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Recommended Citation

Jayakar, Reema; King, Tricia Z.; Morris, Robin; and Na, Sabrina, "Hippocampal Volume and Auditory Attention on a Verbal Memory Task with Adult Survivors of Pediatric Brain Tumor" (2015). *Psychology Faculty Publications*. 148.
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Hippocampal Volume and Auditory Attention on a Verbal Memory Task with
Adult Survivors of Pediatric Brain Tumor

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Author note: All authors are members of the Department of Psychology and Neuroscience Institute, Georgia State University (GSU). This research was supported in part by the American Cancer Society (Research Scholar Grant, Principal Investigator: T.Z. King, #RSGPB-CPPB-114044) and graduate student fellowships from the GSU Brains and Behavior initiative (R. Jayakar, S. Na). This article is based in part on the first author's Master's thesis, completed at GSU (December, 2013); preliminary findings were presented to the International Neuropsychological Society (February, 2011, 2012, 2013, 2014). We are grateful to the individuals and families who participated in this study and generously contributed their time and effort. Also, we would like to acknowledge Dr. Christopher Henrich for his assistance with the statistical analyses, staff at the GSU/GA Tech Joint Center for Advanced Brain Imaging (CABI), and the King Developmental Neuropsychology Research Team, including but not limited to, Drs. Jackie Micklewright, Matthew Mumaw, Aimilia Papazoglou, and John Ryan, and graduate students Kristen Smith, Ryan Brewster, and Alyssa Ailion. Correspondence should be addressed to Tricia Z. King, Department of Psychology, Georgia State University, 140 Decatur Street., Urban Life Bldg 11th floor, Atlanta, GA 30303. Email: tzking@gsu.edu

Abstract

Objective: We examined the nature of verbal memory deficits and the possible hippocampal underpinnings in long-term adult survivors of childhood brain tumor. **Method:** 35 survivors (M=24.10±4.93 years at testing; 54% female), on average 15 years post-diagnosis, and 59 typically developing adults (M=22.40±4.35 years, 54% female) participated. Automated FMRIB Software Library (FSL) tools were used to measure hippocampal, putamen, and whole brain volumes. The California Verbal Learning Test – Second Edition (CVLT-II) was used to assess verbal memory. **Results:** Hippocampal ($F(1,91)=4.06$, $\eta_p^2=.04$), putamen ($F(1,91)=11.18$, $\eta_p^2=.11$), and whole brain ($F(1,92)=18.51$, $\eta_p^2=.17$) volumes were significantly lower for survivors than controls ($p<.05$). Hippocampus and putamen volumes were significantly correlated ($r=.62$, $p<.001$) with each other, but not with total brain volume ($r=.09$; $r=.08$), for survivors and controls. Verbal memory indices of auditory attention list span (Trial 1) ($F(1,92)=12.70$, $\eta^2=.12$) and final list learning (Trial 5) ($F(1,92)=6.01$, $\eta^2=.06$) were significantly lower for survivors ($p<.05$). Total hippocampal volume in survivors was significantly correlated ($r=.43$, $p=.01$) with auditory attention, but none of the other CVLT-II indices. Secondary analyses for the effect of treatment factors are presented. **Conclusion:** Volumetric differences between survivors and controls exist for the whole brain and for subcortical structures on average 15 years post-diagnosis. Treatment factors seem to have a unique effect on subcortical structures. Memory differences between survivors and controls are largely contingent upon auditory attention list span. Only hippocampal volume is associated with the auditory attention list span component of verbal memory. These findings are particularly robust for survivors treated with radiation.

Key words: memory, brain tumor survivorship, long-term, volumetrics, hippocampus

Hippocampal Volume and Auditory Attention on a Verbal Memory Task with Adult Survivors of Pediatric Brain Tumor

Higher brain tumor survival rates, achieved over the past several decades, have led to increased interest and research on quality of survivorship (Ris, 2007). Extant research has shown that a wide range of neuropsychological domains are negatively impacted in pediatric brain tumor survivors (Edelstein et al., 2011; Maddrey et al., 2005; Reimers et al., 2003). Within neuropsychological domains, pediatric brain tumor survivors have specific deficits in the domain of memory (Dennis et al., 1991; Edelstein et al., 2011; Ellenberg et al., 2009; Nagel et al., 2006; Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001). The nature of these memory deficits is an important area of study because deficits in memory could contribute to learning difficulties in school (Edelstein et al., 2011; Gimenez et al., 2004); the rate of information acquisition during these formative years is dependent, at least in part, on underlying memory abilities. Furthermore, if neuropsychological impairment in the domain of memory continues into adulthood, it could impact survivors' adaptive functioning at the work place, in interpersonal relationships, and in daily living activities. Thus, there is a need to further our understanding of memory abilities in adult survivors of pediatric brain tumor.

Verbal memory is defined as the ability to learn, retain, and recall verbal items or words. Many survivorship studies have reported on verbal memory abilities following brain tumor diagnosis and treatment, but findings are mixed with regard to the specific memory profile observed. In one adult brain tumor study, free recall of a word list was negatively affected (Armstrong, Stern, & Corn, 2001). Similarly, in two childhood brain tumor studies, one study showed that free recall and recognition were significantly poorer in survivors compared to controls (Nagel et al., 2006), and another showed that list learning and delayed list recall were

impaired (King et al., 2004). In addition, child survivors have been shown to have retrieval deficits (Micklewright, King, Morris, & Morris, 2007) and significantly impaired auditory attention. The inconsistencies in the specific nature of verbal memory difficulties seen in survivors are not surprising given the differences in study samples. Samples were different with regard to developmental stage (i.e., child, adult), as well as tumor type and location (e.g., low-grade supratentorial, third ventricle, cerebellar, medulloblastoma). Moreover, differences in the memory tests used also could be contributing to the mixed findings (see Helmstaedter, 2013; Loring et al., 2008; for varying sensitivity and specificity of different memory tests). As such, whether the memory profile in adult survivors of pediatric brain tumor would show poor encoding, retention, or retrieval is difficult to predict based solely on the extant verbal memory literature.

Furthermore, there is a large gap in the brain tumor literature with regard to long-term outcomes because most research on survivors takes place within the first 5-10 years following treatment. In a past review paper on long-term neurobehavioral outcomes for pediatric brain tumor patients (Ris & Noll, 1994) most of the memory studies reporting problems were short-term (i.e., survivors were on average 4 years or less post-diagnosis), which precluded exploration of long-term sequelae. Although two newer studies reported neurocognitive impairments that extended into adulthood (Edelstein et al., 2011; Ellenberg et al., 2009), there are methodological limitations. For one of these studies the results were based on self-report measures, not objective neuropsychological test performance (Ellenberg et al., 2009). For the other study, results were based on a composite score derived from analogous measures across different tests or tests versions (Edelstein et al., 2011), which is psychometrically problematic. In two long-term studies of pediatric brain tumor survivors, one with a heterogeneous sample of tumors (5-10 years after

diagnosis) and another with only posterior fossa tumors (2-18 years after diagnosis), cognitive dysfunction and significant memory problems were reported (Lannering, Marky, Lundberg, & Olsson, 1990; Steinlin et al., 2003). However, these two long-term studies were limited, in that most of their participants were children at the time of testing, despite relatively long-term follow-up. Thus, while many studies have demonstrated a high risk for memory impairment during childhood, none have examined cognitive sequelae in young adults more than a decade past diagnosis and treatment, using objective neuropsychological performance measures.

From a developmental standpoint, pediatric brain tumor survivors are diagnosed and treated when the brain and memory systems are maturing. The presence and removal of a tumor may impact not only the memory systems that are already in place, but also the systems that have yet to develop. Therefore, short-term outcomes from childhood studies preclude an understanding of adult patterns of verbal memory abilities. Long-term research allows the exploration of how *adult* memory function is affected by pediatric brain tumor.

A comprehensive picture of verbal memory in adult survivors of pediatric brain tumor also requires an understanding of the underlying brain structures that support verbal memory function. Verbal memory is a type of declarative memory that is highly dependent on the integrity of the hippocampus and other anatomically related structures (Squire, 1992). Many studies in patient populations as varied as Alzheimer's disease (Libon et al., 1998), ischemic vascular dementia (Libon et al., 1998), adults with temporal lobe epilepsy with adolescent onset (Reminger et al., 2004), combat veterans with and without PTSD (Tischler et al., 2006), elderly women (Ystad et al., 2009), and adolescents with a history of prematurity (Gimenez et al., 2004), have established a link between hippocampal volume and verbal memory.

Research on typically aging adults and aging adults with neurodegenerative diseases (e.g., Alzheimer disease) shows that hippocampus related pathology is associated with an encoding deficit profile (Carlesimo & Oscar-Berman, 1992; Fernandez et al., 1998), whereas non-hippocampus related pathology (e.g., white matter disease) is associated with a retrieval deficit profile (Libon et al., 1998; Tierney et al., 2001; Van Petten et al., 2004). An encoding deficit profile is characterized by deficits in free recall and recognition, whereas a retrieval deficit profile is marked by deficits in free recall but intact recognition. Two neuroimaging studies have reported structural differences in hippocampal regions in childhood brain tumor survivors (Nagel et al., 2004; Riggs et al., 2014). The Riggs et al. (2014) study also reported reductions in global white matter volume and damage to the uncinate fasciculus. Neither of these studies examined profiles of memory performance. Riggs and colleagues reported a general memory index on a small subset of their sample and Nagel et al (2004) did not provide any performance measures. Yet, in a separate study without neuroimaging, Nagel et al. (2006) reported predominantly encoding deficits evidenced by impairments in both retrieval and recognition on a child list learning test. Even so, memory performance profiles in *adult* survivors of pediatric brain tumor and research on the related underlying hippocampal volumes is a critical next step. As the hippocampus is a critical structure supporting verbal memory function, the current study focuses on examining hippocampal volume and verbal memory profiles in a survivorship sample that is on average 15 years past diagnosis and treatment.

Before proceeding with such an examination it is important to highlight what is known about typical and atypical hippocampal development, as memory systems and hippocampal structures were developing when the survivors were diagnosed with brain tumors and underwent treatment. Studies of neurotypical children have shown increases in volume of the hippocampus

and other temporal gray matter structures, as well as increases in temporal cortex white matter integrity, during childhood and adolescence (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). Utsunomiya, Takano, Okazaki, and Mitsudome (1999) studied volumes of the hippocampal formation in 42 children aged 3 weeks to 14 years. Their results suggest that the volume of the hippocampal formation across their sample increased sharply until the age of two, at which point the volume increase became much slower. In addition, the results of Benes, Turtle, Khan, and Farol (1994) suggest that typical hippocampal development continues into early adulthood.

The potential for injury to the hippocampus during these early developmental stages, as a result of the presence of a brain tumor, its surgical removal, and related treatments, has been examined by only two neuroimaging studies. A 5-year longitudinal study of 25 newly diagnosed childhood medulloblastoma survivors (mean age at diagnosis = 8 years) evidenced hippocampal volume decline for the initial 2 years post-diagnosis (Nagel et al., 2004). These volume declines were observed over the course of 6 magnetic resonance imaging (MRI) scans, with the first scan taking place at 0.31 years (mean) after diagnosis. The study showed that a normal positive growth pattern resumed after the initial 2 years. However, the study was not designed to address whether atypical hippocampal development in the early years was ultimately compensated for by return to normal growth in later life. Furthermore, 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. Building on the study by Nagel et al. (2004), a recent study of children with posterior fossa tumors showed that survivors exhibited a smaller right hippocampus compared to controls, an average of 5 years post-diagnosis (Riggs et al., 2014). However, the study focused mainly on the pathophysiology of memory structures and did not examine the memory profile of

the entire sample of children. A subset of their sample ($n=10$) underwent neuropsychological testing, and only the General Memory Index scores are reported. As such, how the hippocampus may have related to specific memory deficits is not clear. Furthermore, no data were available on comparisons of verbal memory outcomes between the survivors and healthy controls. Therefore, in the current study we set out to extend the neuroimaging investigations of Nagel et al. (2004) and Riggs et al. (2014) by examining the long-term developmental outcomes (average time since diagnosis = 15 years) of not only the hippocampus, but also the verbal memory abilities that it is believed to support.

We also chose to examine another subcortical control brain structure, the putamen, as a comparison region, because it is not believed to have a significant influence on verbal memory functioning. Total brain volume also was investigated to determine whether treatment-mediated volume changes uniformly affect the whole brain or have a particularly negative impact on the hippocampus. Examining a subcortical comparison region was important because some research suggests that the hippocampus is neurofunctionally unique (i.e., structure, function, potential for plasticity), and therefore particularly susceptible to insult compared to other brain areas (Araujo & Lapchak, 1994; Franklin, Parmentier-Bateur, Walter, Greendberg, & Stella, 2003; Williamson & Bilbo, 2013). Brain-derived neurotropic factor (BDNF) plasticity in the hippocampal formation renders it vulnerable to damage and also modulates neuron survival and apoptosis (Murray & Holmes, 2011). Also, putative accounts of putamen function suggest that it is involved in the procedural and not declarative (e.g., verbal memory) memory system. As such, including the putamen as a contrast region in our study increased the specificity of hippocampus and verbal memory associations. Furthermore, correcting for total brain volume when examining between group differences in subcortical structure volumes allowed us to address whether these

structures are uniquely susceptible to damage or whether they mimic the entire brain's lower volume relative to controls.

The *first aim* of our study was to examine the differences between adult survivors of pediatric brain tumor and neurotypical controls in the volume of the hippocampus, putamen, and total brain using magnetic resonance imaging (MRI). It was predicted that survivors would exhibit smaller hippocampal and total brain volumes as compared to neurotypical adults. Moreover, we examined whether the size of the hippocampus would be different between the two groups after controlling for total brain size. Based on research that the hippocampus is particularly susceptible, it was hypothesized that hippocampal volume differences would persist after controlling for total brain size.

The *second aim* was to examine whether treatment affected performance on a standardized test of learning and memory. It was predicted that survivors' learning performance, delayed free recall, and delayed recognition memory would be lower when compared to healthy controls. In other words, it was likely that survivors would show problems with encoding *and* retrieval, i.e., an encoding deficit memory profile.

The *third aim* was to examine whether or not the hippocampus was associated with performance on verbal learning and memory. We predicted that hippocampal volume would be significantly correlated with learning and memory, whereas putamen and whole brain volume would not be correlated with learning and memory.

An important consideration in studies of memory outcomes for brain tumor survivors is the complex influence of medical variables because of their known effects on cognitive function. These include, but are not limited to, presence of radiation, chemotherapy, endocrine dysfunction, and history of hydrocephalus. Therefore, it is important to examine treatment and

medical complication variables within the study's survivor sample. Although the limited sample size makes it impossible to address all potential medical factors by methodologically controlling for each in the study design, detailed descriptive information is presented regarding these variables and the implications are discussed. In addition, we conducted *secondary analyses* within the survivor group for each of the aims and also examined the cumulative effect of treatment variables on brain volumes. Furthermore, information about memory performance for the radiation treatment and no radiation treatment subgroups in our survivor sample and effect sizes and means for these subgroups are presented.

Method

Participants

All participants provided written informed consent and the study protocol was approved by the Institutional Review Boards. The sample of participants ($N=94$) consisted of long-term adult survivors of childhood brain tumors ($n=35$) and demographically matched healthy controls ($n=59$). 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 newsletter, and (3) to survivors treated at Children's Health Care of Atlanta, a large south eastern hospital system over 10 years ago. For detailed information about survivor recruitment, please refer to the Appendix. Survivors were on average 15.4 years past their date of diagnosis. Healthy controls were recruited through the undergraduate Psychology participant pool at a large public south eastern university (Georgia State University (GSU)), a research imaging center (the GSU/GA Tech Joint Center for Advanced Brain Imaging), friends

of survivors, and community fliers. Of the 59 control group participants, 48 (i.e., 81%) were college students.

Control group participants were not significantly different from the survivor group with regard to sex, age, socioeconomic status (SES), or financial independence. In the final sample of participants, survivors (54% female) had a mean age of 24.10 ± 4.93 years and controls (54% female) had a mean age of 22.40 ± 4.35 years at the time of study participation. The Hollingshead Four Factor Index of Social Status (Hollingshead, 1975) was used to estimate SES of each participant. Family SES was used for cases where the individual was considered financially dependent and individual SES was used for cases in which the individual was independent. Fifty-one percent of the survivor sample and sixty-one percent of the control sample was identified as financially dependent. Furthermore, the ethnic diversity of the control sample was representative of the state census. For detailed demographic characteristics of controls and survivors, see Table 1. Survivors were on average 8.17 ± 4.43 years old at diagnosis and an average of 15.38 ± 5.34 years has passed since their diagnosis. Two of the survivors in our sample had recurrences and their scores on all dependent variables, age at recurrence, and years since recurrence (6.58 for one survivor and 10.50 for the other) were not outliers nor appreciably different from the rest of our survivor sample.

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, indicated a diagnosis of Neurofibromatosis, or had experienced any other significant neurological insult (e.g., traumatic brain injury, stroke). They also were considered ineligible if they did not pass the hearing screening and were not using a hearing aid. For healthy controls,

there were additional exclusion criteria based on a Structured Clinical Interview of the DSM-IV (SCID) Axis I Disorders.

For all of our aims, we chose to combine the group of survivors who had received radiation therapy ($n=16$) with the group of survivors who had not ($n=19$) for two 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 et al., 2009; King et al., 2004; Lannering et al., 1990; Micklewright et al., 2007; Steinlin et al., 2003); (2) it is important to examine non-radiotherapy survivors as hippocampus development may also be affected by the tumor, brain surgery, and diagnostic variables including but not limited to hydrocephalus history and chemotherapy. In addition, we conducted secondary analyses to compare the radiotherapy and non-radiotherapy subgroups. More information about these secondary analyses follows in the Study Design and Analyses section.

Measures

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) = 2,250 ms, echo time (TE) = 3.98 ms, field of view (FOV) = 256 mm, slice thickness = 1.0 mm, flip angle = 9°.

Hippocampal volume. Segmentation and volumetric analysis of the hippocampus was performed with FMRIB's Integrated Registration and Segmentation Tool (FIRST) (see

Patenaude, Smith, Kennedy, & Jenkinson, 2011). FIRST is a model-based registration and segmentation tool in FSL 4.0 (Smith 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 (see Patenaude et al., 2011). 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; it did not include the fimbria/fornix behind the posterior commissure. FIRST has been successfully used to obtain total hippocampal volume by other published empirical studies (see de Jong et al., 2008; O’Dwyer et al., 2012; Turner, Furey, Drvets, Zarate, & Nugent, 2012). We visually checked the hippocampal segmentations for errors, and no errors were noted. The volume of each participant’s left and right hippocampus was measured in mm^3 , and the sum of these two values yielded **Total Hippocampal Volume** values to be used in all subsequent analyses. See Figure 1a for a sample FIRST segmentation of the left and right hippocampus.

Putamen volume. We acquired putamen volumes using the same methods and software as that used to obtain hippocampal volume. As the metabolic needs and function of the putamen are different from the hippocampus, we used the putamen as a control structure. See Figure 1b for a sample FIRST segmentation of the left and right putamen.

Brain volume. We performed segmentation and volumetric analysis of the whole brain using the FMRIB tool SIENAX, which is a part of FSL. SIENAX is a package that estimates total brain tissue volume from a single image normalized for skull size (Smith et al., 2002; Smith

et al., 2004). SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to MNI 152 space. Estimates of total brain volume included white matter and grey matter volumes; they did not include CSF. We visually checked the whole brain segmentations for errors, and errors were noted for 3 survivors whose data were excluded from the study analyses. The volume of each participant's brain was measured in mm³.

California Verbal Learning Test – Second Edition (CVLT-II). The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) is an individually administered assessment tool that measures several aspects of verbal memory. It has adequate reliability and validity overall, with internal consistency estimates usually in the range of .80 or higher (Delis et al., 2000; Hubley, 2004). The CVLT-II has been shown to predict residual brain damage in various psychiatric and neurological populations (Alexander, Stuss, & Fansabedian, 2003; Delis et al., 2000).

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 **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 and short-term memory span. (2) The **Trial 5** score is the number of items learned and recalled after five repeated presentations of the word list. (3) 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 encode, retain, and retrieve. (4) 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.

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI was used to estimate general cognitive functioning (Wechsler, 1999). It provides an index (FSIQ) of crystallized (semantically-based) and fluid (based on online problem-solving) components of cognitive functioning and captures the complex coordinated functioning of many brain networks (Benson, Hulac, & Kranzler, 2010). The FSIQ score was presented (see Table 1) in order to better describe our sample, as recommended by reviewers.

Neurological Predictor Scale (NPS). The NPS (Micklewright, King, Morris, & Krawiecki, 2008) is a brief measure based on medical record reviews. It incorporates information about the tumor treatment, and other related neurological sequelae into one cumulative score, based on the presence/absence of neurological risk factors (i.e., prescription of seizure medications, presence/absence of hydrocephalus and presence/absence of hormone deficiency), type of neurosurgery, type of radiation treatment and the presence/absence of chemotherapy. We selected it for the current study in order to quantify the cumulative neurological risk within the survivor group (see Table 4).

Procedure

All participants were tested individually. Survivors and families in the study were interviewed to gather information about medical variables, such as age at diagnosis and presence of radiation. Medical record review verified these details. Testing typically took place over two visits; the first visit lasted approximately 5 hours and the second one lasted approximately 2

hours. At the first visit, trained psychology graduate students (under supervision of a licensed clinician TZK) administered a medical and developmental history interview, the SCID for DSM-IV TR Axis I, 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 participants' memory during the 20-minute time delay between the Trial 5 and LDFR trials would not be taxed. 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. 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.

Study Design and Analyses

All analyses were conducted using SPSS 17. Values of $p < .05$ were considered statistically significant. Data analyses for each of the aims, including imaging data, involved tests of data assumptions to check for extreme values, normality, homogeneity of variance, heteroskedasticity, non-independence of residuals, where appropriate.

We evaluated demographic variables of age, sex, education, and ethnicity as potential confounds or potential covariates to be used in analyses (see Table 1). A confound was defined as a variable that was significantly different between groups *and* was also highly correlated with outcome (r values with a large effect size). None of the demographic variables met this criteria. Additionally, we used a variable as a covariate if that variable emerged as significantly ($p < .05$) and highly correlated (r values with a large effect size) with the dependent variable of interest.

Omission of potential covariates has been shown to lead to potential bias in the statistical estimates of population parameters (Cohen, Cohen, West, & Aiken, 2003) and including such covariates increases precision.

Sex was significantly and highly correlated with total hippocampal volume ($r = -.48$, $p < .001$) and total putamen volume ($r = -.36$, $p < .001$). Although education was significantly correlated with hippocampal volume, the effect size was not large ($r = .25$, $p = .02$). Good covariates increase power by reducing the error term. However, there is a reduction of power when the relationship between the covariate and the dependent variable is not high enough to compensate for the loss in degrees of freedom. Therefore, of the demographic variables, only sex was included as a covariate for the planned group comparisons of Aim 1. The *a priori* plan was to analyze results with and without co-varying whole brain volume with hippocampus and putamen for Aim 1. If whole brain volume emerged as being significantly correlated with any of the CVLT-II indices it would be used as a covariate for Aim 3.

Survivor-specific variables. There are many neurobiological treatment variables that are heterogeneous in survivors (e.g., tumor location, tumor type, presence of radiation, chemotherapy, and history of hydrocephalus) that could potentially impact the outcomes of interest (see Reimers et al., 2003; Scott, Fletcher, & Brookshire, 1998). For a thorough description of these survivor-specific variables see Table 1. Larger subsamples of these survivor-specific variables are needed to address the complexities of these treatment factors on outcomes. However, given that 46% of the survivor sample received radiation therapy ($n = 16$) and the sample is heterogeneous with regard to their neurobiological and treatment variables, we categorized survivors into two subgroups based simply on whether they received cranial radiation: survivors who received radiation therapy (RT) and survivors who did not receive

radiation therapy (noRT). All survivors in the RT subgroup, but none in the noRT subgroup, had received radiation therapy by definition. The mean radiation dose for individuals in the RT group was 5409.44 ± 135.20 Gy (Range: 5000 – 5580 Gy). One of these individuals received whole brain radiation, five received focal radiation, nine received craniospinal radiation with a boost to the tumor site, and one did not have this information about the dose available. 69% of survivors in the RT subgroup had received chemotherapy, whereas only 5% of survivors in the noRT subgroup had received chemotherapy. More detailed information about the treatment variables can be seen in Table 4. We examined effect sizes for differences between these subgroups for all analyses, instead of null hypothesis significance testing because of limited sample size.

We chose to divide the survivor sample based on radiation because the literature provides strong support for the deleterious effects of radiation. Evidence for radiation leading to pathological processes in the hippocampus has been documented in animal models. Several hippocampal changes, including neuro-inflammation and reduction in neurogenesis in pediatric rodent brains (Greene-Schloesser et al., 2012), alterations in neuronal function of molecular pathways (Greene-Schloesser, Moore, & Robbins, 2013), and alterations in cerebrovasculature (Monje, Mizumatsu, Fike, & Palmer, 2002; Monje & Palmer, 2003), occur in response to radiation. Ischemic injury in hippocampal regions and white matter is also linked to radiation therapy (Tsuruda et al., 1987; Abayomi, 1996). Moreover, Riggs et al. (2013) provided preliminary data at a conference presentation that hippocampal volume is linked to cranial radiation for medulloblastoma survivors in a dose-dependent way. Specifically, Riggs et al. (2013) found significant group differences when comparing children treated with standard dose radiation to those treated with reduced dose and healthy controls. As the study of hippocampal structure and function in brain tumor survivors is a focus of the current study, a consideration of

potential radiation related damage was required. However, it should be noted that presence of radiotherapy is comorbid considerably with other medical factors (e.g., chemotherapy, endocrine dysfunction) and therefore interpretations of results should not be linked to radiotherapy alone. Therefore, in addition to examining subgroup differences, we examined the correlation of volumes with the NPS, which captures the cumulative nature of the treatment variables.

Group comparisons. In order to evaluate whether survivors differ from healthy controls in terms of hippocampal and putamen volume, we used one-way between-groups analysis of covariance (ANCOVA), with sex as the covariate. The independent variable was the group (survivors, controls), and the dependent variable consisted of volume measurements. We also evaluated whether survivors differed from healthy controls in terms of total brain volume, by using an ANOVA. In addition, we examined whether group differences in hippocampal and putamen volumes persist after controlling for total brain volume by using ANCOVA.

We used CVLT-II indices to evaluate differences between survivors and controls on verbal memory performance, and to determine the nature of verbal memory deficits in the survivor group. First, we compared survivors and controls on Trial 1 z scores and on Trial 5 z scores. This allowed us to examine whether auditory attention list span and level of learning after repeated word-list presentation differed between the two groups. We further evaluated whether Trial 5 z scores were significantly different between groups after controlling for Trial 1 z scores. This analysis helped us understand whether it was auditory attention list span or the level of learning after repeated learning trials that was accounting for differences in the number of words learned and recalled by Trial 5. Second, we evaluated whether survivors' LDFR z scores were affected. Then, in order to test whether initial learning or retention was impacting the LDFR z

scores, we compared survivors and controls on the LDFR z score after controlling for the Trial 5 z score. Finally, we compared survivors and controls' Recognition Discriminability Index z scores, as intact recognition in the context of recall deficits would discriminate between encoding versus retrieval deficit memory profiles.

Correlation analysis. Pearson bivariate correlations were obtained to examine the association between measures of brain structures and CVLT-II indices of verbal memory performance. Brain structures included in the analysis were total hippocampal volume, total putamen volume, total brain volume; CVLT-II indices included were Trial 1, Trial 5, LDFR, and Recognition Discriminability.

Results

For descriptive statistics demonstrating group similarities and differences on the dependent variables of interest see Table 2. Overall, group averages for verbal memory abilities were within normal limits for most survivors; 60-85% of survivors had scores that were above the -1.5 standard deviation clinical cut off from normative means.

Aim 1: Volumes

We conducted five separate ANCOVAs that were determined *a priori* to compare the subcortical structures' and total brain volume of survivors and controls. The independent variable was group (survivors, controls) and the dependent variables were measurements of hippocampal volume, putamen volume, and total brain volume, respectively. Participants' sex was used as a covariate in all analyses for subcortical structures because it was highly correlated with subcortical volumes. After adjusting for sex, there was a significant difference between the two groups on measured hippocampal volume ($F(1,91)=4.06, p=.047$), with a small effect size

($\eta_p^2=.04$), and a significant difference for putamen volume ($F(1,91)=11.18, p=.001$), with a medium effect size ($\eta_p^2=.11$) (see Figure 2). Total brain volume also was significantly different between the groups ($F(1,92)=18.51, p<.01$), with a medium effect size ($\eta_p^2=.17$). For means and effect sizes of the noRT and RT treatment subgroups, with regard to group differences in volumes, see Table 3.

We also compared the two groups on their hippocampal and putamen volumes, after controlling for total brain volume. There was no statistically significant difference in hippocampal volumes between the two groups ($F(1,90)=2.26, p=.14, \eta_p^2=.02$), after controlling for total brain volume. There was a statistically significant difference in putamen volumes between the two groups ($F(1,90)=9.60, p<.01, \eta_p^2=.10$), after controlling for total brain volume.

Furthermore, we conducted Pearson bivariate correlations for the entire sample to examine associations of the subcortical structures and total brain volumes with each other. Hippocampus and putamen volumes were significantly correlated ($r=.62, p<.001$), but neither were significantly correlated with total brain volume ($r=.09, p=.37; r=.08, p=.45$). Associations of subcortical structures and total brain volumes displayed a similar pattern for controls and survivors, with hippocampus and putamen being significantly correlated (Controls: $r=.50, p<.01$; Survivors: $r=.64, p<.01$), but neither being significantly correlated with total brain volume (r values ranging from $-.12 - .13$).

Post-hoc we examined the effects of having received chemotherapy, having a history of hydrocephalus, hormone deficiency, and seizure medication. Independent samples t-tests were used to compare volumes across these subgroups. Results indicated that survivors who had received chemotherapy had significantly lower hippocampal volume ($t(33)=-2.52, p=.02, d=-.90$), marginally significantly lower putamen volume ($t(33)=-2.06, p=.05, d=-.73$), and no

significant difference in total brain volume ($t(33)=-1.42, p=.16, d=-.51$). Individuals who had a history of hydrocephalus did not show any significant differences in hippocampal ($t(33)=-.33, p=.75, d=-.11$), putamen ($t(33)=-.97, p=.34, d=-.33$), or total brain volumes ($t(33)=-.68, p=.50, d=-.22$). Those who had a hormone deficiency had marginally significantly lower hippocampal volume ($t(30)=-2.01, p=.05, d=-.72$), significantly lower putamen volume ($t(30)=-3.07, p=.01, d=-1.09$), and no significant difference in total brain volume ($t(30)=-.92, p=.37, d=-.33$).

Survivors who were taking seizure medication did not show any significant differences in hippocampal ($t(31)=.31, p=.76, d=.13$), putamen ($t(31)=.38, p=.71, d=.16$), or total brain volumes ($t(31)=1.02, p=.32, d=.44$). We also explored associations of cumulative neurological risk factors on the NPS with subcortical structures and total brain volumes, within the survivor group. We found that volumes of the subcortical structures were significantly correlated with NPS (Hippocampus: $r=-.39, p=.02$; Putamen: $r=-.46, p<.01$), but total brain volume was not significantly correlated with NPS ($r=-.17, p=.33$).

Aim 2: Verbal Memory

Initial learning performance. A one-way between groups analysis of variance (ANOVA) showed that there was a statistically significant difference in CVLT-II Trials 1 z scores ($F(1,92)=12.70, p=.001$) between the two groups (see Table 2 & Figure 3a). On average, survivors scored lower than controls. The actual difference in mean scores between the groups was a medium effect size ($\eta^2=.12$). The performance of 10 survivors (29%) and 7 controls (12%) was in the clinically impaired range (i.e., $z\leq-1.5$). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired ($\chi^2(1, n=94)=3.09, p=.08$). In other words, survivors' scores on Trial 1 were statistically lower, and rates of clinical impairment displayed a non-significant trend for more impaired participants in

the survivor group. For means and effect sizes of the noRT and RT treatment subgroups, with regard to group differences on Trial 1, see Table 3.

An ANOVA also showed that there was a statistically significant difference in CVLT-II learning Trials 5 z scores ($F(1,92)=6.01, p=.02$) between the two groups (see Table 2 & Figure 3a). On average, survivors scored lower than controls. The actual difference in mean scores between the groups was a small effect size ($\eta^2=.06$). For means and effect sizes of the noRT and RT treatment subgroups, with regard to group differences, see Table 3. The performance of 14 survivors (40%) and 7 controls (12%) was in the clinically impaired range (i.e. $z \leq -1.5$). A Pearson chi-square test for independence with Yates continuity correction was significant for percent clinically impaired ($\chi^2(1, n=94)=8.47, p=.004$). In other words, survivors' scores were statistically lower and more frequently clinically impaired. Because rates of clinical impairment were differently represented across the groups for Trial 5, but not Trial 1, we inspected raw scores for these trials. We found that from Trial 1 to Trial 5, the increase in number of words recalled was the same for survivors and controls (average increase of 6 words). However, the distribution of scores for controls was similar at Trial 1 and 5, whereas the distribution of scores for survivors doubled in its range from Trial 1 to 5.

An 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). There was no statistically significant difference in adjusted Trial 5 z scores between the two groups ($F(1,91)=1.03, p=.31, \eta_p^2=.01$), after controlling for Trial 1 z scores (see Figure 3b).

Delayed free recall performance. An ANOVA showed that there was no statistically significant difference in CVLT-II LDFR z scores ($F(1,92)=3.02, p=.09$) between the two groups (see Table 2 & Figure 3a). The actual difference in mean scores between the groups was a small

effect size ($\eta^2=.03$). The performance of 7 survivors (20%) and 10 controls (17%) was in the clinically impaired range (i.e. $z \leq -1.5$). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired ($\chi^2 (1, n=94)=.009, p=.93$). As such, survivors' scores were not statistically lower and clinical impairment was not differently represented across the groups. For means and effect sizes of the noRT and RT treatment subgroups, with regard to group differences in delayed free recall, see Table 3.

An ANCOVA was conducted to compare the two groups on their CVLT-II LDFR z scores, after controlling for Trial 5 z scores. The independent variable was group (Survivors, Controls). There was no statistically significant difference in adjusted LDFR z scores between the two groups ($F (1,91)=.001, p=.97, \eta_p^2 < .001$), after controlling for Trial 5 z scores (see Figure 3b).

Recognition performance. An ANOVA showed that there was no statistically significant difference ($F (1,91)=3.15, p=.08$) in CVLT-II Recognition Discriminability z scores between the two groups (see Table 2 & Figure 3a). The actual difference in mean scores between the groups was a small effect size ($\eta^2=.03$). The performance of 5 survivors (15%) and 7 controls (12%) was in the clinically impaired range (i.e. $z \leq -1.5$). A Pearson chi-square test for independence with Yates continuity correction was not significant for percent clinically impaired ($\chi^2 (1, n=93)=.005, p=.94$). Therefore, survivors' scores were not statistically lower and not clinically impaired. For means and effect sizes of the noRT and RT treatment subgroups, with regard to group differences on recognition, see Table 3.

Aim 3: Association between Structural Measures and Memory Performance

For the control group, neither total hippocampal volume, total putamen volume, or total brain volume, were significantly correlated with CVLT-II Trial 1, Trial 5, LDFR, or Recognition

Discriminability (see Table 5 for r values & Figure 3A). For the survivor group, total hippocampal volume emerged as being significantly correlated ($r=.43$, $p=.01$) with Trial 1 (see Figure 3B), but not with Trial 5, LDFR, or Recognition Discriminability (see Table 5 for r values). Total putamen volume and total brain volume were not significantly correlated with Trial 1, Trial 5, LDFR, or Recognition Discriminability (see Table 5). Within the survivor sample, correlations between total hippocampal volume and total putamen volume were high for the noRT ($r=.36$) and RT ($r=.50$) subgroups. Furthermore, for the RT subgroup correlations were also high for Trial 5, LDFR, and Recognition Discriminability (see Table 5).

Discussion

The purpose of our study was to examine verbal memory profiles in adult survivors of childhood brain tumor, as well as possible specific correlations of verbal memory with hippocampal volume. The current study is among the first to examine differences in hippocampal size and verbal memory profiles between long-term adult survivors of childhood brain tumor and neurotypical controls. It appears that volumetric differences occur at the level of the whole brain as well as specific subcortical structures. Survivors do not exhibit a specific vulnerability of the hippocampus. Also, survivors and controls *both* evidence tight coupling between the volumes of subcortical structures, but not between subcortical structures and the whole brain. This lack of association between the size of the subcortical structure volumes and the size of the whole brain is consistent with the findings of Riggs et al. (2014) in childhood medulloblastoma survivors. Furthermore, we were able to describe the specific nature of verbal learning and memory performance deficits in adulthood and link those deficits to hippocampus volume. The relevance of our findings in the context of past research is discussed.

Hippocampal Volume

Two studies in the research literature have examined the short-term changes that occur in hippocampal volume after diagnosis and treatment of a childhood brain tumor. Nagel et al. (2004) demonstrated declines until 2 years post-diagnosis in their 5-year longitudinal study of medulloblastoma survivors (mean age at diagnosis = 8 years). Likewise, Riggs et al. (2014) reported that children with posterior fossa tumors had smaller right hippocampi five years post-diagnosis and treatment when compared to controls. As predicted, in the current study adult survivors (mean age at diagnosis = 8 years) exhibited smaller hippocampi as compared to controls on average 15 years post-diagnosis. Thus, early declines in hippocampal volume (Nagel et al., 2004; Riggs et al., 2014) are not fully compensated for in later life when child survivors grow to become young adults, as evidenced by volumes remaining lower than controls.

Of note, even though hippocampal volume was significantly lower for survivors, a similar pattern was also observed for the putamen and whole brain volumes. In fact, the effect sizes for differences between survivors and controls in putamen and whole brain volumes were medium in magnitude, whereas the effect size of the hippocampus was small in magnitude. Furthermore, after controlling for whole brain volume, the differences in hippocampal volume were no longer significant. These findings highlight the importance of using control structures and total brain volume in neuropsychological studies of brain tumor survivors. As noted by Riggs et al. (2014), many neuroimaging studies (e.g., Nagel et al., 2004) report only change in raw hippocampal size, making it impossible to ascertain a particular structure's vulnerability and inter-relationships among different brain regions.

One possible conclusion from these findings is that disruption to brain development for survivors is more global in nature and that the hippocampus is not more vulnerable, despite

putative accounts of its higher metabolic needs. However, a closer review of the means and effect sizes of survivor subgroups (i.e., RT and noRT) indicates that treatment may affect subcortical structures differently than the remaining brain parenchyma (see Table 3).

Specifically, the volumes for subcortical structures (i.e., hippocampus and putamen) of the noRT subgroup are similar to those of controls, with the RT subgroup showing the largest effect sizes; whereas the whole brain volume of the RT and noRT subgroups are similar, with the control group showing the largest effect size. Together, these findings indicate that simply having a brain tumor is associated with having a lower total brain volume, regardless of other medical variables. However, greater medical complexity is associated with having lower volumes with regard to subcortical structures. In other words, cumulative neurological risk factors appear to have a unique effect on subcortical structures.

Given that cumulative neurological risk factors affect the volume of subcortical structures differently than whole brain volume, we examined the effects of having received chemotherapy, having a history of hydrocephalus, hormone deficiency, and seizure medication. These individual exploratory analyses detected the importance of chemotherapy and hormone deficiency with regard to hippocampal and putamen volumes. This is consistent with significant NPS correlations with hippocampus and putamen volumes. There appeared to be no effect of having a history of hydrocephalus or seizure medication on any of the volumes. There are two things of note with regard to these analyses: (1) Presence of chemotherapy is confounded with presence of radiation, as all individuals who received chemotherapy, except one, also received radiation (see Table 4); (2) Hormone deficiency in our sample typically co-occurs with other diagnostic and treatment variables (e.g., craniopharyngioma, medulloblastoma, radiotherapy) (see Table 4). As

such, these effects may not be a product of simply chemotherapy drugs or endocrine dysfunction, but rather are a product of complex neurological health factors.

Verbal Memory

Although no existing research has tested verbal memory profiles in long-term (>15 years since diagnosis) adult survivors of pediatric brain tumor, some short-term childhood studies (King et al., 2004; Micklewright et al., 2007; Nagel et al., 2006) and some adult studies (Armstrong et al., 2001; Ellenberg et al., 2009) suggest memory difficulties in the context of brain tumor survivorship. Building upon previous research findings, we found that performance scores for auditory attention list span, as well as level of learning after repeated word-list presentation, are significantly poorer in adult survivors of childhood brain tumor, compared to controls. Previous research in children with third ventricle and cerebellar tumors has documented elevated attentional problems, as measured by Trial 1 of a list learning task (Micklewright et al., 2007; Papazoglou, King, Morris, Morris, & Krawiecki, 2008), and our data show that auditory attentional impairments extend into adulthood. As shown by another childhood study, poor attention is associated with lower adaptive functioning (Papazoglou et al., 2008) and could place our adult survivors at risk for deficits in daily living skills compared to their neurotypical peers.

Our findings of poorer auditory attention list span in the context of a verbal memory task are also consistent with the verbal memory findings reported for child medulloblastoma survivors by Nagel et al. (2006). In contrast to our results that delayed free recall and recognition are not significantly different between survivors and controls, Nagel et al. (2006) found that performance scores for delayed recall and recognition were significantly lower. These findings relative to those of the current study may be explained by methodological differences across the studies. First, their memory profiles are based on the California Verbal Learning Test for

children (CVLT-C) as they were testing a child sample (Age at testing $M=9.34\pm 3.10$), whereas the current study data are based on the CVLT-II in an adult sample (Age at testing $M=24.10\pm 4.93$). Second, they administered the test 0-30 months after diagnosis, and 70% of the children in their study were receiving treatment at the time of testing. In contrast, we administered the test 5-24 years after diagnosis, and none of the adults in our study were receiving treatment. Third, their sample included only medulloblastoma survivors, whereas ours is a heterogeneous sample. The different verbal memory profile captured by the long-term approach of our study suggests that future research should follow memory outcomes for a period of time that is, on average, greater than 10 years in pediatric survivors with a variety of tumor types. Such research will further improve our understanding of the development of memory abilities in this population.

Critically, with regard to the memory profiles demonstrated in our sample, differences between the amount of material learned after repeated presentation (i.e., Trial 5) seemed to be largely contingent upon the initial auditory attention list span; level of learning was not significantly different between the two groups after controlling for auditory attention list span. Likewise, delayed recall was not significantly different. Interpreted as a whole, this pattern of findings suggests that the rate of learning (i.e., number of new words gained at each trial) and level of retention (i.e., amount of learned information that is maintained in memory) are relatively intact. If the rate of learning and level of retention were critical factors differentiating the verbal memory abilities of survivors and controls, then we would have seen significant differences in later memory trials after controlling for performance at earlier trials.

Furthermore, survivors' scores with regard to clinical impairment (i.e., $z \leq -1.5$) on Trial 1 were not differently represented across the groups, but on Trial 5 significantly more survivors'

than controls' scores were in the clinically impaired range. An examination of raw scores showed that the average number of words gained from Trial 1 to Trial 5 was similar for survivors and controls, but the distribution of scores at each of those times points was different. One potential reason for differences in level of clinical impairment across Trials 1 and 5 is that some survivors' performance showed only small gains from repetition, but others showed large gains. These findings highlight the importance of examining levels of clinical impairment, in addition to group means.

Brain Structure and Memory Function Relationships

The third aim of our study was to examine whether or not the hippocampus is associated with performance on verbal learning and memory. Building upon the existing brain tumor research on verbal memory, hippocampal volume of the survivors was found to be significantly correlated to auditory attention list span, in the context of a verbal memory task. Furthermore, larger hippocampal volumes of the RT *and* noRT subgroups were associated with higher scores on CVLT-II Trial 1. Our confidence in the specificity of our findings is increased by the fact that we did not find a significant correlation between putamen volume of survivors and any of the verbal memory indices, despite putamen volumes being highly correlated with hippocampal volumes. Consistent with prior studies (e.g., Riggs et al., 2014), whole brain volume of the survivors was not significantly correlated with any of the memory indices. As such, it appears that the reductions in auditory attention list span scores are specifically associated with reduced hippocampal volume and the deficits in other structures do not contribute to the auditory attention aspect of verbal memory function.

In addition, for the control group, there was no relationship between hippocampal volume and any of the verbal memory indices. This finding is consistent with Van Petten et al.'s (2004)

account that “bigger” is not always “better”. Based on a meta-analysis, their account posits that in neurologically intact adults the “bigger is better” explanation of regional structure-function relationships may be too simplistic, because size reveals little about relative proportions of neurons and astrocytes, synaptic densities, ratios of excitatory to inhibitory synapses, and patterns of synaptic connectivity.

The current study’s finding of the association between hippocampal volume and auditory attention list span has not been hypothesized in the existing research on childhood brain tumors. There are two potential explanations for our unique findings: (1) The association between these constructs may be unique to adult survivors of childhood brain tumor because their brains were developing at the time of diagnosis and treatment. (2) Other studies linking the hippocampus to verbal memory do not scrutinize components of the memory system of their sample in this manner. As such, it is difficult to comment on whether or not the hippocampus plays a role in the auditory attention span aspect of verbal memory function in these studies. Although poorer verbal learning has been shown to be related to smaller hippocampus size in various patient populations, our study demonstrates that this relationship extends to auditory attention span aspects of learning for adult survivors of childhood brain tumor. Historically, the declarative memory system has consistently been shown to depend on a network of structures within the medial temporal lobe (MTL) and the prefrontal cortex, with which the MTL interacts (Reber et al., 2002; Simons & Spiers, 2003; Squire, 2004; Squire, Stark, & Clark, 2004; Tulving & Markowitsch, 1998). Within the MTL-based memory networks, the hippocampus is believed to be a central structure (Tulving & Markowitsch, 1998). Ample research shows that it is heavily involved in the execution of declarative memory functions (for a review, see Squire, 1992, 2004; Squire et al., 2004). Specifically, the hippocampus consolidates, or binds together, information

about objects and events (Bucci & Robinson, 2014). In addition, it mediates elemental cognitive processes (i.e., associative representation, sequential organization, and relational networking), beginning with the learning stage and continuing on to consolidation over a prolonged period of time (Eichenbaum, 2004). Finally, research using intracranial recordings of cognitive potentials indicates that the hippocampus also participates in the recall of information (Grunwald, 2008). However, in recent years, animal models and functional neuroimaging research findings have called into question the assumption that the hippocampus plays a primary role in memory. Indeed, the “best” characterization of functions associated with specific MTL regions remains a matter of debate (Moscovitch, 2008); there is still much unknown about the precise contributions to memory of the hippocampus. As research on the declarative memory system continues, it is possible that the historical account of the hippocampus being primarily responsible for memory performance will prevail; but it is also possible that our knowledge about the role of the hippocampus will evolve.

Limitations and Future Directions

As participants were recruited through large mailings inviting individuals to participate, selection bias must be considered regarding these results and their limitations. For detailed information on the number of survivors included and retention rates see the Appendix. It is possible that individuals chose to participate in the study because cognitive problems were salient. Alternatively, it may be that survivors with fewer cognitive concerns were more able to participate because of higher levels of independence. Given the large proportion of survivors who performed within normal limits on the verbal memory task, it is possible that this sample is higher functioning than survivors who did not participate. In addition, because the current study allowed for the recruitment of a survivor group with varied tumor pathologies (i.e., tumor type

and location) the study design does not have the ability to specify the effects of particular tumor types or locations. Therefore, all interpretations and clinical recommendations that could emerge from the current research should be considered in these contexts.

Another limitation is the study's inability to conduct MRI scans on some individuals in the study sample (see the Appendix): (1) 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 in the scanner). Although most present day neurological devices are MRI-safe, exact specifications of type of device, manufacturer name, and serial number are essential in order to determine safety. These devices, when deemed unsafe for MRI, or in the absence of sufficient information about implanted devices, prevented the acquisition of neuroimaging data; (2) Survivors lost to follow-up; (3) Individuals who declined to participate in the imaging component of the study. Thus, survivors who met criteria for MRI safety, as well as those who remained in contact to attend the imaging visit, may represent a "better outcome" group. As such, findings may not generalize to survivors with medical devices and to those who we were unable to follow-up.

To this end, we examined the CVLT-II scores for the individuals who met the eligibility criteria for the study and had completed cognitive testing but did not have imaging data available. We found that the CVLT-II mean scores for this no MRI survivor group were significantly lower on Trial 5 ($M=-1.40\pm 1.15$; $t(64)=-2.19$, $p=.03$, $d=-.54$) and LDFR ($M=-1.39\pm 1.09$; $t(64)=-2.81$, $p=.01$, $d=-.70$), but not Trial 1 ($M=-1.08\pm .80$; $t(64)=-1.54$, $p=.13$, $d=-.38$) and Recognition Discriminability ($M=-.92\pm 1.48$; $t(63)=-1.85$, $p=.07$, $d=-.46$), than the means of those included in the study (see Table 2). These differences in memory performance between survivors who were unable to participate in the neuroimaging component of the study and

survivors who were able to participate illustrate that we must be cautious when interpreting the findings about cognitive outcomes from the current and other neuroimaging studies. Also, if such studies have additional cognitive data available it is helpful to report these data so that readers know more about the generalizability of their findings. Our results suggest that memory deficits are more pronounced, on average, in the no MRI survivor group. It is possible that more robust relationships between performance and brain volumes may be identified with the inclusion of these individuals.

Given our findings of the prominent role of CVLT-II auditory attention list span, a limitation of the study is that there was no diagnostic information available for Attention Deficit Hyperactivity Disorder (ADHD). Therefore, concerns that their attentional functioning may impact CVLT-II Trial 1 performance cannot be addressed. We excluded control participants with a self-reported history of developmental conditions, such as diagnosis of ADHD. And although the SCID – Axis I was administered, unfortunately, it does not assess for a diagnosis of ADHD. Obtaining detailed information about ADHD symptoms could be particularly important for future studies, to determine if survivors meet full criteria for ADHD and whether any participants were on medication for attention problems.

As survival rates for childhood brain tumors continue to be maintained and improved, describing the specific patterns of verbal memory abilities or deficits, in adult survivors of childhood brain tumor is an important endeavor. Results from our study may inform the development of interventions focused on improving attention and cognitive performance (see Castellino, Ullrich, Whelen, & Lange, 2014). Studies may explore the efficacy of various clinical recommendations for neurocognitive rehabilitation, including home-based computerized protocols that are starting to show some promise for improving memory and attention (Castellino

et al., 2014). For example, one recommendation would be to provide survivors with multiple formats (i.e., auditory + visual) of the material to be learned in order to boost the initial encoding of that material. Another recommendation would be to provide multiple opportunities to learn the material and a longer time frame to learn new content, as this may allow them to eventually encode the same amount of total material as a neurotypical adult.

Posterior regions of the hippocampus have been implicated as being more vulnerable in individuals with cerebellar tumors due to a treatment regimen that includes whole brain radiation, as well as a boost to the posterior fossa (see Nagel et al., 2004). At least one functional MRI study of neurotypical adults has shown that the posterior part of the hippocampus is engaged in verbal encoding during a word-list learning paradigm (Fernandez et al., 1998). Together, these studies indicate that there may be a specific link between posterior regions of the hippocampus and encoding of verbal material. Manually delineating the posterior region of the hippocampus for volumetric analysis could be a useful next step.

Finally, lateralization of hippocampal function with regard to verbal versus visual memory has been reported in the adult literature (de Toledo-Morrell et al., 2000; Milner, 1971; Kelley et al., 1998; Ystad et al., 2009), with the left hippocampus being sensitive to verbal material. However, generalizing these adult findings to developing populations is problematic. Helmstaedter & Elger (2009) have shown that only the mature brain shows left/right temporal lobe differences in verbal memory and that such lateralization is not evident in children or the elderly. Our current data show that, on average, the left and right hippocampi each have lower volumes in survivors compared to controls (see Table 2), with the left being significantly lower and more vulnerable ($F(1,91)=5.42, p=.02, \eta_p^2=.06$). The pattern of findings with regard to the association of left and right hippocampi to total brain volume, as well as their association to

verbal memory measures, are the same for all analyses conducted in the study. These findings suggest that both left and right hippocampal volumes are associated with auditory attention list span and learning on Trial 1 of CVLT-II. Future studies should consider expanding upon these findings by exploring white matter integrity of specific memory and attention pathways using diffusion tensor imaging tractography (e.g., Brewster, King, Burns, Drossner, & Mahle, in press; Law, Bouffet, & Laughlin, 2011; Smith, King, Jayakar, & Morris, 2014).

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Table 1. Demographic, diagnostic, and treatment variables

Demographic Variables	Survivors (n=35)	Controls (n=59)
Female (n, %)	19 (54%)	32 (54%)
Education (mean ± SD)*	13.57 ± 1.88	14.39 ± 1.67
Age at testing (mean ± SD)	24.10 ± 4.93	22.40 ± 4.35
Range	17-36	18-41
Ethnicity (n, %)*		
Caucasian	27 (77%)	26 (46%)
African-American	5 (14%)	18 (32%)
Other‡	3 (9%)	13 (23%)
SES§	2.32 ± 1.20	2.86 ± 1.44
Range	1-5	1-5
Financially dependent	18 (51%)	36 (61%)
WASI Full Scale IQ (FSIQ)*	101.82 ± 16.28	109.86 ± 10.32
Diagnostic & Treatment Variables		
Years post diagnosis (mean ± SD)	15.38 ± 5.34	
Range	5 – 24	
Median	16.21	
Age at diagnosis (mean ± SD)	8.17 ± 4.43	
Range	1 – 17	
Median	9.00	
Tumor location (n, %)		
Posterior fossa	20 (57%)	
Pituitary	6 (17%)	
Frontal lobe	3 (9%)	
Temporal lobe	3 (9%)	
Other^	3 (9%)	
Tumor type (n, %)		
Astrocytoma	10 (29%)	
Medulloblastoma	9 (26%)	
Craniopharyngioma	5 (14%)	
Ganglioglioma	3 (9%)	
Other†	8 (23%)	
Radiation (n, %)	16 (46%)	
Chemotherapy (n, %)	12 (34%)	
History of hydrocephalus (n, %)	16 (46%)	
History of seizure medication (n, %)	7 (20%)	
Hormone deficiency (n, %)	15 (43%)	

Note. *Significantly different between groups at $p=.05$; independent samples t-test for education, age, SES, and FSIQ; chi-square test for sex, ethnicity, and financial dependence.

^1 Parietal, 1 Occipital, 1 Thalamus.

†1 PNET, 2 Glioma, 1 Mixed Astrocytoma and Teratoma, 1 Meningioma, 1 Mixed germ cell, 1 Choroid plexus papilloma, 1 Cerebral neuroblastoma

‡Survivors: 1 Asian, 1 Hispanic, 1 Mixed; Controls: 7 Asian, 5 Hispanic, 1 Mixed. . §SES = Current socioeconomic status, estimated using the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). Family SES was used for cases where the individual was financially dependent and individual SES was used for cases where the individual was financially independent.

Table 2. Comparison of outcome variables for the two groups

	Survivors (n=35)	Controls (n=59)
	Mean \pm SD	Mean \pm SD
Volume		
Total Hippocampus*	7.56 \pm 1.01	7.91 \pm .89
Left Hippocampus*	3.70 \pm .58	3.93 \pm .49
Right Hippocampus	3.86 \pm .60	3.98 \pm .51
Total Putamen*	9.88 \pm 1.21	10.63 \pm 1.09
Whole Brain Volume*	1544.00 \pm 63.00	1597.60 \pm 55.41
CVLT-II		
List A Trial 1 z score*	-.80 \pm .69	-.07 \pm 1.09
Number Impaired (%)	10 (29%)	7 (12%)
List A Trial 5 z score*	-.73 \pm 1.33	-.11 \pm 1.09
Number Impaired (%)*	14 (40%)	7 (12%)
Long Delay Free Recall z score	-.57 \pm 1.25	-.14 \pm 1.13
Number Impaired (%)	7 (20%)	10 (17%)
Recognition Discriminability Index z score	-.34 \pm 1.03	.05 \pm 1.01
Number Impaired (%)	5 (15%)	7 (12%)

Note. *Significantly different between groups at $p=.05$. Volumes are reported in cubic centimeters. Impaired: $z \leq -1.5$

Table 3. Means and effect sizes for treatment subgroups.

	Mean \pm SD			Subgroup Difference Effect Sizes		
	RT ($n=16$)	noRT ($n=19$)	Controls ($n=59$)	RT vs. noRT	RT vs. Control	noRT vs. Control
Hippocampal Volume	7.28 \pm .89	7.80 \pm 1.07	7.91 \pm .89	-.52	-.71	-.12
Putamen Volume	9.25 \pm 1.00	10.41 \pm 1.14	10.63 \pm 1.09	-1.08	-1.29	-.20
Brain Volume	1541.70 \pm 70.58	1546.00 \pm 57.76	1597.60 \pm 55.41	-.07	-.95	-.92
Trial 1	-.91 \pm .66	-.71 \pm .71	-.07 \pm 1.09	-.29	-.83	-.63
Trial 5	-.44 \pm 1.30	-.97 \pm 1.34	-.11 \pm 1.09	.40	-.29	-.75
LDFR	-.56 \pm 1.34	-.58 \pm 1.20	-.14 \pm 1.13	.02	-.36	-.38
Recognition	-.28 \pm .86	-.39 \pm 1.18	.05 \pm 1.01	.11	-.34	-.42

Note. Effect sizes reported are Cohen's *d*. RT: Survivors who received radiation therapy; noRT: Survivors who did not receive radiation therapy.

Table 4. Diagnostic and treatment variables in survivor subgroups

Diagnostic & Treatment Variables	RT (n=16)	noRT (n=19)
Female (n, %)	9 (56%)	10 (53%)
Education (mean ± SD)	13.00 ± 1.21	14.05 ± 2.22
Age at testing (mean ± SD)	24.01 ± 4.42	24.17 ± 5.44
Range	18-32	17-36
Tumor type (n, %)*		
Medulloblastoma	9 (56%)	1 (5%)
Craniopharyngioma	4 (25%)	1 (5%)
Astrocytoma	1 (6%)	10 (53%)
Ganglioglioma	0 (0%)	3 (16%)
Tumor location (n, %)		
Cerebellum/Post. fossa	7 (44%)	11 (58%)
Pituitary	5 (31%)	1 (5%)
Temporal lobe	0 (0%)	3 (16%)
Years post diagnosis (mean ± SD)	15.64 ± 4.62	15.16 ± 6.00
Range	5 - 23	6 - 24
Age at diagnosis (mean ± SD)	7.56 ± 3.81	8.68 ± 4.93
Range	1 - 16	1 - 17
Radiation (n, %)*	16 (100%)	0 (0%)
Chemotherapy (n, %)*	11 (69%)	1 (5%)
History of hydrocephalus (n, %)	7 (44%)	9 (47%)
History of seizure medication (n, %)	1 (6.3%)	6 (32%)
Hormone deficiency (n, %)*	13 (81%)	2 (11%)
NPS Score (median)*	8	4
Range	5-9	2-6

Note. *Significantly different between groups at $p < .05$. RT: Survivors who received radiation therapy; noRT: Survivors who did not receive radiation therapy. NPS: Neurological Predictor Scale (Micklewright et al., 2008); a brief measure based on medical record reviews that incorporates information about the tumor treatment, and other related neurological sequelae into one cumulative score

Table 5. Correlations between brain structure volumes and verbal memory indices

	Hippocampus	Putamen	Whole Brain	Trial 1	Trial 5	LDFR	Recognition
Controls (n=59)							
Hippocampus	1	.50*	-.06	.13	.15	.11	.08
Putamen	--	1	-.12	-.02	.13	.09	.02
Whole Brain	--	--	1	.03	.10	.11	.13
Survivors (n=35)							
Hippocampus	1	.64*	.13	.43*	.06	.12	-.02
Putamen	--	1	.03	.05	-.04	.03	.01
Whole Brain	--	--	1	.12	-.09	-.15	-.12
noRT (n=19)							
Hippocampus	1	.73*	.19	.36	-.11	-.25	-.27
Putamen	--	1	.24	.01	-.01	.04	.03
Whole Brain	--	--	1	-.01	-.16	-.38	-.29
RT (n=16)							
Hippocampus	1	.41	.07	.50*	.46*	.62*	.51*
Putamen	--	1	-.24	-.07	.17	.04	.07
Whole Brain	--	--	1	.24	-.03	.05	.09

Note. *Significant at $p < .05$ (one-tailed). RT: Survivors who received radiation therapy; noRT: Survivors who did not receive radiation therapy.

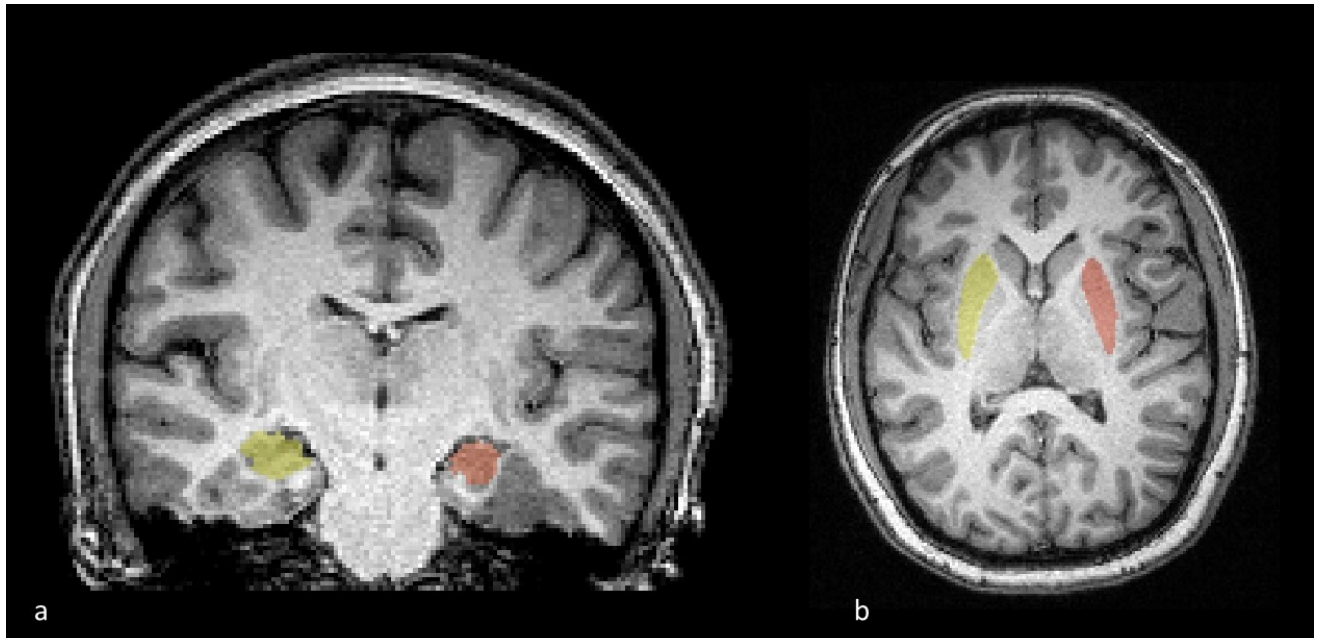


Figure 1. MRI-based example of FIRST segmentation. (a) Yellow and red regions represent right and left hippocampi. (b) Yellow and red regions represent right and left putamens.

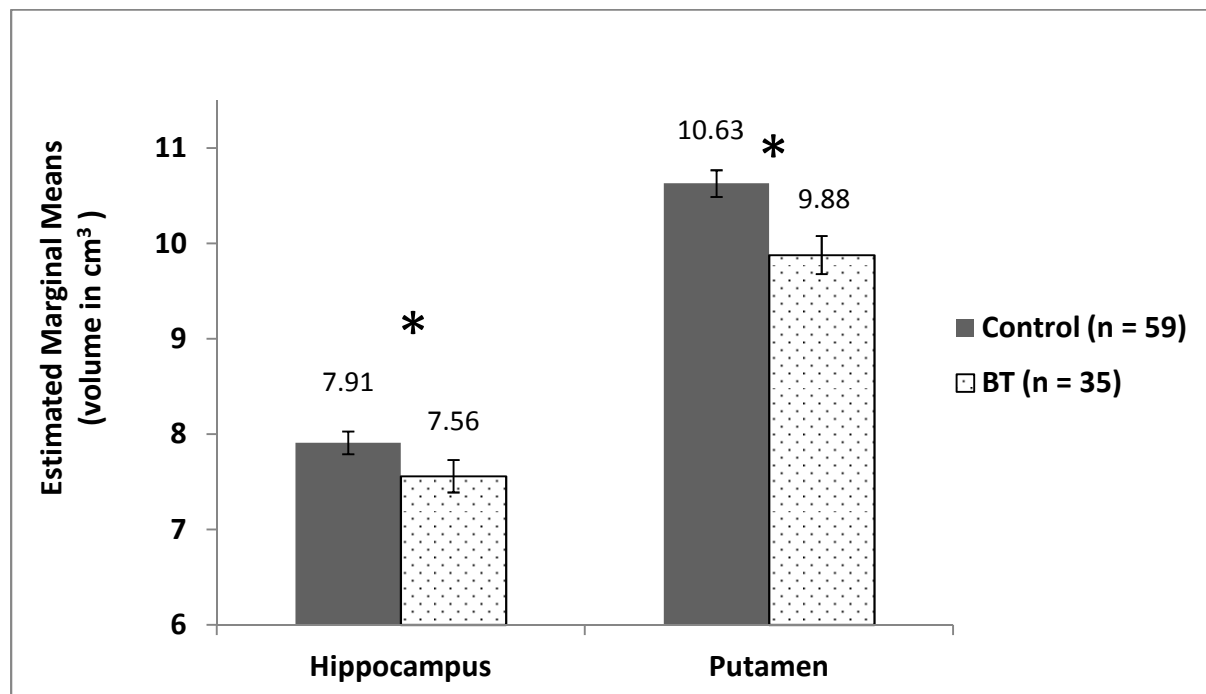


Figure 2. Total hippocampal and putamen volumes. *Indicates significant difference at $p=.05$.

Error bars represent standard error. BT: Brain tumor survivors

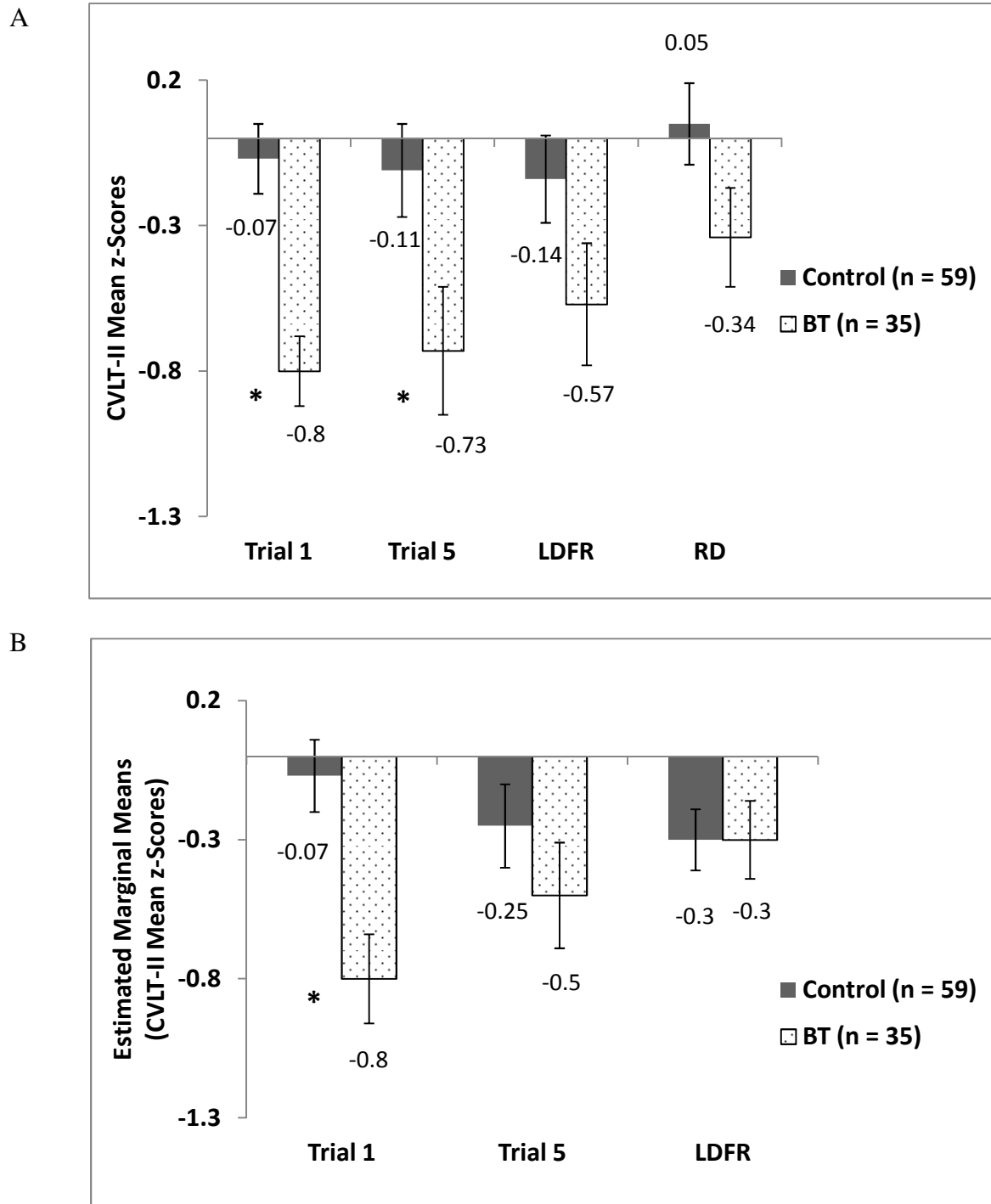
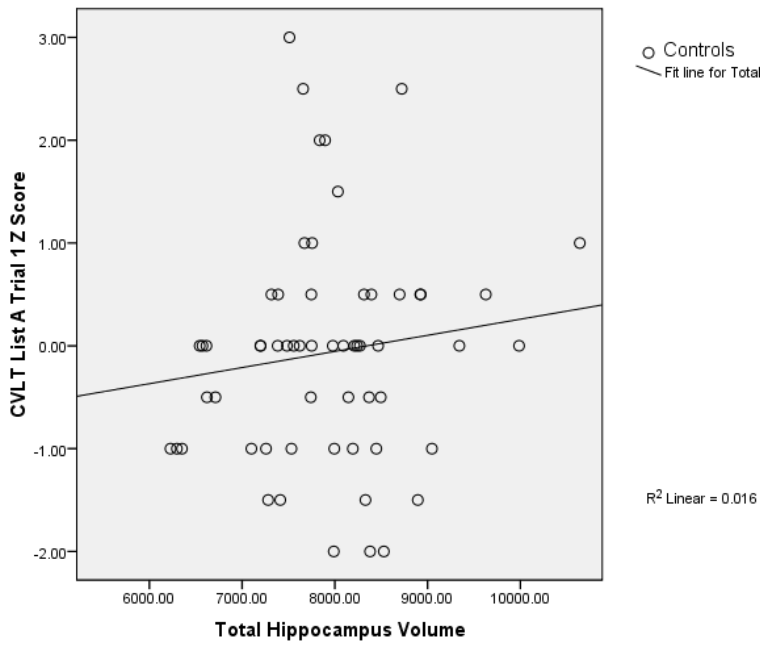


Figure 3. A) Unadjusted performance on select indices of the CVLT-II. B) Adjusted performance (ANCOVA) on select indices of the CVLT-II. *Indicates significant difference at $p=.05$. Error bars represent standard error. Means shown are estimated marginal means (except Trial 1). LDFR=Long Delay Free Recall. RD=Recognition Discriminability. BT: Brain tumor survivors

A



B

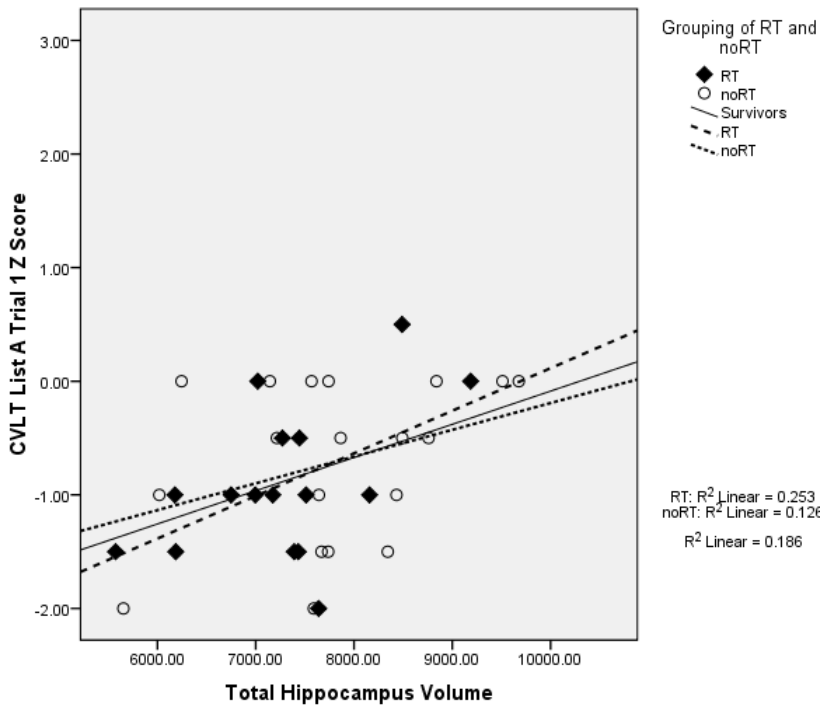


Figure 3. Scatterplots: A) Control group B) Survivor group. Volume are in cubic millimeters.

Appendix
Survivor Recruitment

