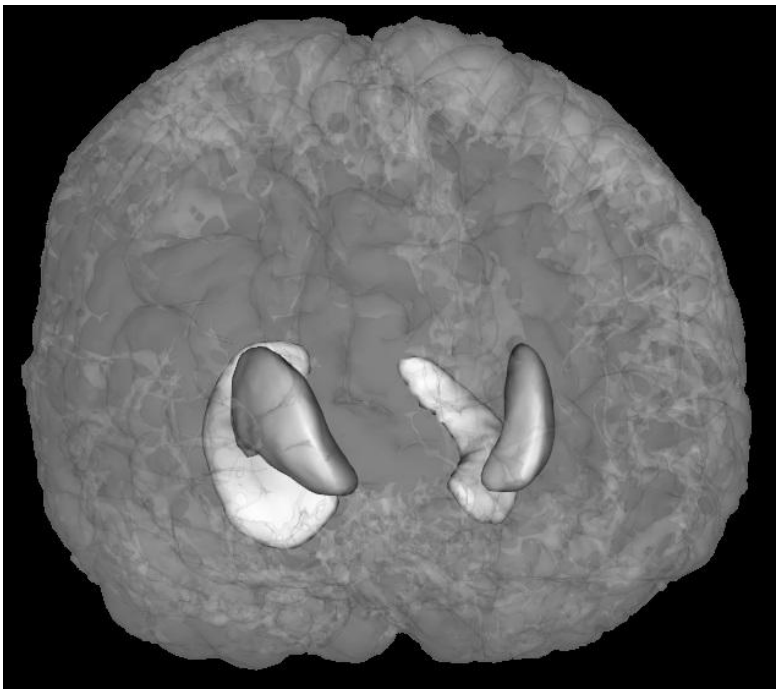

Figure 2.2 3D view of sample FIRST segmentation of the hippocampus and putamen

2.2.7 Putamen volume

We acquired putamen volumes using the same methods and software as that used to obtain hippocampal volume. The putamen is traditionally not thought to have the same metabolic needs as the hippocampus and also not thought to be involved in explicit (i.e. declarative) verbal memory. While it would be ideal to use total brain volume as a control measure, obtaining total brain volumes for survivors is problematic. Many of the brain images of survivors have artefacts at the site of the surgery and/or in the region of shunts, making it problematic to obtain tissue volumes for those regions. Given that the putamen, like the hippocampus, is a subcortical structure we were able to obtain tissue volumes for the entire sample of survivors. See Figures 2.2 & 2.3 for a sample FIRST segmentation of the left and right putamen.

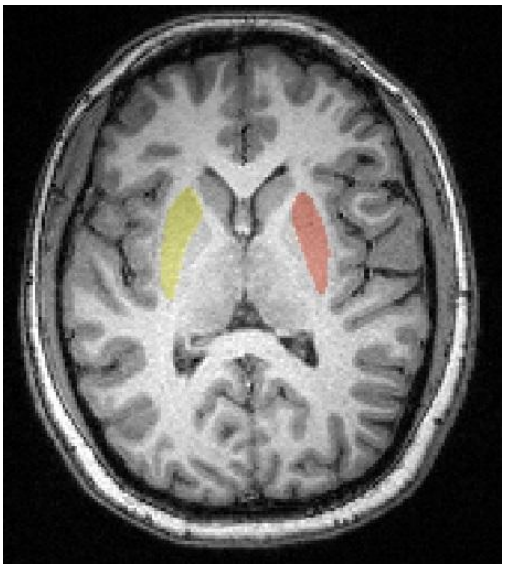

Figure 2.3 Sample FIRST segmentation of the putamen

2.3 Procedure

All participants were tested individually in the Psychology Clinic at GSU or GSU/GA Tech Joint Center for Advanced Brain Imaging. Testing took place over two visits; the first one lasting approximately 5 hours and the second one lasting approximately 2 hours. At the first visit, trained psychology graduate students, under the supervision of a licensed clinician administered a medical and developmental history interview, the SCID, self-report paper-and-pencil questionnaires, and the CVLT-II as part of a larger battery of cognitive tests. The larger battery was designed such that the participant's memory during the 20-minute time delay between the Learning and LDFR trials would not be taxed. Also, the CVLT-II was administered during the first 30 minutes of the larger battery so fatigue effects were not of concern. The examiner also checked hearing and mental status of the participant. Course credit was given to the undergraduate control participants as per GSU guidelines. The researchers compensated adult brain tumor survivors and community controls with $50. At the second visit, brain imaging

took place in an MRI scanner at the GSU/GATech Joint Center for Advanced Brain Imaging, Atlanta. A trained MRI technician operated the MRI scanner. All participants received $50 compensation for their time and travel at the completion of the second visit.

2.4 Design

All analyses were conducted using SPSS 17. *p*-values less than .05 were considered statistically significant.

2.4.1 Test of Data Assumptions

Proposed data analyses for each of the aims involved a number of steps. As part of preliminary analyses, each of the CVLT indices to be used in the current study, measurements of hippocampal volume, and of putamen volume were examined for extreme values, assumptions of normality, homogeneity of variance, heteroskedasticity, non-independence of residuals, normality of residuals, and absence of specification error where appropriate.

2.4.2 Potential Confounds

A confound was defined as a variable that was both significantly different between groups and correlated with outcome. As two of the aims of our study are based on comparing groups, demonstrating group equivalence on relevant demographic variables and identifying confounding variables was important. Demographic variables that could act as potential confounds, such as gender, age at testing, level of education, and ethnicity, were compared across the two groups (survivors vs. controls). Independent samples t-tests were used for continuous variables (i.e. age and education). Chi-square tests of independence were used for

categorical variables (i.e. gender and ethnicity). We also obtained Pearson bivariate correlations for the demographic variables and outcomes of interest. If a variable emerged as significantly different between groups and had a significant correlation with the dependent variable being examined then it was considered a potential confounding variable.

2.4.3 Potential Covariates

Omission of potential covariates that should theoretically be included in a model leads to potential bias in the statistical estimates of population parameters (Cohen, Cohen, West, & Aiken, 2003). In order to obtain unbiased estimates of the true values in the population it is a good idea to estimate a model with these variables included. Even though inclusion of covariates in a model reduces degrees of freedom, and thus seemingly power, it actually increases precision of the model if the covariates are well-chosen (Cohen, Cohen, West, & Aiken, 2003). A well-chosen covariate is a variable that is related to the outcome but unrelated to the independent variable and it increases precision by reducing standard error. A reduction in standard error is possible because a good covariate increases the amount of variance in the outcome explained by the independent variable (without increasing the amount of variance explained in each independent variable by all other covariate variables).

Thus, in order to reduce potential bias in our statistical procedures we used a demographic variable as a covariate if that demographic variable was not significantly different between the groups but emerged as significantly correlated with the dependent variable. We determined covariates separately for each aim, contingent upon the dependent variable of interest for the specific analysis of an aim.

2.4.4 Survivor-specific Diagnostic & Treatment Variables

There are many neurobiological treatment variables that are heterogeneous in our sample of survivors, such as tumor location, tumor type, presence of radiation, chemotherapy, presence of hydrocephalus (see Reimers, Ehrenfels, Mortensen et al., 2003; Scott, Fletcher, & Brookshire, 1998) that could potentially impact the outcomes of interest. Our sample was thoroughly described with regard to these neurological variables. As they are known to be associated with poor outcomes, we explored their impact on our outcomes, where possible. The subsequent steps of specific data analyses for each aim were different and are outlined separately.

2.4.5 Aim 1: Is hippocampal volume lower in survivors compared to controls?

In order to evaluate whether survivors differ from healthy controls in terms of hippocampal volume, we used a one-way between-groups analysis of variance. The independent variable was the group (survivors, controls), and the dependent variable consisted of measurements of hippocampal volume obtained during the study. In order to increase model specificity (i.e. are volume reductions unique to the hippocampus compared to other structures), we also examined volumes of the putamen for the two groups.

2.4.6 Aim 2: Comparing survivors and controls on verbal memory indices

In order to evaluate whether survivors differ from demographically matched healthy controls on verbal memory indices, we conducted separate analyses using CVLT-II data. First, we compared survivors and controls on Trials 1-5 Total T score. We decided that if a significant difference was found with this index we would evaluate learning strategies. Evaluating learning

strategies consisted of (a) examining whether the Trial 5 z-score was significantly different between groups after controlling for the Trial 1 z-score and (b) comparing the Learning Slope z-score. Second, we evaluated whether the LDFR z-score was affected. We decided that if survivors had a significantly lower score than controls on this index then we would examine whether it is initial learning or retention that is impacting this score. In order to do so, we compared survivors and controls on (a) the LDFR z-score after controlling for the Trial 5 z-score and (b) the change in number of words from Trial 5 to LDFR. Third, we compared survivors and controls with regard to their Recognition Discriminability Index z scores.

2.4.7 Aim 3: Hippocampus volume correlations with verbal memory indices in survivors

In order to examine if total hippocampal volume is associated with various verbal memory indices, we used correlation analyses. Specifically, one-tailed Pearson bivariate correlations were obtained for hippocampal volume with each of the various verbal memory indices. We examined correlations between volume and verbal memory outcomes in the group of survivors alone, separately from controls. We did this because in neurologically intact adults the "bigger is better" account of regional structure-function relationships may be too simplistic (Van Petten et al., 2004), as size reveals little about relative proportions of neurons and astrocytes, synaptic densities, ratios of excitatory to inhibitory synapses, patterns of synaptic connectivity, and numbers of receptors for various transmitter substances. However, in samples with neuropathology, below-normal volumes have been associated with cognitive deficits and the "bigger is better" account may be useful (Van Petten et al., 2004). Therefore, we had decided a priori that Aim 3 would be contingent upon significant findings in Aim 1.

Specifically, if survivors were not significantly lower than controls with regard to hippocampal volume then we would not conduct the analyses planned for Aim 3.

Furthermore, if the correlation analyses were carried out, we needed to increase confidence that any findings reported were related specifically to the hippocampus. Therefore, we also conducted all of the correlational analyses with a control structure – the putamen. Examination of correlations across the structure of interest (hippocampus) and a control structure (putamen) would help us determine whether global brain changes or local hippocampal related changes are affecting verbal memory outcomes. Similarly, we also included a control task – Grooved Pegboard Test – that involves fine-motor dexterity skills and should theoretically be unrelated to hippocampal volume as part of these correlational analyses.

3. RESULTS

3.1 Extreme Values

As part of the preliminary data analyses, 5 outliers (>3 standard deviations from mean) were identified that were considered extreme: one control on the total hippocampal volume measurements (10,641 mm^3), one control on the CVLT-II recognition scores (z= -3), and two survivors and one control on the Grooved Pegboard Test (z= -6.19, -9.31, -3 respectively). Three of these values were assigned a raw score that was one unit larger or smaller than the next most extreme score in the distribution (see Tabachnick & Fidell, 2001). Two of these values (z= -6.19, -9.31), both from the Grooved Pegboard Test, were excluded from all further analyses.

3.2 Potential Confounds

Demographic characteristics and mean scores on the variables of interest are presented in Table 3.1. Pearson chi-square tests for independence with Yates continuity correction indicated no significant association between gender and group χ^2 (1, n=80) = .002, p = .96 and no significant relation between ethnicity and group χ^2 (2, n=75) = 4.09, p = .13. Thus, gender and ethnicity distributions were equivalent between the two groups. Furthermore, independent samples t-tests revealed that participants in the control and survivor groups were equivalent (p > .05) on level of education but significantly different (p<.001) on age (see Table 3.1). However, when we conducted bivariate correlations age was not significantly correlated with hippocampal volume or any of the CVLT-II indices, except recognition (See Table 3.2). Thus, there were no demographic confounds that needed to be controlled for in subsequent analyses, except analyses involving recognition.

Table 3.1 Comparison of demographic variables

Demographic Variables	Survivors (*n*=32)	Controls (*n*=48)
Female (n, %)	17 (53%)	27 (56%)
Education (mean ± SD)	13.38 ± 1.68	13.88 ± 1.20
Age at testing (mean ± SD)*	25.15 ± 4.52	21.41 ± 3.90
Range	17-36	18-41
Ethnicity (n, %)		
Caucasian	22 (71%)	21 (48%)
African-American	6 (19%)	14 (32%)
Other	3 (10%)	9 (21%)

*Note. *Significantly different between groups at p=.05*

Table 3.2 Pearson bivariate correlations of demographic variables with outcomes of interest

	Gender	Education	Age at Testing	Ethnicity
Hippocampal Volume	-.40*	.32*	-.09	-.04
Putamen Volume	-.26*	.15	-.22	-.02
CVLT-II				
Trials 1-5 Total T Score	-.18	.21	-.21	-.01
List A Trial 1 z-score	-.31*	.04	-.34*	-.05
List A Trial 5 z-score	-.23*	.16	-.16	.002
Learning Slope z-score	-.07	.16	.18	.06
Long Delay Free Recall z	-.03	.22	-.20	-.05
Recognition Discrimin.	.04	.33*	-.24*	.03
Grooved pegboard	-.26*	-.17	-.27*	.03

*Note. * Significant at p=.05*

3.3 Potential Covariates

We also conducted bivariate correlations for the demographic variables with hippocampal volume, CVLT-II indices, putamen volume, and grooved-pegboard scores (see Table 3.2) for the whole sample in order to identify covariates for Aim 1 and Aim 2. The covariates that are described in the subsequent analyses are not confounding variables because they are not significantly different between the survivor and control group.

It was found that gender (r= -.40, p<.001) and level of education (r=.32, p=.004) were significantly correlated with hippocampal volume, with females and those with lower education having lower volumes. Therefore, we used gender and education as covariates in the analysis of the hippocampus in Aim 1. No significant correlation was identified between ethnicity or age and hippocampal volume (p > .05). Also, gender was significantly correlated with putamen volume (r= -.26, p=.02), with females having lower volumes. Therefore, we used gender as a covariate in the analysis of the putamen in Aim 1. No significant correlation was identified between age, education or ethnicity and putamen volume (p>.05).

No significant correlations were identified between gender, ethnicity, level of education, age and all CVLT-II indices (p>.05), except Recognition Discriminability. A significant correlation was identified between level of education and Recognition Discriminability (r=.33, p<.01), as well as age and Recognition Discriminability (r= -.24, p=.03). We did not use both education and age as covariates for Recognition Discriminability because they were also significantly correlated with each other (r=.26, p=.02). Instead, we chose to use participants' education level alone as a covariate. We did this because unlike age it was not a confound, and thus uncorrelated to the independent variable – making it a better covariate statistically. We did not use any demographic covariates in analyses involving other CVLT-II indices.

3.4 Survivor-specific Diagnostic & Treatment Variables

There were many neurobiological (e.g. tumor type) and treatment (e.g. presence of radiation) variables that were heterogeneous in our sample of survivors. Characteristics and mean scores on these variables are presented in Table 3.3. These variables were not included as covariates in any of the analyses due to limited sample size. However, within the survivor group, we explored whether some of these variables were associated with reduced hippocampal volume.

Table 3.3 Survivor-specific Variables

Diagnostic & Treatment Variables	Survivors (*n*=32)
Years post diagnosis (mean ± *SD*)	17.04 ± 1.08
Range	5-28
Median	18.45
Age at diagnosis (mean ± *SD*)	7.84 ± .84
Range	1-19
Median	8.50
Tumor location (*n*, %)	
Posterior fossa	16 (50%)
Pituitary	4 (13%)
Frontal lobe	2 (6%)
Parietal lobe	2 (6%)
Occipital lobe	1 (3%)
Temporal lobe	1 (3%)
3rd ventricle	1 (3%)
Brainstem	1 (3%)
Unknown	4 (13%)
Tumor type (*n*, %)	
Medulloblastoma	11 (34%)
Craniopharyngioma	6 (19%)
Astrocytoma/Glioma	10 (31%)
Other (PNET, Astroteratoma, Meningioma, Mixed germ cell, Choroid plexus papilloma)	5 (16%)
Radiation (*n*, %)	19 (59%)
Chemotherapy (*n*, %)	14 (44%)
Hydrocephalus (*n*, %)	14 (44%)
Seizure disorder (*n*, %)	8 (25%)
Hormone deficiency (*n*, %)	16 (50%)

3.5 Aim 1

A one-way between-groups analysis of covariance was conducted to compare the hippocampal volume of survivors and controls. The independent variable was group (survivors, controls), and the dependent variable was measurements of hippocampal volume. Participants' sex (r= -.40, p<.01) and education level (r=.32, p<.001) were used as covariates in this analysis because they were each significantly correlated with hippocampal volume (see Table 3.2). The use of well-chosen covariates can help reduce error and increase precision when examining group differences.

Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariates. All of these assumptions were acceptable. After adjusting for sex and education level, there was a significant difference (F (1,76)=5.34, p=.02) between the two groups (see Table 3.4 & Figure 3.1) on measured hippocampal volume, with a medium effect size (partial η^2=.07). Also, there was a strong association between sex and hippocampal volume (partial η^2=.26) and education level and hippocampal volume (partial η^2=.17), with males and those with higher education having higher volumes.

We conducted similar analyses using total putamen volumes, in order to test the specificity of our hypothesis with regard to the hippocampus. After adjusting for sex, there was a significant difference (F (1,79)=15.14, p<.001) between the two groups (see Table 3.4 & Figure 3.1) on measured putamen volume, with a large effect size (partial η^2=.16).

Table 3.4 Comparison of outcome variables for the two groups

	Survivors (*n*=32) Mean ± *SD*	Controls (*n*=48) Mean ± *SD*
Total Hippocampal Volume*		
Unadjusted	7411.31±914.38	7888.60±833.88
Adjusted (Mean ± SE)[†]	7464.73±129.43	7852.99±105.35
Total Putamen Volume*		
Unadjusted	9626.53±1341.02	10628.60±1094.57
Adjusted (Mean ± SE)[†]	9613.35±203.80	10637.39±166.39
CVLT-II		
Trials 1-5 Total T score*	46.88±11.70	52.21±11.08
Number Impaired (%)	5 (15%)	3 (6%)
List A Trial 1 z-score	-.80±.74	-.10±1.08
List A Trial 5 z-score	-.59±1.36	-.05±1.12
Learning Slope z-score	.05±.95	-.24±.99
Long Delay Free Recall z-score	-.55±1.25	-.05±1.08
Number Impaired (%)	7 (22%)	6 (13%)
Recognition Discriminability Index z-score		
Unadjusted	-.28±1.05	.08±.97
Adjusted (Mean ± SE)	.04 ± .14	-.22 ± .17
Number Impaired (%)	6 (19%)	6 (13%)

*Note. *Significantly different between groups at p=.05. [†]Adjusted means for hippocampal volume = means adjusted by sex and education as part of the ANCOVA. Adjusted means for putamen volume = means adjusted by sex as part of the ANCOVA.*

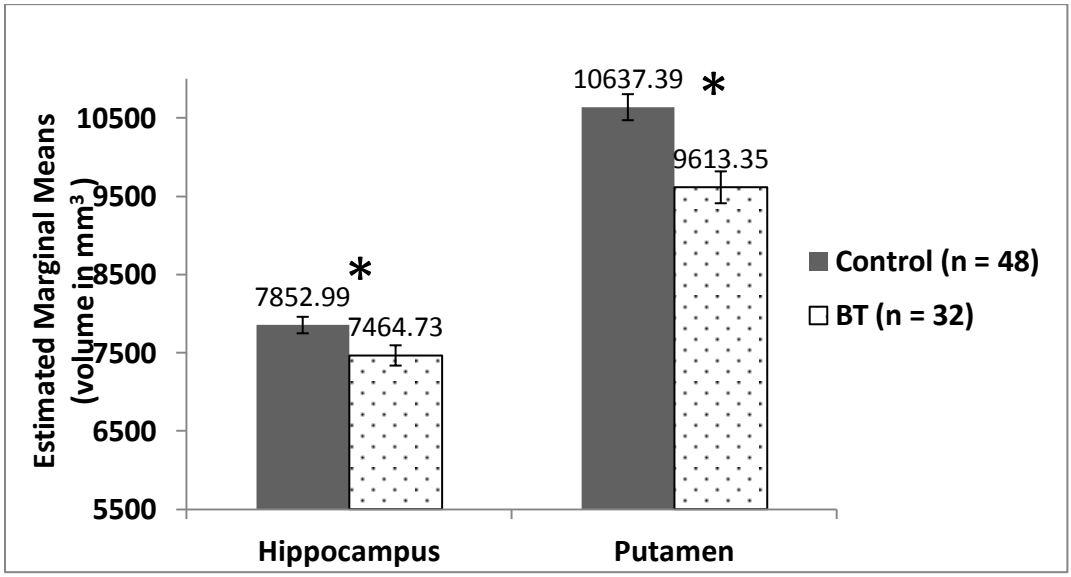

Figure 3.1 Total hippocampal & putamen volumes

Note. *Indicates significant difference at *p*=.05. Error bars represent standard error.

3.6 Aim 2

In order to explore the impact of group (survivors vs. controls) on the chosen verbal memory performance indices, we conducted one-way analysis of variance. All CVLT-II indices used as dependent variables in these analyses, unless otherwise indicated, consisted of standardized scores derived from the CVLT-II normative sample. There was no violation of the assumptions of normality and homogeneity of variances for all scores, except Recognition Discriminability. The assumption of normality was violated for the Recognition Discriminability index scores. The distribution of the sample was negatively skewed. We transformed the variable to attempt to correct for this violation using a square root and a logarithmic transformation. However, the transformations did not help normalize the distribution and did not impact the relations of interest. Therefore, the untransformed variable was used in all subsequent analyses.

3.6.1 2a Immediate free recall performance

A one-way between groups analysis of variance (ANOVA) showed that there was a statistically significant difference (F (1,78)=4.26, p=.04) in Trials 1-5 Total T scores for the two groups (see Table 3.4 & Figure 3.2). On average, survivors scored lower than controls. The actual difference in mean scores between the groups was a medium effect size of .05, calculated using partial η^2. Furthermore, the performance of 5 survivors (15%) and 3 controls (6%) was in the clinically impaired range (i.e. T≤35). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired (χ^2 (1, n=80) =

.98, p = .32). In other words, survivors' scores were statistically lower but not clinically impaired.

A one-way between-groups analysis of covariance (ANCOVA) was conducted to compare the two groups on their Trial 5 z-scores, after controlling for Trial 1 z-scores. The independent variable was group (Survivors, Controls). The dependent variable consisted of z-scores on Trial 5, administered after all consecutive presentations of the word list were complete. There was no statistically significant difference (F (1,77)=.33, p=.57) in Trial 5 z-scores for the two groups, after controlling for Trial 1 z-scores (see Figure 3.3). Similarly, a one-way between groups ANOVA showed that Learning Slope z-scores were not significantly different between the two groups (F (1,78)=1.66, p=.20).

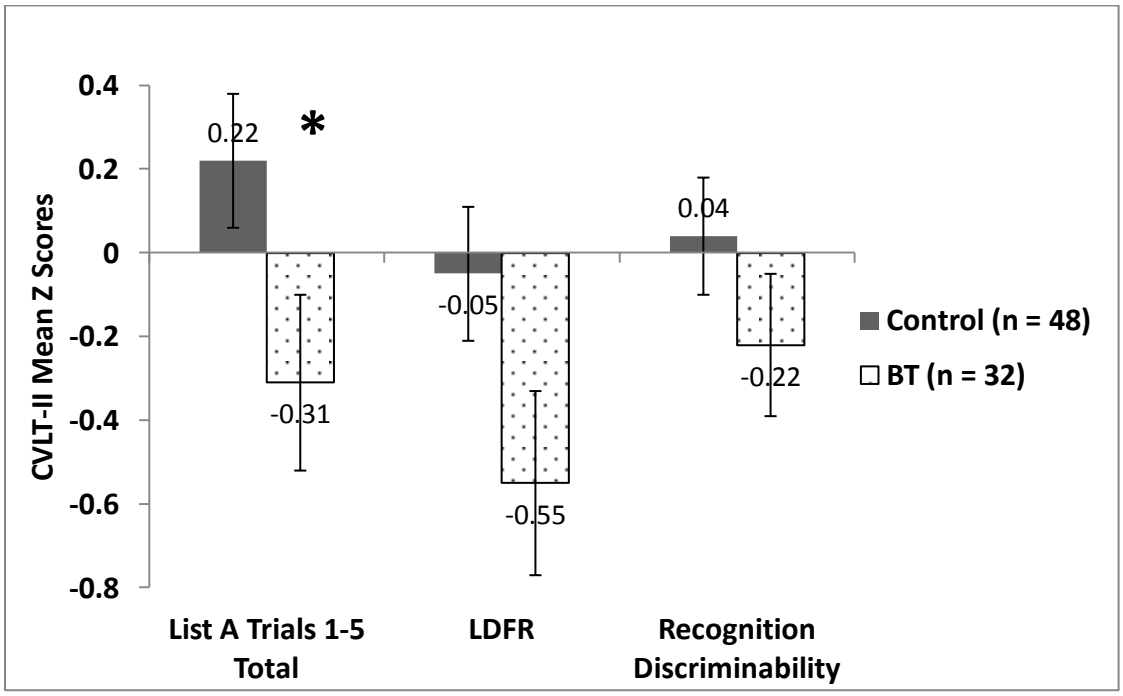

Figure 3.2 Performance on average within normal limits across 3 indices

Note. *Indicates significant difference at p=.05. Error bars represent standard error. Means for recognition discriminability are estimated marginal means. LDFR = Long Delay Free Recall

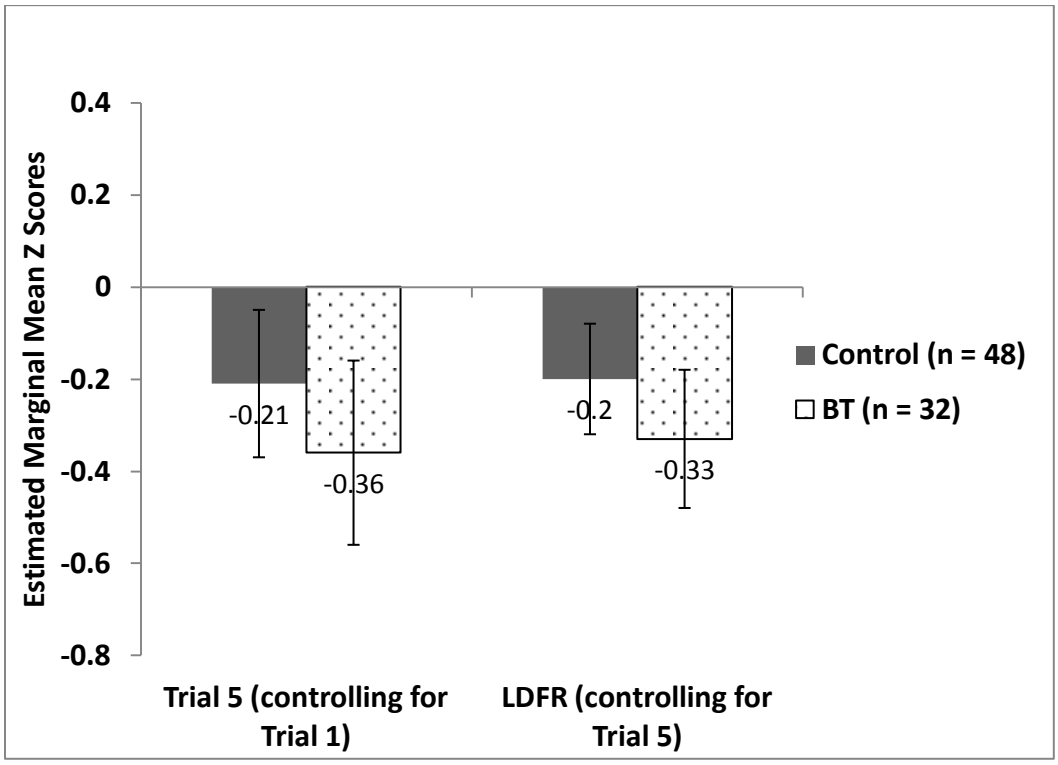

Figure 3.3 ANCOVA results

Note. Error bars represent standard error. Means shown are estimated marginal means. LDFR = Long Delay Free Recall

3.6.2 2b Delayed free recall performance

A one-way between groups ANOVA showed that there was no statistically significant difference (F (1,78)=3.55, p=.06) in LDFR z-scores for the two groups (see Table 3.4 & Figure 3.2). However, on average, survivors did show a trend for scores that were lower than controls. The actual difference in mean scores between the groups was a small-medium effect size of .04, calculated using partial η^2. Furthermore, the performance of 7 survivors (22%) and 6 controls (13%) was in the clinically impaired range (i.e. z≤ -1.5). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired (χ^2 (1, n=80) = .65, p = .42). In other words, survivors' scores showed a trend for being significantly lower but were not clinically impaired.

A one-way between-groups ANCOVA was conducted to compare the two groups on their LDFR z-scores, after controlling for Trial 5 z-scores. The independent variable was group (Survivors, Controls). The dependent variable consisted of z-scores on LDFR, administered after a 20 minute delay. There was no statistically significant difference (F (1,77)=.47, p=.50) in LDFR z-scores for the two groups, after controlling for Trial 5 z-scores (see Figure 3.3).

A mixed between-within subjects ANOVA was conducted to assess the impact of group (Survivors, Controls) on participants' recall performance, across the time delay (Trial 5, LDFR). There was no significant interaction between group and time (F (1,78)=.77, p=.38). In other words, the change in number of words from Trial 5 to LDFR was the same for both groups.

3.6.3 2c Recognition Performance

The assumption of normality was violated for each of the two groups. As mentioned before, transforming the variable did not help. However, ANOVA is robust to this violation if the sample sizes are relatively equal and there are no outliers. Given that our sample meets these criteria, we proceeded with the analysis despite the assumption violation. Participants' education level was used as a covariate in this analysis because it was significantly correlated (r=.33, p<.001) with Recognition Discriminability. Age at exam was also significantly correlated (r= -.24, p=.03) with Recognition Discriminability but was not used as a covariate, because it was also significantly correlated with education (r=.26, p=.02).

After adjusting for education, there was no statistically significant difference (F (1,77)=1.30, p=.25) in Recognition Discriminability z scores for the two groups (see Table 3.4 & Figure 3.2). The actual difference in mean scores between the groups was a small effect size of

.02, calculated using η^2, with survivors scoring lower. Furthermore, the performance of 6 survivors (19%) and 6 controls (13%) was in the clinically impaired range (i.e. z≤ -1.5). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired (χ^2 (1, n=80) = .20, p = .66).

A one-way between-groups ANCOVA was conducted to compare the two groups on their Recognition Discriminability z-scores, after controlling for LDFR z-scores. The independent variable was group (Survivors, Controls). The dependent variable consisted of z-scores on Recognition Discriminability, administered immediately after the LDFR trial was completed. There was no statistically significant difference (F (1,77)=.12, p=.73) in Recognition Discriminability z-scores for the two groups, after controlling for LDFR z-scores.

3.7 Aim 3

The associations between hippocampal volume, putamen volume (control structure), verbal memory indices (as measured by the CVLT-II), and fine motor skill (as measured by Grooved Pegboard), were investigated using Pearson product moment correlation coefficient. We used one-tailed significance values as we did not expect to find negative associations. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. As mentioned before, the assumption of normality was violated for the Recognition Discriminability variable but we were unable to correct for this violation. All other assumptions were acceptable.

We examined correlations between volume and verbal memory outcomes in the group of survivors alone (separately from controls). We did this because in neurologically intact adults

the “bigger is better” account of regional structure-function associations is considered too simplistic by some researchers (see Van Petten et al., 2004). There was a significant positive correlation (*r*=.34, *n*=32, *p*=.03) between hippocampal volume and LDFR of medium effect size. Higher hippocampal volume was associated with higher LDFR. The correlations of hippocampal volume with all other CVLT-II indices were not significant (see Table 3.5). Likewise, for the group of controls there were no significant correlations.

Furthermore, to increase confidence that the aforementioned findings were related specifically to the hippocampus, we conducted correlation analyses with a control structure and control task: putamen and fine motor skill. None of the correlations of putamen volume and CVLT-II verbal memory indices were significant (see Table 3.5). Likewise, for the hippocampus the correlation with fine motor skill was not significant.

Table 3.5 Associations between brain structure volumes and cognitive tasks

	1	2	3	4	5	6
1. Hippocampal Volume	1	.72*	.25	.34*	.22	.25
2. Putamen Volume	--	1	.13	.13	.14	.13
3. Trials 1-5 Total T score	--	--	1	.82*	.64*	-.03
4. Long Delay Free Recall z-score	--	--	--	1	.73*	-.12
5. Recognition z-score	--	--	--	--	1	-.23
6. Grooved Pegboard z-score	--	--	--	--	--	1

Note. *Significant at p=.05 (one-tailed)

4. DISCUSSION

4.1 Interpretation of Findings for Aims 1, 2, and 3

The purpose of this study was to examine hippocampus size and verbal memory performance in adult survivors of pediatric brain tumor, as well as possible associations of verbal memory with hippocampal volume. We confirmed the prediction that survivors who had

been diagnosed with a brain tumor at an average age of 8 years had significantly lower hippocampus volumes than neurotypical controls. Thus, even an average of 17 years after diagnosis disruption to a maturing brain was detectable. One study had observed declines in hippocampal volume until 2 years post-diagnosis (Nagel, Palmer, Reddick, et al., 2004). Together with current findings, this suggests that declines in the early years are not fully compensated for in later life for young adult survivors.

It should be noted that even though hippocampal volume was significantly lower for survivors a similar pattern was also observed for the control structure, the putamen. In fact, the effect size for difference in putamen volume was larger than that of hippocampal volume. There could be several reasons for this finding. One hypothesis is that the hippocampus is not specifically vulnerable despite its purportedly higher metabolic needs and disruption to brain development for survivors is more global in nature. This finding also highlights the importance of using control structures in neuropsychological studies of brain tumor survivors. It indicates that claims about structure-function relations, made by other research studies, need to be interpreted with caution. If structure-function associations are not supported by control region data, damage to the region of interest may not be local and could depict global brain changes.

Although no existing research has tested verbal memory profiles in long-term (>5 years since diagnosis) adult survivors of pediatric brain tumor, short-term childhood and some adult brain tumor literature suggests memory difficulties. With regard to immediate free recall and learning characteristics we predicted lower immediate free recall compared to controls, lower auditory attention, and an intact learning slope. We confirmed that immediate free recall performance (Trials 1-5 T score) in survivors was significantly lower than controls. However, as

immediate free recall is a global measure of performance on the initial learning trials we analyzed the participants' learning characteristics further in order to interpret these low immediate free recall scores. This revealed that when controlling for auditory attention (Trial 1 z-score), the level of verbal information learned and recalled on the final trial (Trial 5 z-score) after repeated presentation of the word list was comparable for the survivor and control groups. This indicates that auditory attention problems could be contributing to their lower immediate free recall and confirms our prediction. Furthermore, we confirmed that the rate of new learning, i.e. average number of new words per trial per trial (Learning Slope), of survivors paralleled that of the controls although their overall level of immediate free recall was lower than controls.

With regard to delayed free recall and retention we predicted lowered delayed recall and lowered retention compared to controls. We confirmed that delayed free recall (LDFR) showed a trend for being significantly lower in the survivors group. However, when controlling for initial level of verbal material learned (Trial 5 z-score), the level of verbal information recalled after the delay period (LDFR z-score) was comparable for the survivor and control groups. This suggests that the initially lower number of words learned could be contributing to their lower delayed free recall and our prediction about problems with retention was refuted. Intact retention was further supported by the finding that the change in number of words from Trial 5 to LDFR was not significantly different for the two groups.

Furthermore, counter to predictions, delayed recognition performance of the survivors was comparable to controls indicating that an encoding deficit profile (impairment at the level of recall and recognition) was not supported by the data in this group of adult survivors of

childhood brain tumor. In light of intact recognition, the pattern of similar rates of learning for the two groups but lower overall level of immediate and delayed free recall could point to mild retrieval problems.

Moreover, it should be noted that 78% of survivors in our sample were performing within normal limits on delayed free recall (only 7/32 had impaired LDFR; $z<-1.5$). This suggests that that the despite initial difficulties with auditory attention and lowered overall level of immediate learning and free recall the verbal memory systems of these survivors are not impaired even though they may not be functioning at the same level as their neurotypical peers.

Extant research, primarily in dementia and adult brain tumor survivors, shows that hippocampal abnormalities in adults should be predictive of impairments on both recall and recognition (encoding deficit profile). Many studies in patient populations as varied as Alzheimer's disease (Libon, Bogdanoff, Cloud, Skalina, Giovannetti, Gitlin, & Bonavita, 1998), ischemic vascular dementia (Libon, Bogdanoff, Cloud, Skalina, Giovannetti, Gitlin, & Bonavita, 1998), adults with temporal lobe epilepsy with adolescent onset (Reminger, Kaszniak, Labiner, et al., 2004), combat veterans with and without PTSD (Tischler, Brand, Stavitsky et al., 2006), elderly women (Ystad, Lundervold, Wehling et al., 2009), and adolescents with a history of prematurity (Gimenez, Junque, Narberhaus, Caldu, Salgado-Pineda, Bargallo, Segarra, & Botet, 2004), have established a link between hippocampal volume and verbal memory. Moreover, some of these studies used the CVLT-II to measure verbal memory performance. However, the specific relationship between hippocampal volume and memory functioning is not well established among developing children.

The results of our study showed that the size of the hippocampus was significantly associated with delayed recall, for a group of adult survivors whose brains were still developing at the time of diagnosis and treatment during childhood. We did not find hippocampus size to be linked to any of the other verbal memory indices, even recognition and learning slope, used in the current study. One potential explanation for why the brain structure – cognitive outcome relations in our sample are slightly different from the existing literature is that brain tumor diagnosis and treatment occurred during childhood, when the hippocampus was still developing. Another possible explanation for the lack of an association between hippocampal volume and recognition is that memory performance for our survivor was on average within normal limits across all three verbal memory indices. The severity of verbal memory problems in our sample is mild compared to the other aforementioned populations studied with regard to hippocampus size and memory.

Nonetheless, we were able to demonstrate that survivors do have a smaller hippocampus size even though their verbal memory difficulties are mild and likely attributable to initial auditory attention and retrieval inefficiencies. Moreover, our confidence in the specificity of the relationship between the hippocampus and delayed free recall is increased by two other findings: (1) there was an absence of significant correlations between putamen volume and delayed free recall, despite lower putamen volume in survivors (2) the correlation between hippocampal volume and performance on a fine motor task was not significant.

4.2 Treatment Variables

We explored the role of radiation therapy because it has been well linked to difficulties in cognitive performance for CNS and non-CNS cancer patients (Ellenberg, Liu, Gioia, et al., 2009; Kadan-Lottick, Zeltzer, Liu et al., 2010; Temming & Jenney, 2010; Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001). Given that 59% of the survivors in our sample had received radiation therapy we examined effect sizes for differences between each of the three groups (survivors with radiation, survivors with no radiation, controls). As expected, we found the strongest effect sizes when comparing survivors with radiation to controls across all of our dependent variables (see Table 4.2). When comparing survivors with no radiation to controls the effect sizes were consistently lower across all of our dependent variables (see Table 4.2). Hippocampal volume and CVLT-II performance scores were always lowest for the radiation group and the highest for the control group, with the no radiation group scores always being in between the scores for the radiation and control groups. This pattern of findings is consistent with the original planned analyses of each of our aims and suggests that more pronounced deficits exist for those who have received radiation therapy.

Furthermore, it has been theorized that radiation therapy may be impacting neurocognitive function through several neurobiological processes. Pathological processes in the hippocampus in animal models have been shown to be caused by irradiation (Nagel et al., 2004; Ris, 2007). Therefore, we explored if the associations between hippocampal volume and verbal memory indices were stronger for survivors who had received radiation. We found a significant ($p=.02$) positive correlation between hippocampal volume and LDFR in the radiation group ($n=19$), with a large effect size ($r=.49$), but not for the no radiation group ($p=.28$). No

other significant correlations between hippocampal volume and verbal memory indices were found for the radiation group but effect sizes were consistently larger than those found when examining the survivor group as a whole. These findings are in line with research on radiation therapy. Again these findings speak to the important role of radiation in below-normal volumes being associated with cognitive deficits.

Our sample of survivors was heterogeneous with regard to neurobiological and treatment variables, such as time since diagnosis, age at diagnosis, presence of seizure disorder, chemotherapy, presence of hydrocephalus, and hormone deficiency. All of these variables have been shown to negatively impact cognitive outcomes in research studies with other populations. In addition, the 59% of survivors in our sample who had received radiation therapy had, on average, the lowest hippocampal volume. Therefore, we explored the overlap of radiation with these other variables. A look at Table 4.1 shows that many of the survivors who received radiation therapy also received chemotherapy and had a diagnosis of hormone deficiency, whereas the ones that did not receive radiation therapy generally did not receive chemotherapy or have hormone deficiency. These exploratory findings raise an important question about the relative contribution of various factors that contribute to hippocampal development during childhood and ultimately to total hippocampal volume in adulthood. They also raise the question of whether it is diagnostic and treatment complexity that disrupts hippocampal and memory development, rather than any single variable (e.g. radiation therapy). Capturing diagnostic and treatment complexity would involve quantifying the influence of tumor and treatment-related risk factors by using a measure such as the Neurological Predictor Scale (NPS) (see Micklewright, King, Morris, Krawiecki, 2008). Future research studies, with a

higher number of adult survivors of pediatric brain tumor in the no radiation group would be better positioned to answer these questions. They could examine the relative contribution of each of these variables to hippocampal volume using a technique such as multiple regression.

Table 4.1 Overlap of radiation therapy with other neurobiological variables

Diagnostic & Treatment Variables	Radiation (n=19)	No Radiation (n=13)
Years post diagnosis (mean ± SD)	16.60 ± 5.87	17.69 ± 6.60
Range	5 - 28	7 - 27
Age at diagnosis (mean ± SD)	7.95 ± 4.60	7.69 ± 5.09
Range	1 - 19	2 - 17
Chemotherapy (n, %)	13 (68%)	1 (8%)
Hydrocephalus (n, %)	8 (42%)	6 (46%)
Seizure disorder (n, %)	4 (21%)	4 (31%)
Hormone deficiency (n, %)	13 (68%)	3 (23%)

Table 4.2 Effect sizes for group comparisons

	Radiation (n=19) (Mean±SD)	No Radiation (n=13) (Mean±SD)	Controls (n=48) (Mean±SD)	d
Hippocampal Volume	7212.4±922.9	7702.1±853.3		-.55
	7212.4±922.9		7888.6±833.9	-.79
		7702.1±853.3	7888.6±833.9	-.22
CVLT-II Trials 1-5 Total	43.84±12.86	51.31±8.34		-.66
	43.84±12.86		52.21±11.08	-.72
		51.31±8.34	52.21±11.08	-.09
CVLT-II LDFR	-.79±1.4	-.19±.93		-.49
	-.79±1.4		-.05±1.08	-.43
		-.19±.93	-.05±1.08	-.13
CVLT-II Recognition	-.47±1.15	0±.87		-.45
	-.47±1.15		.08±.97	-.54
		0±.87	.08±.97	-.08

4.3 Limitations

As participants for our study were recruited through large mailings inviting individuals to call to participate, selection bias must be considered. It is possible that the group of long-term survivors who participated chose to take part because cognitive problems were salient for this group. Alternatively, it may be that survivors with fewer cognitive concerns were more able to

participate. Given the large proportion of survivors who performed within normal limits, it is possible that our sample is higher functioning. Therefore, all interpretations and clinical recommendations that have emerged should be considered in those contexts. Furthermore, as we studied pre-existing naturally occurring groups – survivors of childhood brain tumors and healthy controls – this posed selection-related threats to validity. Therefore, causal conclusions from the findings cannot be made.

The variable of Recognition Discriminability posed a problem for data analyses because the assumption of normality was violated and transforming the data did not aid with normalizing the distribution. Further exploratory analyses evidence consistent violations with Recognition Discriminability raw scores, Recognition Hits raw and z scores, and Recognition False Positive raw and z scores. Violation of this key assumption could have impacted our ability to detect true differences and associations with regard to this variable. Thus, all interpretations about the recognition performance of this sample should be nested in this context.

Moreover, given problems with the indices, we explored Recognition Hits and Recognition False Positives raw and z-scores further and no significant differences were found between survivors and controls for any of the indices. Also, most of these indices were not correlated significantly with hippocampal volume, except False Positives raw and z-scores ($r = -.37$, $p = .02$, $n = 32$). This suggests that smaller hippocampal volume is related with higher false positives. Thus, the association between Recognition False Positive scores and hippocampal volume may be worth further examination in future studies. A previous study based on a larger sample from the existing data, a subset of which was used in our study, also found significantly higher number of False Positives in survivors compared to controls (Kohl, King, Morris, &

Krawiecki, 2011). None of the recognition indices were significantly correlated with putamen volume.

Another limitation is our study's inability to conduct MRI scans on individuals with certain types of metal in their skull or body and/or certain medical devices implanted at the time of surgery (e.g. shunts which create artefact or pose a safety risk). While most present day neurological devices are MRI-safe, exact specifications on surgery date, type of device, manufacturer name, and serial number are often essential in order to determine safety. These devices, when deemed unsafe for MRI, prevented us from gathering neuroimaging data. We were also unable to gather neuroimaging data in the absence of sufficient information about implanted devices. Therefore, survivors without such devices, who were scanned, may represent a "better outcome" group. It is possible, therefore, that findings may not generalize to survivors with greater neurological complications.

4.4 Strengths and Innovation

Our study has laid some of the foundation for understanding the nature of verbal memory function in adult survivors of childhood brain tumor. This foundation will continue to be a strength while cure rates for childhood brain tumors continue to be maintained and improved. As findings from our study have demonstrated an association of a specific neural substrate (hippocampus) with a specific type of neurocognitive function (verbal memory) and as more data on verbal memory in long-term survivors emerge, they will help clinicians make recommendations for neurocognitive rehabilitation that are grounded in neuropsychological research. Moreover, as most research with survivors takes place in the first decade following

treatment these studies lack the ability to address the extent of deficits that persist in the long-term. Our study has allowed a long-term outlook for future development (i.e. 5-28 years post-diagnosis, mean=17.04, median=17.05) in children treated for brain tumors. It has also allowed us to characterize memory deficits in the context of neurobiological structures that support these memory functions. While biomedical science has taken on the task of increasing survival, behavioural science needs to take on the task of improving the quality of survival. Framed in a broader context, our study is one of many crucial steps in improving the quality of survival for adult survivors of childhood brain tumor.

Moreover, volumetric analysis of the hippocampus in adult survivors has helped us see that the hippocampus is smaller for survivors than controls and thus its development was likely disrupted in childhood. The nature of our study sample – brain insult during childhood and brain imaging in adulthood – has also made it possible to build knowledge from a developmental perspective. The volumetric analysis conducted in the current study have added to the extant literature by showing that declines in hippocampal volume reported during childhood CNS tumors are not ultimately compensated for by return to normal growth in later life.

4.5 Future Directions

Firstly, a functional MRI study (Fernandez, Weyerts, Schrader-Botsche et al., 1998) with healthy adults has shown that the posterior part of the hippocampus is engaged in verbal encoding when performing a word list learning task. Thus, it will be interesting for future research to manually delineate the posterior region of the hippocampus in brain tumor

survivors and examine whether the volume of this region yields stronger associations with verbal memory.

Secondly, left hippocampal volume may be more sensitive to verbal memory. With regard to verbal memory function, it has been reported by several previous studies that there is greater left medial temporal lobe involvement (de Toledo-Morrell, Dickerson, Sullivan, et al., 2000; Milner, 1971). Also, in a study of hemispheric specialization in the human medial temporal lobe, sensitivity of the left hippocampus to verbal material has been shown (Kelley, Meizin, McDermott, et al., 1998). In regions within or near the hippocampal formation word-encoding, face-encoding, and object-encoding task all produced significant activations but in left medial temporal regions only word-encoding produced significantly greater left than right activation. In another study of elderly women, CVLT-II long delay free recall values were largely predicted by left hippocampal volume (Ystad, Lundervold, Wehling, et al., 2009). Given that our study used left and right hippocampus composite volumes, we may have reduced sensitivity the hippocampal volume – verbal memory associations. Therefore, it will be important to investigate potential lateralization of hippocampal function in brain tumor survivors using left and right volumes separately with material-specific memory tasks.

Third, from a developmental perspective, age at diagnosis holds promise in terms of predicting verbal memory abilities in adult survivors of childhood brain tumor. Some researchers have noted that a younger age at diagnosis predicts poorer neuropsychological outcomes (Ellenberg, McComb, Siegel, & Stowe, 1987; Reimers, Ehrenfels, Mortensen et al., 2003; Sands, Kellie, Davidow, Diez, Villablanca, & Weiner, 2001). Given the role development may play in the association of hippocampal volume and memory, it will be important for future

studies to examine more fully the role of age at diagnosis and time since diagnosis in explaining associations between hippocampal volume and memory performance.

5. SUMMARY

Our findings have provided us with a long-term outlook for hippocampal and memory development in children treated for brain tumors. Mainly, we know that disruption to a developing brain is associated with lower hippocampal and putamen volume on average 17 years after diagnosis. This indicates that survivors, whose brain development has likely been disrupted due to tumor or treatment related factors, do not have volumes comparable to controls in later life. Furthermore, we know that even though insults to a developing memory system may have occurred only during childhood, there are specific verbal memory weaknesses that are detectable long-term. These weaknesses likely continue to impact broader outcomes such as adaptive functioning and quality of life. These variables deserve continued attention for deciphering the complex impact of disease and treatment factors on developing brain structure and cognition.

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