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RESEARCH ARTICLE

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Smaller hippocampal subfield volumes predict verbal associative memory in pediatric brain tumor survivors

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Abstract

The developing hippocampus is highly sensitive to chemotherapy and cranial radiation treatments for pediatric cancers, yet little is known about the effects that cancer treatents have on specific hippocampal subfields. Here, we examined hippocampal subfield volumes in 29 pediatric brain tumor survivors treated with cranial radiation and chemotherapy, and 30 healthy developing children and adolescents. We also examined associations between hippocampal subfield volumes and short-term verbal memory. Hippocampal subfields (Cornus Ammonis (CA) 1, CA2-3, dentate gyrus (DG)-CA4, stratum radiatum—lacunosum—moleculare, and subiculum) were segmented using the Multiple Automatically Generated Templates for Different Brains automated segmentation algorithm. Neuropsychological assessment of short-term verbal associative memory was performed in a subset of brain tumor survivors ($N = 11$) and typically developing children ($N = 16$), using the Children's Memory Scale or Wechsler's Memory Scale—third edition. Repeated measures analysis of variance showed that pediatric brain tumor survivors had significantly smaller DG-CA4, CA1, CA2-3, and stratum radiatum-lacunosum-moleculare volumes compared with typically developing children. Verbal memory performance was positively related to DG-CA4, CA1, and stratum radiatum-lacunosum-moleculare volumes in pediatric brain tumor survivors. Unlike the brain tumor survivors, there were no associations between subfield volumes and memory in typically developing children and adolescents. These data suggest that specific subfields of the hippocampus may be vulnerable to brain cancer treatments, and may contribute to impaired episodic memory following brain cancer treatment in childhood.

KEYWORDS
CA1, CA2-3, chemotherapy, craniospinal radiation, DG-CA4

1 | INTRODUCTION

Studies have begun to characterize developmental differences in hippocampal subfields (Daugherty, Bender, Raz, & Ofen, 2016; Krogsrud et al., 2014) and associations with episodic memory (Lee, Ekstrom, & Ghetti, 2014; Tamnes et al., 2014). Although these studies provide important links between hippocampal subfield structure and memory abilities in healthy children and adolescents, less is known about regional effects within the hippocampus in the injured developing brain. Instead, the majority of clinical studies in children have measured the hippocampus as a single region, rather than examining its various subfields (Beauchamp et al., 2008; Frodl, 2010; Isaacs et al., 2000; MacMaster et al., 2008; Riggs et al., 2014). Importantly, studies suggest that mature hippocampal subfields are differentially vulnerable to various neurological conditions (Kerchner et al., 2012; Pereira et al., 2013, 2014). Like the mature hippocampus, the developing hippocampus may exhibit age—and region—specific responses to neurological conditions and injuries. Therefore, evaluating regional vulnerabilities is important for understanding early hippocampal pathology.

Previous research suggests that the developing brain is highly sensitive to cranial radiation (CR) and chemotherapy treatments for central nervous system cancers. Both chemotherapy and CR are linked to

altered white matter microstructure (de Blank, Berman, & Fisher, 2016; (Deprez et al., 2012) Moxon-Emre et al., 2016), altered hippocampal function (Cheng et al., 2017; Monje et al., 2013), and smaller hippocampal volumes (Kesler et al., 2013; Nagel et al., 2004; Riggs et al., 2014). Smaller hippocampal volumes after CR and chemotherapy are unrelated to smaller overall brain volumes (Riggs et al., 2014), suggesting that the developing hippocampus may be particularly vulnerable to treatments. In addition to hippocampal abnormalities, pediatric brain tumor survivors (PBTS) treated with CR and chemotherapy exhibit episodic memory deficits for both verbal and visual information (Mabbott et al., 2011; Nagel et al., 2006; Riggs et al., 2014). Although few attempts have been made to correlate smaller hippocampal volumes with impaired episodic memory, we previously found a relationship between smaller right hippocampal volumes and memory performance in PBTS (Riggs et al., 2014). However, in this study, as in other prior studies in PBTS, the hippocampus was assessed as a single region, without examining its distinct subfields.

Neuroanatomically, the hippocampus is comprised of the Cornus Ammonis (CA; further divided into CA1, CA2, CA3, and CA4), the dentate gyrus (DG), and the subiculum (Duvernoy, 2005). The CA is formed of thin parallel stacked layers including the stratum pyramidal, stratum radiatum, stratum lacunosum, and stratum moleculare (Duvernoy, 2005). Developmental studies suggest that these distinct hippocampal regions exhibit unique developmental trajectories (Daugherty et al., 2016; Jabès, Lavenex, Amaral, & Lavenex, 2011; Tamnes et al., 2014). For example, the CA2 and subiculum are more volumetrically mature earlier in development than the DG and CA3. Interestingly, cross-sectional studies have reported positive associations between age and CA1, CA3 and DG volumes until ~13 years of age (Krogsrud et al., 2014; Lee et al., 2014) and one of these also found positive age-related differences in the subiculum (Krogsrud et al., 2014). In contrast, longitudinal studies report age-related declines in CA1, CA3, and DG volumes across adolescence (Daugherty et al., 2016; Tamnes et al., 2014). Studies also suggest different developmental trajectories across the anterior–posterior hippocampal axis (DeMaster, Pathman, Lee, & Ghetti, 2014; Gogtay et al., 2006; Riggins, Blankenship, Mulligan, Rice, & Redcay, 2015). For example, Gogtay et al. (2006) found age-related increases in posterior and decreases in anterior hippocampal volumes overtime.

In addition to exhibiting unique maturational trajectories, hippocampal subfields are implicated in different aspects of memory processing. Neuroimaging studies in adults suggest that the DG and CA3 are involved in encoding, memory precision and short-term retrieval, and the CA1 and subiculum in intermediate and long-term retrieval (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Mueller, Chao, Berman, & Weiner, 2011; Yassa et al., 2011; Zeineh, Engel, Thompson, & Bookheimer, 2003). Interestingly, developmental work suggests that the maturation of distinct hippocampal regions coincides with the development of different forms of episodic memory in children (Jabès et al., 2011; Lavenex & Banta Lavenex, 2013). One study in children and adolescents found larger right CA3-DG and subiculum volumes were related to accurate memory for item-color associations (Lee et al., 2014), and another found positive associations between delayed recall and CA1 and combined CA2–3 volumes (Tamnes et al., 2014). Given regional variations in hippocampal development and function, it is critical to examine how immature hippocampal subfields are affected following cancer treatments in childhood.

Despite the known vulnerability of the developing hippocampus to cancer treatments, no previous study has assessed *regional* vulnerabilities in specific hippocampal subfields in humans in vivo. However, both post-mortem human and animal studies suggest that the DG may be particularly vulnerable. One human postmortem study (Monje et al., 2007) showed significant decreases in DG neurogenesis, even decades following CR and chemotherapy. In rodents, radiation decreases DG volumes (de Guzman et al., 2015; Hellström, Björk-Eriksson, Blomgren, & Kuhn, 2009) and neurogenesis (Madsen, Kristjansen, Bolwig, & Wörtwein, 2003; Monje, Mizumatsu, Fike, & Palmer, 2002; Raber et al., 2004). These findings highlight the importance of examining how cancer treatments affect regional hippocampal structure.

The goal of this study was to assess the effects of CR and chemotherapy on developing hippocampal subfields. We first compared hippocampal subfield volumes in a cohort of PBTS ($N = 29$) to typically developing children and adolescents (TDC; $N = 30$). Hippocampal subfield segmentations were performed using an automated segmentation algorithm, Multiple Automatically Generated Templates (MAGeT; Chakravarty et al., 2013; Pipitone et al., 2014), in conjunction with high resolution 3T hippocampal subfield atlases (Winterburn et al., 2013). These tools produce subfield segmentations across the entire hippocampal longitudinal axis. Based on findings from animal literature and post-mortem human data that the DG is highly vulnerable to radiation, we hypothesized that PBTS would have smaller DG volumes than TDC.

A second goal of our study was to assess the relationship between hippocampal subfields and demographic and medical variables. For PBTS, we measured subfield volume associations with age, sex, diagnosis age, and time since diagnosis, and for TDC, we assessed associations with age and sex. It was hypothesized that there would be a quadratic relationship between age and subfield volumes in TDC, based on cross-sectional studies showing positive associations between hippocampal subfield volumes and age in childhood (Krogsrud et al., 2014; Lee et al., 2014), and longitudinal studies showing decreases in subfield volumes in adolescence (Daugherty et al., 2016; Tamnes et al., 2014); however, we predicted that this relationship would be absent in PBTS, owing to disrupted volumetric development.

An exploratory aim of this study was to assess whether smaller hippocampal subfield volumes in PBTS were related to lower memory performance. Short-term verbal associative memory was assessed using a word pair task from the Children's Memory Scale (CMS) or the Wechsler's Memory Scale—third edition (WMS-III) in a subset of PBTS ($N = 11$) and TDC ($N = 16$) on the same day as their MRI scan. Two previous studies have reported associations between hippocampal subfield volumes and memory performance in children and adolescents (Lee et al., 2014; Tamnes et al., 2014). However, one of these studies limited segmentations to the hippocampal body (Lee et al., 2014). The

other (Tamnes et al., 2014) found non-significant relationships between subfield volumes and short-term memory, but that longitudinal volume declines overtime in CA2–3 and DG-CA4 predicted learning. Importantly, in healthy children and adolescents, larger whole hippocampal volumes are infrequently related to better memory (Van Petten, 2004). Since we segmented the entire hippocampal longitudinal axis using cross-sectional data, we had no specific hypotheses for the TDC group. However, in clinical populations with known hippocampal pathology, larger hippocampal volumes frequently predict better memory (Barber, McKeith, Ballard, Gholkar, & O'Brien, 2001; de Toledo-Morrell et al., 2000; Giménez et al., 2004; Riggs et al., 2014; Yee, Hannula, Tranel, & Cohen, 2014). Therefore, we hypothesized that hippocampal subfield volumes that were smaller in PBTS compared with TDC would correlate with episodic memory performance. Although verbal memory lateralization is not present in all individuals (Catani et al., 2007), lesion studies in adults (Saling et al., 1993) and children with epilepsy (Gleissner et al., 2002; Leunen et al., 2009) suggest that the left hemisphere plays a particularly important role in verbal memory in most individuals (for a review, see Saling, 2009; Willment & Golby, 2013). Based on this research, we expected that the left hippocampal subfields would have stronger associations with verbal memory in PBTS than the right subfields.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-nine PBTS treated with CR and 30 TDC participated as part of three larger studies between 2009 and 2016 at the Hospital for Sick Children in Toronto, Canada. The PBTS had been treated for medulloblastoma ($N = 26$), pineoblastoma ($N = 2$) and ependymoma ($N = 1$). Twenty of the PBTS had a tumor located in the cerebellum, 7 in the posterior fourth ventricle, one in the posterior third ventricle, and one around the pineal region. Despite the heterogeneity of tumor location, all PBTS were treated with whole brain CR, and all except for two received chemotherapy. All PBTS were treated on standardized protocols with a fixed duration of treatment for chemotherapy and radiotherapy. The only differences in disease severity amongst patients were whether they relapsed, and required additional treatment. Participant demographic and medical information is detailed in Table 1.

Participants or a parent (where applicable) provided written informed consent. The PBTS were identified through a database review and recruited during a clinic visit to the hospital, or through letter mailings. The TDC were recruited through hospital advertisements, or through families of PBTS. The PBTS were considered eligible if they were diagnosed with a brain tumor at least one year prior to participation, had been treated with CR, were not receiving palliative care or treatment for recurrent disease, and had no pre-morbid history of neurological disorder or learning disability. The two groups did not differ with respect to sex ($\chi^2_{[1]} = 0$, $p = 1$), handedness ($\chi^2_{[1]} = 0.19$, $p = .67$), age (t [56.6] $= -0.03$, $p = .98$) or years of parental education (Mother: (t [40.85] $= -1.43$, $p = .16$); Father: (t [38.43] $= -1.09$, $p = .28$).

TABLE 1 Participant demographic and medical information

Parameter	PBTS ($N = 29$)	TDC ($N = 30$)
Sex (Male:Female [No.])	17:12	17:13
Age at assessment (years)	12.95 ± 3.75	12.92 ± 3.55
Handedness (Right:Left)	24:5	27:3
Full Scale IQ	86 ± 17.2	
Parental Education (years)[a]		
Mother	15.44 ± 2.17	16.52 ± 2.87
Father	15.64 ± 3.59	16.57 ± 2.02
Age at diagnosis (years)	6.19 ± 2.31	
Range	2.3 – 11.6	
Time since diagnosis to assessment (years)	6.75 ± 3.64	
Range	1.15 – 14.65	
Tumor Location		
Cerebellum	20	
Fourth ventricle	7	
Posterior third ventricle	1	
Pineal region	1	
Extent of surgical resection		
>95% of the tumor resected	24	
Between 50 and 95% of the tumor resected	4	
Biopsy	1	
Number of resections		
1	26	
2	2	
3	1	
Chemotherapy (No.)[b]	27	
Number of Recurrences		
0	26	
1	2	
2	1	

Note: Sample means ± SDs are shown. Tests used to assess intellectual functioning in PBTS included the Wechsler Abbreviated Scale of Intelligence, Wechsler Adult Intelligence Scale (ed 4), Wechsler Intelligence Scale for Children (ed. 4), and the Stanford Binet (ed. 5). IQ data was collected between 0 and 18 months of study participation and was available for 23 of the 29 PBTS.

[a]Data on the number of years of parental education for both mother and father was missing in 4 PBTS and 7 TDC.

[b]Chemotherapy agents included various combinations of Cisplatin, Cyclophosphamide, Vincristine, Lomustine, Etoposide, Amifostine.

2.2 | Image acquisition

T1-weighted MR images were acquired for each participant at the Hospital for Sick Children using a Siemens 3T whole body scanner with a 12-channel head coil. Images were acquired using a 3D magnetization prepared rapid acquisition gradient echo sequence (TR/TE = 2300 ms/3.91 ms, inversion time = 900 ms, Flip angle 9°, voxel size = 1 mm isotropic, number of excitations = 1, pixel bandwidth = 240, acquisition matrix = 256 × 224, 160 contiguous axial slices, FOV= 256 × 224 mm).

2.3 | Hippocampal subfield atlases

For the purposes of this study, five high-resolution (0.3 mm isotropic) 3T T1-weighted manually labeled hippocampal subfield atlases were used for segmentation (Winterburn et al., 2013). These atlases have separate labels for the CA1, CA2–3, DG-CA4, and the subiculum in both the left and right hemispheres. In addition, segmentations were produced for the synapse-rich stratum radiatum, lacunosum, moleculare (SRLM) layers of the Cornus Ammonus, which contain dendrites and axonal fasciculi (Amaral & Witter, 1989; Duvernoy, 2005). The subfield segmentations span the length of the hippocampal longitudinal axis and include the head, body and tail regions (Pipitone et al., 2014; Winterburn et al., 2013). To generate the atlas labels, the pyramidal layer of the CA was subdivided into a label for the CA1 and a combined label for CA2–3. The SRLM layers of the CA were segmented into a single label (referred to as "SRLM"). The granule, molecular, and polymorphic layers of the DG were combined into a single label referred to as "DG-CA4". Notably, the polymorphic layer of the DG has been referred to as the "hilus" of the DG and "CA4" (Amaral, Scharfman, & Lavenex, 2007; Scharfman & Myers, 2013). A single label was derived for the subiculum (Winterburn et al., 2013).

2.4 | MAGeT for different brains

Hippocampal subfield segmentation was performed using the MAGeT Brain algorithm (Chakravarty et al., 2013; Pipitone et al., 2014) and were carried out on SciNet (Loken et al., 2010). The hippocampal subfield segmentations produced by MAGeT Brain have previously been validated on 3T images (Chakravarty et al., 2013; Pipitone et al., 2014). This algorithm begins with five high-resolution atlases with manually labeled hippocampal subfields (Winterburn et al., 2013). A subset of MR images in the dataset are specified as "templates". For each template, five candidate labels are generated for each subfield through pairwise template-to-atlas nonlinear registration. For the purposes of this study, the pool of templates included a random selection of 21 images from TDC (mean age = 13.16, 11 female). Once labeled, the 21 templates were matched through pairwise nonlinear registration to each image in the dataset ($N = 59$). This process generated 105 candidate labels for each subfield on each image. The candidate labels were then fused using a "voxel voting" procedure, in which the most commonly occurring label at each voxel was retained to produce a single accurate subfield label. One of the authors (A.L.D.) visually inspected the final segmentations using Display software to verify segmentation quality (Figure 1a–f). All subfield labels adequately covered the hippocampus, and there were no labels appearing in extra-hippocampal areas. No manual edits were made for any segmentation, before we extracted volumetric information for each label. All segmentations were included in the final analysis.

2.5 | Adjusting raw hippocampal subfield volumes for intracranial volumes

Prior to analysis, raw subfield volumes were adjusted for individual differences in intracranial volume (ICV). Measures of ICV were obtained using the functional magnetic resonance imaging of the brain Software Library (FSL) Brain Extraction Tool (Smith, 2002). The FSL Brain Extraction Tool automatically generates an outline that separates the brain from nonbrain tissue on each MR image. This outline was manually corrected, slice-by-slice, in the axial plane. Estimates of ICV for each participant were derived from this outline (Jenkinson, Pechaud, & Smith, 2005). Raw hippocampal subfield volumes were then adjusted for estimates of ICV using a regression approach previously described in Free et al., (1995) and Arndt, Cohen, Alliger, Swayze, & Andreasen, (1991). Specifically, raw subfield volumes in each hemisphere were regressed onto ICV (collapsed across groups). To adjust volumes for ICV, the residual value from the regression (the raw minus the predicted volume for each subfield) was accounted for, in that the variance shared between raw volumes and ICV was removed. This step is critical, because smaller *raw* volumes may reflect smaller overall ICVs in PBTS. In contrast, smaller volumes *after* adjusting for ICV may reflect a particular vulnerability of hippocampal subfields to treatment. In order to ensure reliability of our manual editing procedure for ICV, one of the authors re-segmented ICV for ten participants (five TDC and five PBTS). Reliability of ICV manual editing was assessed using an interclass correlation coefficient, and was high at 0.99.

2.6 | Neuropsychological assessment

A subset of PBTS ($N = 11$) and TDC ($N = 16$) completed assessments of verbal associative memory and information processing speed on the same day as their MRI scan. The processing speed task was used to control for the specificity of the relationship between hippocampal subfield volumes and memory. The PBTS who completed cognitive assessments did not differ from remainder of the PBTS in terms of sex ($\chi^2 = 0.67$, df = 1, $p = .41$), diagnosis age (t [19.63] = −0.83, $p = .42$), time since diagnosis (t [18.28] = −1.50, $p = .15$), or hippocampal subfield volumes (left, right, or bilateral; $ps > .08$). However, those PBTS who completed memory testing were older on average (t [24.95] = 2.27, $p = .03$). The TDC who completed memory and processing speed assessments were no different from the rest of the TDC in terms of age (t [26.01] = 1.31, $p = .2$), sex ($\chi^2 = 0.18$, $P = 0.68$), or hippocampal subfield volumes (left, right, and bilateral; $ps > .56$). See Supporting Information Table S1 for a description of the demographic and medical information for the subset of PBTS and TDC who completed cognitive assessments.

To assess verbal associative memory, the word-pairs subtest of the CMS was administered to children aged 8 to 16 years (PBTS: $N = 6$, TDC: $N = 13$) and the Verbal Paired Associates 1 from the WMS–III to children aged > 16 years (PBTS: $N = 5$, TDC: $N = 3$). In these tasks, a list of word pairs (e.g., truck-arrow) was read to participants. Immediately after, the first word of each word pair (e.g., "truck") was read, and participants had to recall the corresponding second word pair from memory (e.g., "arrow"). If a participant could not recall the correct word pair, the correct word was stated by the experimenter. This process was repeated for a total of three times for the CMS and four times for the WMS–III. We derived *raw learning* scores from the CMS, and *raw immediate recall* scores from the WMS–III, based on the

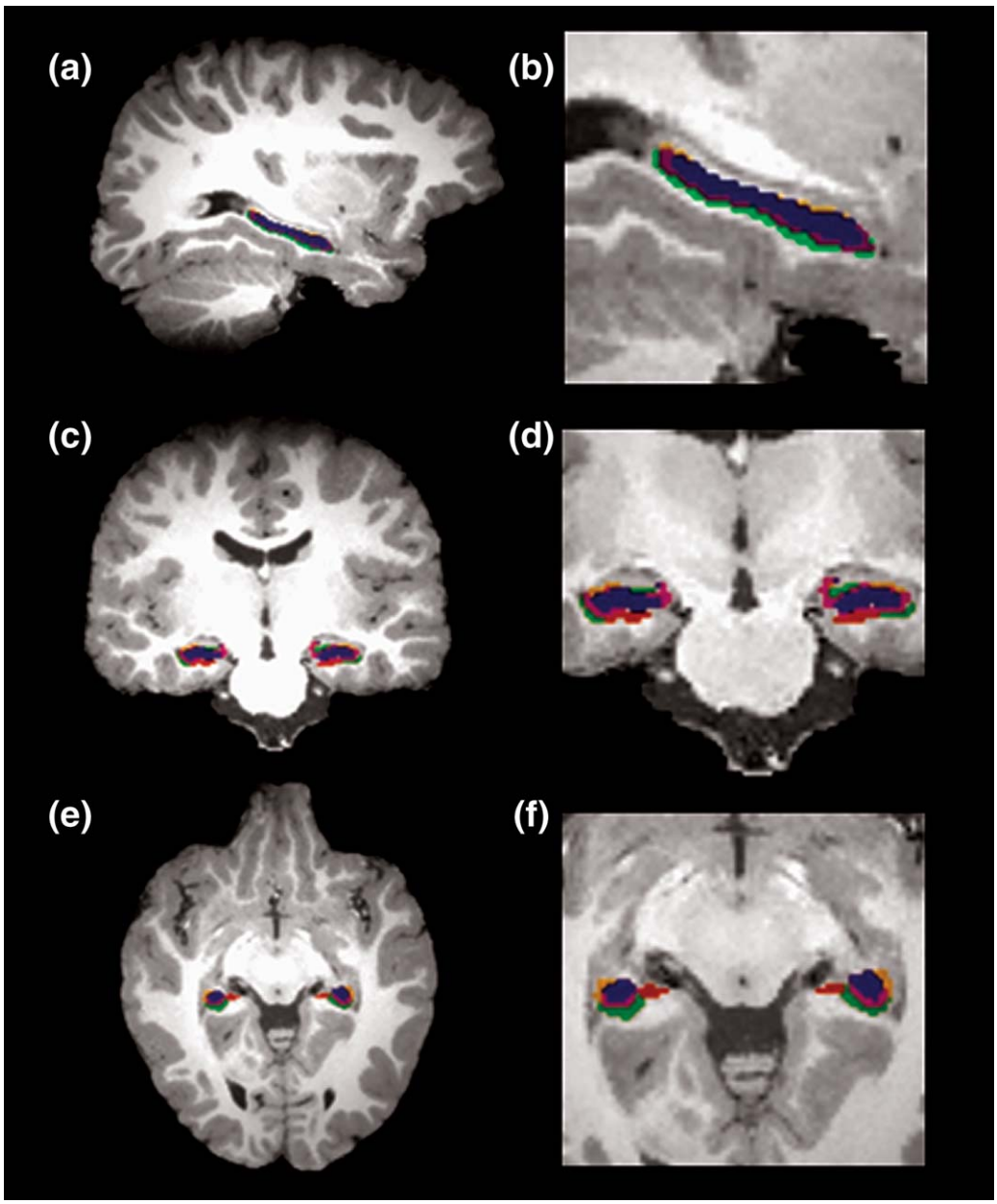

FIGURE 1 Hippocampal subfield segmentations using MAGeT Brain shown in right sagittal (a,b), coronal (c,d), and axial (e,f) views for a representative subject. Subfields are represented in different colors in MNI space as follows: dark blue, DG/CA4; pink, SRLM; green, CA1; orange, CA2/3; red, Subiculum.

number of correctly recalled words over the course of the trials. We acknowledge that the number of trials, and number and types of words differed between the tasks. To account for these differences, participants' raw scores were converted into scaled scores prior to being included in the analysis. Since both tasks were designed to test the same mnemonic function (i.e., short-term verbal associative memory), normalizing raw scores into scaled scores may provide means to overcome the task differences. Despite the differences, analogous index scores, calculated based on performance across multiple subtests on the CMS and WMS–III, are highly correlated (Cohen, 1997).

The visual matching subtest of the Woodcock Johnson—third edition (WJ–III) was used to measure information processing speed. Participants were asked to locate and circle two identical numbers in a row of 6 numbers, with 60 rows of numbers in total. Participants were given 3 min to circle as many identical number pairs as possible. A raw score was calculated based on the number of correctly circled number pairs. Raw scores were converted into scaled scores for statistical analysis.

In addition to processing speed, full scale and verbal IQ in PBTS were used to test the specificity of the relationship between memory and hippocampal subfield volumes. IQ data was collected between 0 and 18 months from the time of study participation. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence, Wechsler Intelligence scale for Children (ed. 4), or the Wechsler Adult

Intelligence Scale (ed. 4). IQ data were available for 10 of the 11 PBTS in the subsample and is reported in Table 4.

2.7 | Statistical analyses

All statistical analyses were conducted using R statistical software (R Core Team, 2013). We first tested whether ICVs and subfield volumes had distributions allowing for parametric statistics. We used a Shapiro Wilk's test to examine assumptions of normality, a Fisher's *F*-test to examine homogeneity of variance, and a Mauchley's test to evaluate sphericity in our repeated measures ANOVA. Assumptions of normality were met for intracranial and subfield volumes in both groups (groups were examined both separately and together). The homogeneity of variance assumption was violated for ICV (F [28, 29] = 2.17, $p = .04$) and SRLM volumes (F [28, 29] = 2.1, $p = .05$). Therefore, a Welch *t*-test for unequal variances was used to examine group differences in ICVs. Similarly, post hoc testing for group differences in SRLM volumes were done using Welch *t* tests.

To quantify whether there were group differences in subfield volumes, we used a repeated measures ANOVA, with group (PBTS, TDC) as the between subject factor, and hemisphere (right, left) and subfield (CA1, CA2–3, DG-CA4, SRLM, subiculum) as within subject factors. A mauchley's test revealed that the sphericity assumption was violated for subfields in the repeated measures ANOVA, and therefore Greenhouse-Geisser corrected values are reported. Paired *t* tests with Bonferroni correction were used to test significant interactions and *p*-values $\leq .05$ were considered statistically significant. Cohen's *d* effect sizes were calculated to characterize the magnitude of group differences in subfield volumes. Based on previously reported effect sizes for group differences in whole hippocampal volumes ($\eta_p^2 = 0.16$; Riggs et al., 2014), our sample size enables us to have a power of at least 80% to detect group differences in subfields (alpha of 0.05, two tailed), assuming that similar group differences are present in the hippocampal subfields.

A second analysis was carried out to assess the effects of demographic (age and sex) and medical variables (age at diagnosis, time since diagnosis) on hippocampal subfield volumes (each group assessed separately). We examined sex differences using post hoc *t* tests, instead of including sex as a covariate in our main model, because existing studies do not report sex differences in whole hippocampal volumes in PBTS (Riggs et al., 2014). Pearson's *r* correlations were used to evaluate the relationship between subfield volumes and age at diagnosis and time since diagnosis. To examine age effects, both quadratic and linear models were tested. *p*-values were adjusted for the family-wise error rate (i.e., the number of independent tests conducted for demographic and medical variables), using false discovery rate correction. Contrasts surviving 5% false discovery rate correction were considered significant.

Last, we evaluated whether subfield volumes were related to verbal memory, and processing speed in the subset of PBTS ($N = 11$) and TDC ($N = 16$) who completed cognitive testing. We also evaluated whether verbal and full scale IQ were related to subfield volumes in PBTS. Pearson's r correlations were used to evaluate relationships between bilateral hippocampal subfield volumes and cognitive performance for each group separately. Out of concern that the left hippocampus may play a greater role in verbal memory than the right hippocampus (Nagel, Herting, Maxwell, Bruno, & Fair, 2013), we also tested associations between verbal memory and left and right hippocampal subfields separately. Given our limited sample size for this analysis, we report bias-corrected and accelerated (BCA) bootstrapped 95% CIs for the memory—volume correlations based on 5,000 bootstrap replicates. Additionally, to assess whether verbal memory was lateralized to the left hippocampus, we compared the strength of the memory—volume correlations for analogous left and right subfields using a Steiger's *Z* test. If verbal memory were lateralized to the left hippocampus, we would expect stronger correlations between memory and left hippocampal subfield volumes.

Only one existing paper has examined relations between memory performance and hippocampal volumes in PBTS (Riggs et al., 2014). This article reported a strong relationship between right hippocampal volumes and the general index of learning and memory from the CMS ($r = 0.71$; Riggs et al., 2014). Based on this effect size, our expected power with our sample of 11 PBTS is reasonably high (>0.75, alpha < 0.05, two tailed). However, since the previously reported study included a small number of PBTS ($N = 10$; Riggs et al., 2014), and because of our small sample ($N = 11$), this analysis is considered purely exploratory, and should be interpreted with caution.

3 | RESULTS

3.1 | Group differences in ICV

Although PBTS had smaller ICVs than TDC, the difference was nonsignificant (t [1,57] = 1.29, $p = .26$).

3.2 | Group differences in hippocampal subfield volumes

The repeated measures ANOVA with Greenhouse Geisser correction revealed a significant main effect of group (F [1, 57] = 19.07; $P \leq .001$), subfield (F [2.72, 154.95] = 2,431, $P \leq .001$, $\varepsilon = 0.68$), and hemisphere (F [1, 57] = 9.70, $p = .003$). There was also a significant subfield × group interaction (F [2.72, 154.81] = 3.94, $p = .01$, $\varepsilon = 0.68$), and subfield × hemisphere interaction (F [2.42, 137.94] = 20.48, $p < .001$, $\varepsilon = 0.61$), but no significant group × subfield × hemisphere interaction (F [2.42, 137.94] = 0.90; $p = .42$, $\varepsilon = 0.61$). Post hoc *t* tests revealed that the significant group × subfield interaction was driven by smaller volumes in PBTS compared with TDC in bilateral DG-CA4 (t [53.23] = −2.98, $p = .02$, $d = 0.78$, M difference = 95 mm^3), CA1 (t [56.59] = −2.93, $p = .02$, $d = 0.76$, M difference = 90 mm^3), SRLM (t [49.40] = −4.86, $p \leq .001$, $d = 1.27$, M difference = 135 mm^3), and CA2–3 (t [55.07] = −3.61, $p \leq .01$, $d = 0.94$, M difference = 47 mm^3; Figure 2a–d). Although PBTS had smaller subiculum volumes than TDC, this difference was nonsignificant (t [56.60] = −2.32, $p = .12$, $d = 0.60$, M difference = 44 mm^3; Figure 2e). Post hoc *t*-tests to investigate the subfield × hemisphere interaction revealed larger right than left CA1 (t [115.42] = −3.73, $p = .001$) and CA2–3 volumes

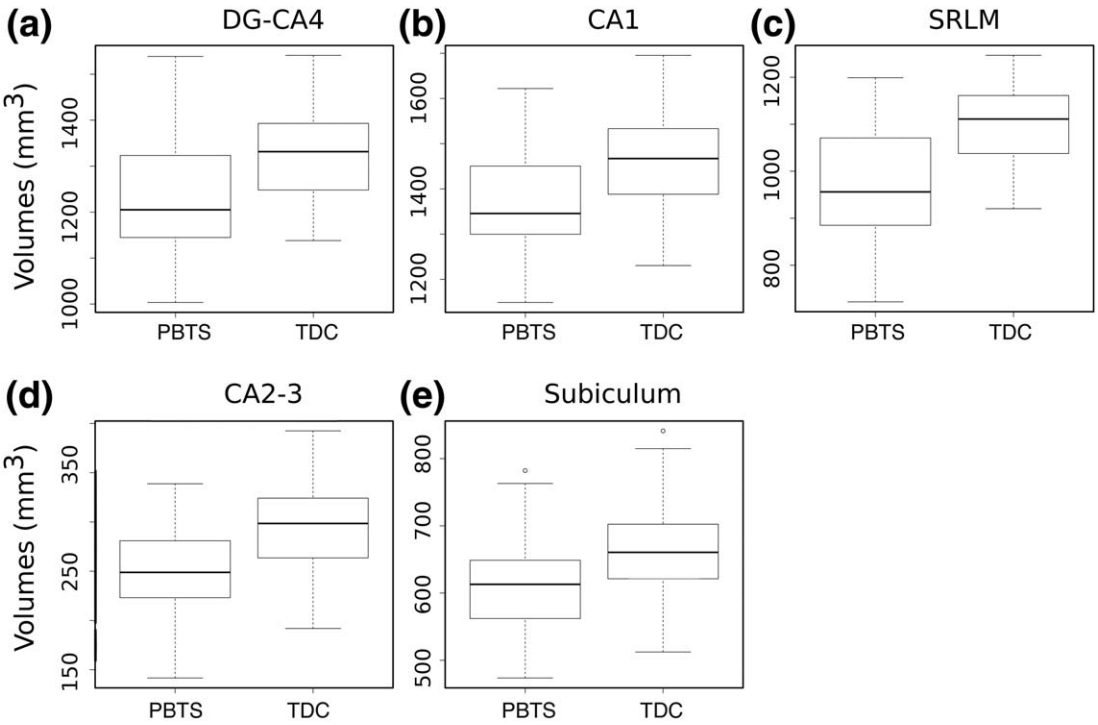

FIGURE 2 Group differences in bilateral hippocampal subfield volumes in pediatric brain tumor survivors (PBTS) and typically developing children (TDC). All subfield volumes were corrected for ICV prior to being analyzed (see text for details). The PBTS had significantly smaller bilateral DG-CA4 (a), CA1 (b) SRLM (c) and CA2–3 volumes (d) than TDC ($ps < .05$). Group differences in subiculum volumes were nonsignificant (e), but were in the expected direction, in that PBTS had smaller volumes than TDC ($p = .12$). Bonferroni corrected *p*-values are reported

(t [112.57] = −4.66, $p < .001$). For the remaining subfields, there were nonsignificant volume differences between analogous subfields in the two hemispheres ($ps > .19$).

3.3 | Demographic and medical predictors of hippocampal subfield volumes

Results from statistical tests involving demographic and medical variables are presented in Table 2. Given the absence of a significant group × subfield × hemisphere interaction, analyses were performed on bilateral subfield volumes. Bilateral subfield volumes were calculated by summing corresponding subfield volumes in the left and right hemispheres. There were no sex differences in subfield volumes for either group. There were nonsignificant quadratic effects of age on subfield volumes for both groups (see supporting information Table S2). Therefore, we report only linear effects of age (Table 2). In TDC, there was a significant positive linear relationship between subiculum volumes and age ($r = 0.42$, $p < .01$, $q = 0.02$), but no other subfields were related to age in TDC. In PBTS, age was positively related to SRLM ($r = 0.52$, $p < .01$, $q = 0.02$) and subiculum volumes ($r = 0.48$, $p \leq .01$, $q = 0.04$; Figure 3a,b). Diagnosis age in PBTS was positively related to CA1 ($r = 0.53$, $p < .01$, $q = 0.02$), CA2–3 ($r = 0.59$, $p < .01$, $q < 0.01$), and SRLM volumes ($r = 0.68$, $p < .01$, $q < 0.01$; Figure 4a–c), and marginally related to DG-CA4 volumes ($r = 0.43$, $p = .02$, $q = 0.07$). Since diagnosis age and age at assessment were marginally correlated ($r = 0.35$, $p = .06$), we repeated the analysis examining correlations between subfield volumes and diagnosis age after controlling for age at assessment. After controlling for age, the effects of diagnosis age remained the same for all subfields except for the subiculum, which became negatively correlated with diagnosis age ($r = -0.51$, $p < .01$, $q < 0.04$). Time since diagnosis in PBTS was only related to subiculum volumes ($r = 0.66$, $p < .01$, $q < 0.01$).

3.4 | Do hippocampal subfield volumes predict verbal associative memory performance in TDC?

Table 3 contains raw and scaled verbal memory scores for TDCs who completed memory testing. In TDC, there were no significant relationships between hippocampal subfield volumes (left, right, or bilateral), and memory performance or processing speed ($ps > .21$).

3.5 | Do hippocampal subfield volumes predict verbal associative memory performance in PBTS?

Table 4 contains raw and scaled verbal memory scores, full scale IQ, and verbal IQ for PBTS who completed memory testing. In PBTS, there was a significant positive relationship between memory performance and bilateral volumes in CA1 ($r = 0.71$, $p = .01$, 95% BCa [−0.08, 0.92]), DG-CA4 ($r = 0.64$, $p = .03$, 95% BCa [−0.34, 0.87]), and SRLM ($r = 0.61$, $p = .04$, 95% BCa [−0.20, 0.82]; Figure 5a–c), and a marginally significant relationship with CA2–3 volumes ($r = 0.55$, $p = .08$, 95% BCa [−0.19, 0.95]). Subiculum volumes were unrelated to memory

TABLE 2 Summary of results from statistical tests involving demographic and medical variables

Variable	Group	Structure	*r* value	*P* value	*q* value
Age	TDC	DG-CA4	0.33	.08	0.23
		CA2–3	0.10	.61	0.85
		CA1	0.05	.81	0.95
		SR-L-M	0.09	.62	0.85
		Subiculum	0.42	<.01	0.02*
Age	PBTS	DG-CA4	0.31	.11	0.26
		CA2–3	0.38	.04	0.15
		CA1	0.32	.09	0.26
		SR-L-M	0.52	<.01	0.02*
		Subiculum	0.48	<.01	0.04*
Sex	TDC	DG-CA4	0.15	.43	0.81
		CA2–3	−0.03	.88	0.95
		CA1	−0.04	.85	0.95
		SR-L-M	−0.09	.65	0.85
		Subiculum	−0.02	.93	0.95
Sex	PBTS	DG-CA4	0.1	.61	0.85
		CA2–3	−0.24	.21	0.45
		CA1	0.14	.48	0.85
		SR-L-M	−0.18	.37	0.74
		Subiculum	−0.1	.61	0.85
Age at diagnosis	PBTS	DG-CA4	0.43	.02	0.07.
		CA2–3	0.59	<.01	<0.01*
		CA1	0.53	<.01	0.02*
		SR-L-M	0.68	<.01	<0.01*
		Subiculum	−0.25	.19	0.44
Time since diagnosis	PBTS	DG-CA4	0.04	.83	0.95
		CA2–3	0.02	.93	0.95
		CA1	−0.01	.95	0.95
		SR-L-M	0.1	.61	0.85
		Subiculum	0.66	<.01	<0.01*

Note: * Indicates significance after 5% FDR correction ($q < 0.05$).

performance ($r = -0.05$, $p = .89$, 95% BCa [−0.82, 0.74]). Processing speed, full scale and verbal IQ were unrelated to bilateral hippocampal subfield volumes ($ps > .39$).

We also observed significant positive correlations between memory performance and left DG-CA4 ($r = 0.70$, $p = .02$, 95% BCa [−0.26, 0.95]) and left SRLM volumes ($r = 0.59$, $p = .05$, 95% BCa [−0.41, 0.93]). Left CA1 volumes ($r = 0.58$, $p = .06$, 95% BCa [−0.45, 0.95]) were marginally associated with memory performance. Left subiculum ($r = 0.39$, $p = .23$, 95% BCa [−0.93, 0.69]) and CA2–3 volumes ($r = 0.50$, $p = .12$, 95% BCa [−0.32, 0.96]) were unrelated to memory. There were no relationships between right hippocampal subfield volumes and verbal memory (all $ps > .13$). Although we observed correlations with the left, but not right hemisphere subfields, the Steiger's Z test revealed that the magnitude of memory–volume relationships did not differ significantly between the analogous subfields in the two hemispheres ($ps > .17$). Finally, neither full scale IQ, verbal IQ, nor processing speed were related to left or right subfield volumes ($ps > .31$).

Two of the PBTS in our memory/volume analysis had particularly low IQs (<60; Table 4). Therefore, we reran all analyses excluding these two participants and using the remaining nine participants in our subsample. Although the relationships between subfield volumes and memory remained in the expected positive direction, the relationships were no longer significant after excluding these two participants. Notably, all other previous findings related to volume differences and relations with demographic/medical variables remained significant after excluding these two participants.

4 | DISCUSSION

We examined hippocampal subfield volumes in PBTS to assess the effects of chemotherapy and radiation on regional hippocampal development. Our findings showed that PBTS had significantly smaller volumes than TDC in the SRLM, CA1, CA2–3, and DG-CA4. In addition, a younger diagnosis age predicted smaller volumes in CA1, CA2–3, and SRLM. In PBTS, we observed associations between smaller DG-CA4, CA1 and SRLM volumes and poorer short-term verbal associative memory. While these correlations should be interpreted with caution given the small sample ($N = 11$), these memory–volume relationships may suggest that pathology in specific hippocampal subfields contribute to memory impairments in PBTS. Below, we discuss our findings in the context of the vulnerabilities of hippocampal subfields to disease mechanisms that occur in response to brain cancer treatments.

4.1 | PBTS have smaller hippocampal subfield volumes than TDC

We observed that the majority of hippocampal subfields (SRLM, CA1, CA2–3, and DG-CA4) were smaller in PBTS than TDC. As in Riggs et al. (2014), we observed these differences despite correcting for individual differences in ICV, suggesting that these regions may be particularly vulnerable. The largest effect sizes were observed in the SRLM ($d = 1.27$), and the CA2–3 ($d = 0.94$), followed by the DG-CA4 ($d = 0.78$), and CA1 ($d = 0.76$). In the context of the considerable focus placed on understanding the impact of radiation on the DG in animal models (de Guzman et al., 2015; Raber et al., 2004), our data highlights the need to evaluate histology in other subfields.

Our finding for the DG-CA4 is consistent with animal studies that report smaller DG volumes in irradiated rodents (de Guzman et al., 2015; Hellström et al., 2009). Elucidating the cellular determinants of smaller subfield volumes in PBTS is challenging, as few studies have related histological features to hippocampal subfield volumes. However, two prior studies—one in postmortem human tissue (Bobinski

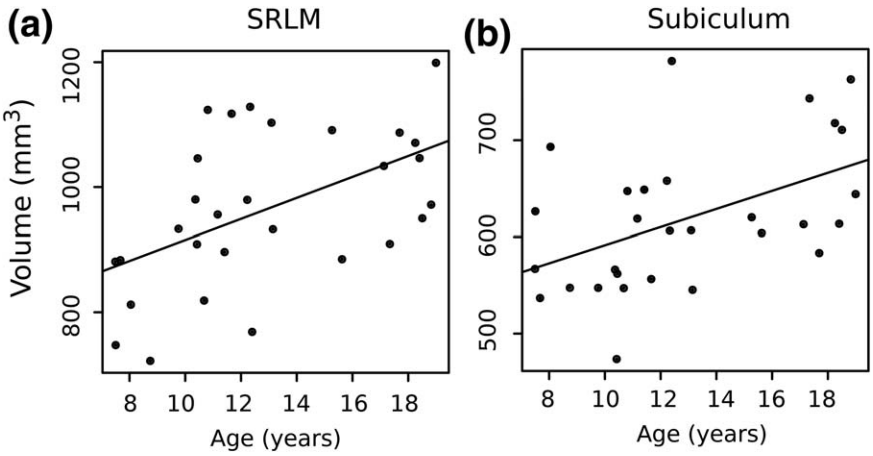

FIGURE 3 The association between age and SRLM and subiculum volumes in PBTS. In PBTS, age was positively correlated with SRLM ($r = 0.52$; a) and subiculum ($r = 0.48$; b) volumes ($ps < .01$, $qs < 0.05$)

et al., 2000) and another in animals (van der Beek et al., 2004)—suggest that fewer DG neurons are correlated with smaller volumes. Moreover, in postmortem animal and human studies, radiation (Monje et al., 2002, 2007) and chemotherapy (Christie et al., 2012; Nokia, Anderson, & Shors, 2012) are linked to apoptosis and reduced neurogenesis in the DG. Based on this research, smaller DG-CA4 volumes in PBTS may reflect increased apoptosis and reduced neurogenesis.

Our data suggest that damage in several subfields contribute to hippocampal pathology following CR and chemotherapy. For instance, we observed smaller CA2–3 volumes in PBTS. The CA2 and CA3 are highly interconnected regions within hippocampal circuitry (Gilbert & Kesner, 2003), and newborn neurons in the DG form synapses with target cells in CA2 and CA3 (Llorens-Martín, Jurado-Arjona, Avila, & Hernández, 2015). In light of previous evidence that radiation alters

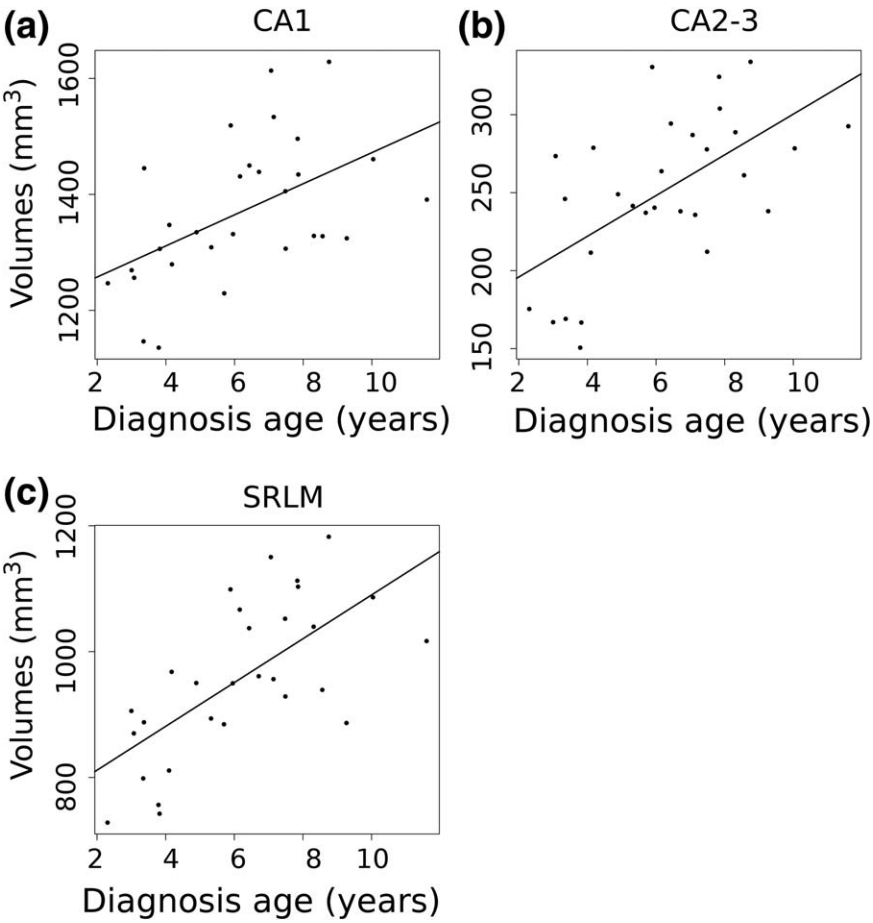

FIGURE 4 The relationship between diagnosis age and subfield volumes in PBTS. Diagnosis age was positively correlated with CA1 ($r = 0.53$; a), CA2–3 ($r = 0.59$; (b) and SRLM volumes ($r = 0.68$; c) in PBTS (ps and $qs < .05$)

TABLE 3 Individual raw and scaled verbal memory scores for the subset of TDC with memory data available

Participant No.	age	CMS raw score	CMS scaled score	WMS raw score	WMS scaled score
1	8.90	23	12	...	...
2	9.05	34	16	...	...
3	10.58	33	15		
4	10.59	38	18	...	...
5	10.94	32	14	...	...
6	11.31	37	16	...	...
7	12.28	21	8		
8	12.33	22	9	...	...
9	14.54	39	15	...	...
10	15.90	35	13	...	...
11	15.90	36	13	...	...
12	16.16	25	8	...	...
13	16.29	...	...	28	12
14	16.90	30	10	...	...
15	18.00	...	...	31	15
16	18.93	...	...	14	7

Scaled scores are adjusted for age and have a mean of 10 and SD of 3. Abbreviations: CMS, Children's Memory Scale; WMS, Wechsler Memory Scale (ed. 3).

dendritic morphology in the hippocampus in rodents (Chakraborti, Allen, Allen, Rosi, & Fike, 2012; Parihar & Limoli, 2013), smaller CA2–3 volumes in PBTS may be evidence of disrupted connectivity in these regions.

We also observed smaller SRLM volumes in PBTS compared with TDC. The SRLM layers of the Cornus Ammonus contain few cell bodies, and are made up of dendrites, axonal fasciculi and synapses that form the basis of hippocampal circuitry (Amaral & Witter, 1989; Duvernoy, 2005). Similar to the CA2–3, radiation-induced alterations to dendritic morphology, complexity, and spine density in the hippocampus (Chakraborti et al., 2012; Parihar & Limoli, 2013) may be a biological mechanism underlying smaller SRLM volumes in PBTS.

A considerable number of studies examining pathology in CA1 highlight its vulnerability to conditions involving vascular pathology and hypoxic ischemia (Gemmell et al., 2012; Hatanpaa et al., 2014). Notably, CR is linked to vascular damage, which has been suggested to lead to hypoxic ischemic injury in the hippocampus (Abayomi, 1996). Although limited work has investigated the vulnerability of CA1 to radiation and chemotherapy, one study has linked radiation exposure in rats to neuronal apoptosis in CA1 (Sun et al., 2013). Future studies that explore the relationship between hippocampal structure and blood flow will help to elucidate how vascular health relates to CA1 volumes following brain cancer treatments.

In contrast to findings in other subfields, group differences in subiculum volumes were nonsignificant. Based on evidence that the subiculum is comparably more mature earlier in development (Jabès et al., 2011), it may be less vulnerable to neurotoxicity.

4.2 | Impact of medical variables on hippocampal subfield volumes

We observed a younger diagnosis age was linked to smaller CA2–3, SRLM, and CA1 volumes, even after controlling for the effects of age. This suggests that older children may display greater resiliency, and younger children, more vulnerability. Time since diagnosis was related only to subiculum volumes, such that greater time since diagnosis

TABLE 4 Individual raw and scaled verbal memory scores, verbal IQ, and full scale IQ for the subset of PBTS with memory data available

Participant No.	age	CMS raw score	CMS scaled score	WMS raw score	WMS scaled score	verbal IQ	Full Scale IQ
1	10.64	16	5			...	...
2	11.65	21	8	...	...	98	87
3	12.29	26	10	...	...	92	84
4	12.32	20	8	...	...	85	86
5	13.08	27	10	...	...	104	94
6	13.18	20	6	...	...	84	85
7	17.11	...	...	18	7	99	88
8	17.3	...	...	8	3	61	58
9	17.67	...	...	29	13	121	94
10	18.33	...	...	20	9	75	53
11	18.8	...	...	22	10	100	95

Scaled scores are adjusted for age and have a mean of 10 and SD of 3.
Note: Tests used to assess intellectual functioning included the Wechsler Abbreviated Scale of Intelligence, Wechsler Adult Intelligence Scale (ed. 4), and the Wechsler Intelligence Scale for Children (ed. 4). IQ data was unavailable for one participant. Abbreviations: CMS, Children's Memory Scale; WMS, Wechsler Memory Scale (ed. 3).

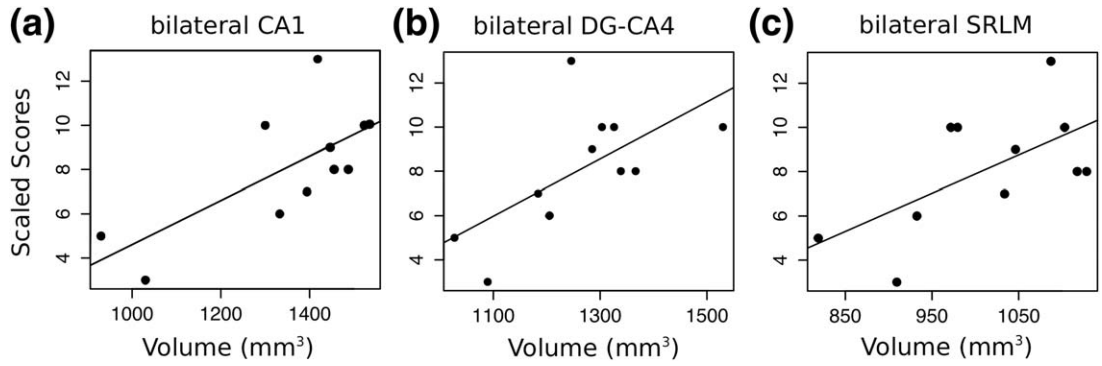

FIGURE 5 The relationship between short-term verbal associative memory performance and hippocampal subfields PBTS. Memory performance scaled scores were significantly related to the volume of bilateral CA1 (a; $r = 0.71$), DG-CA4 (b; $r = 0.64$), and SRLM (c; $r = 0.61$). As this was an exploratory analysis, uncorrected p-values are reported

predicted larger subiculum volumes. Our findings suggest that there may be an age-specific response to treatment-related injury in hippocampal subfields.

4.3 | Impact of age and sex on hippocampal subfield volumes in TDC

We observed non-significant sex differences in hippocampal subfield volumes in TDC. These findings are consistent with one prior longitudinal study (Daugherty et al., 2016), but conflicts with two studies that found larger subfield volumes in males (Krogsrud et al., 2014; Tamnes et al., 2014).

We used both linear and quadratic models to test associations between subfield volumes and age. However, we only observed positive linear associations between age and subiculum volumes in TDC. Previous research suggests that subiculum myelination continues throughout adolescence (Benes, 1989; Benes, Turtle, Khan, & Farol, 1994), which may contribute to volumetric changes. Our finding for the subiculum is consistent with one prior cross-sectional study that observed larger subiculum volumes in older children until the age of 13 (Krogsrud et al., 2014). In contrast, two other studies found non-significant age differences in subiculum volumes (Daugherty et al., 2016; Lee et al., 2014), whereas a longitudinal study found age-related decreases in the subiculum in adolescence (Tamnes et al., 2014). While we only observed age-related differences in the subiculum, other studies have found developmental differences in other subfields. Two cross-sectional studies observed CA1, CA3, and DG volumes were positively associated with age until approximately 13 years (Krogsrud et al., 2014; Lee et al., 2014). Two longitudinal studies observed linear decreases in the CA1, CA3, and DG across adolescence (Daugherty et al., 2016; Tamnes et al., 2014), and one of these studies found quadratic associations with age (Daugherty et al., 2016). Our discrepant findings may reflect the use of different segmentation protocols that measure subfields at separate points along the length of the anterior/posterior hippocampal axis, and therefore have different definitions of the subfield boundaries. Additionally, our sample size was relatively small compared with previous studies that have sample sizes of > 100 (Daugherty et al., 2016; Krogsrud et al., 2014; Tamnes et al., 2014).

4.4 | Impact of age and sex on hippocampal subfield volumes in PBTS

In PBTS, there were no sex differences in hippocampal subfields volumes. However, a positive linear relationship was observed between age and subiculum and SRLM volumes. Given hippocampal volumes may be influenced by neuronal numbers and neuropil content (Qiu et al., 2013; van der Beek et al., 2004), age-related differences in subfields may reflect histological differences in neuron numbers, dendritic complexity, synaptogenesis and myelination.

4.5 | Positive relationships between hippocampal subfield volumes and memory performance in PBTS but not in TDC

An exploratory aim of this study was to examine whether smaller hippocampal subfield volumes in PBTS predicted memory performance. Because of our small sample size for this analysis (PBTS: $N = 11$; TDC: $N = 16$), this aim was considered purely exploratory and future research will be required to verify our findings. In TDC, there were no associations between memory performance and volumes for left, right or bilateral subfields. This finding conflicts with one prior cross-sectional study that found positive relationships between right CA3-DG volumes and associative memory in 8- to 14-year olds (Lee et al., 2014). However, in this study, segmentations were limited to the hippocampal body, which may contribute to our different results. One other developmental study found positive correlations between long-term memory and CA1 and CA2–3 volumes (Tamnes et al., 2014). Notably, our small sample for this analysis may have contributed to our lack of findings for TDC.

In PBTS, we observed a positive relationship between verbal associative memory performance and CA1, DG-CA4 and SRLM volumes. When we measured left and right subfields separately, only the left SRLM and left DG-CA4 were related to memory performance. However, the strength of the relationship between memory and volumes were not different in the left and right hemispheres. Critically, processing speed, full scale, and verbal IQ were unrelated to smaller subfields in PBTS, suggesting that smaller subfields may be associated with poorer memory abilities, but not lower cognitive ability in general. That

we found memory—subfield volume correlations in PBTS and not TDC may suggest that subfield volume—memory associations are stronger in clinical developmental samples with altered hippocampal structure.

The verbal associative memory task involved learning a list of word pairs, and then using a verbal cue (the first word of a pair) to recall the corresponding word pair from memory. Prior research suggests that successful learning and retrieval depend on several processing mechanisms in the hippocampus. Smaller hippocampal subfield volumes may reflect structural damage that perturbs these processing mechanisms, ultimately impairing memory performance. Some evidence suggests that the DG supports memory precision during encoding (Eldridge et al., 2005; Mueller et al., 2011; Yassa & Stark, 2011; Zeineh et al., 2003). Extrapolating from these findings, smaller DG-CA4 may reflect structural damage that impairs hippocampal function at the level of encoding. This would be expected to result in impaired encoding of word pairs and subsequent poor performance. Animal models of radiation injury show that neurogenesis is perturbed following radiation, and relates to performance deficits on hippocampal-dependent memory tasks (Clelland et al., 2009; Madsen et al., 2003; Raber et al., 2004). These studies provide a highly probable explanation for smaller DG-CA4 volumes in PBTS. Namely, perturbed neurogenesis may play a mechanistic role in encoding deficits in PBTS.

In addition to the DG-CA4, the SRLM may also be important for episodic memory maturation. The SRLM contains dendrites, axonal projections and synapses that constitute the basis of hippocampal connections. Smaller SRLM volumes in PBTS may result from disrupted hippocampal synaptic connectivity. Fewer synapses connecting neurons within and between subfields would be expected to impair hippocampal-dependent memory performance.

We also observed a positive association between CA1 volumes and verbal associative memory in PBTS. Neuro-computational models (Wiskott, Rasch, & Kempermann, 2006) and behavioral (Gilbert, Kesner, & Lee, 2001) studies in animals suggest that CA1 is involved in retrieval processes. Smaller CA1 volumes may therefore reflect damage that impairs retrieval processes on our task. This damage would be expected to manifest as poorer retrieval of word pairs.

Our findings must be considered in light of several limitations. First, in the validation study of MAGeT (Pipitone et al., 2014), the thinner or smaller subfields—SRLM, CA2/3—were less reliably segmented compared with the DG-CA4, CA1, and subiculum. Although not ideal, poorer reliability for thinner or smaller subfields may an inherent issue that is not specific to our segmentation protocol, as lower reliability for CA2–3 is observed in studies that implement different segmentation protocols Van Leemput et al., 2009; Wisse et al., 2016; Yushkevich et al., 2015). However, differences in reliability metrics between subfields are important to consider when interpreting our findings. Second, the hippocampal segmentation procedure employed was validated on standard 3T images in a sample of Alzheimer's disease patients and individuals with psychoses (Pipitone et al., 2014). Therefore, it is unclear whether the segmentations are equally reliable in younger children and adolescents. However, one prior study found negligible differences in the reliability of subfield segmentations across child, adolescent and adult age-groups using two different automated segmentation procedures (Schlichting et al., 2016). These findings suggest that automated segmentation methods validated in adults may be reliably applied to developmental samples. Moreover, the manually labeled atlases that we used were registered to 21 "template" images that were directly drawn from our sample, which were then used to segment the entire dataset. This step helps to minimize segmentation errors resulting from neuroanatomical differences between the atlas and subject images (Pipitone et al., 2014). Third, it would have been ideal to use segmentation procedures that have previously been applied to developmental samples, to more easily compare our findings to other studies. However, two prior developmental studies have used manual segmentations limited to slices in the hippocampal body (Daugherty et al., 2016; Lee et al., 2014), whereas we were interested in examining subfields across the hippocampal longitudinal axis. Although the Van Leemput et al. (2009) protocol has been applied to developmental samples (Krogsrud et al., 2014; Tamnes et al., 2014) and segments across the hippocampal long axis, the validity of its segmentations have been questioned (de Flores et al., 2015; Wisse, Biessels, & Geerlings, 2014). Finally, the Yushkevich et al. (2015) protocol would have been a good alternative, but is computationally expensive and requires a large number of manually segmented atlases. Another limitation of our study is that the cross-sectional design prohibited evaluating changes in hippocampal subfield volumes across development. Employing longitudinal designs to examine hippocampal subfield development is required for assessing changes in volume overtime. Further, memory performance was measured using a word pair task either from the CMS or WMS-III, and these tasks differ in terms of the number of trials and types of word pairs. We addressed this issue by including only scaled scores in our analysis, however, a single standardized memory task would have been ideal. Last, the sample size in the present study was relatively small, particularly for the analysis evaluating memory-volume relationships. Future studies should employ a larger sample size to study the relationship between subfield volumes and memory.

5 | CONCLUSION

We provide novel evidence that developing hippocampal subfields are affected by neurotoxic brain cancer treatments. We observed smaller volumes in PBTS compared with TDC in the DG-CA4, CA1, CA2–3, and SRLM. We also observed that PBTS diagnosed earlier in development had smaller hippocampal subfields compared with those diagnosed later—a finding that suggests age-specific responses to injury. Last, we observed a relationship between short-term verbal associative memory performance and DG-CA4, CA1, and SRLM volumes. This finding suggests that pathology in specific hippocampal subfields may play a mechanistic role in impaired memory in PBTS, though a larger sample size is necessary to confirm this finding.

These findings contribute to a greater understanding of the vulnerability of the developing hippocampal subfields to cranial radiation and chemotherapy. Our findings may help guide targeted interventions designed to promote repair in specific hippocampal subfields. For instance, interventions that are known to increase neurogenesis may promote repair in the DG-CA4. Indeed, evidence suggests that physical

exercise may restore neurogenesis in the irradiated rodent DG (Naylor et al., 2008). Moreover, a recent study found that physical activity increases hippocampal volume in PBTS treated with radiation and chemotherapy (Riggs et al., 2016). Future research should aim to characterize whether different types of interventions, such as exercise and cognitive training, promote widespread repair across the hippocampus or local repair in distinct subfields

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REFERENCES

Abayomi, O. K. (1996). Pathogenesis of irradiation-induced cognitive dysfunction. *Acta Oncologica*, *35*(6), 659–663.

Amaral, D. G., & Witter, M. P. (1989). The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience*, *31*(3), 571–591.

Amaral, D. G., Scharfman, H. E., & Lavenex, P. (2007). The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Progress in Brain Research*, *163*, 3–22.

Arndt, S., Cohen, G., Alliger, R. J., Swayze, V. W., & Andreasen, N. C. (1991). Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Research*, *40*(1), 79–89.

Barber, R., McKeith, I. G., Ballard, C., Gholkar, A., & O'brien, J. T. (2001). A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study. *Dementia and Geriatric Cognitive Disorders*, *12*(3), 198–205.

Beauchamp, M. H., Thompson, D. K., Howard, K., Doyle, L. W., Egan, G. F., Inder, T. E., & Anderson, P. J. (2008). Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain*, *131*(11), 2986–2994.

Benes, F. M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophrenia Bulletin*, *15*(4), 585–593.

Benes, F. M., Turtle, M., Khan, Y., & Farol, P. (1994). Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Archives of General Psychiatry*, *51*(6), 477–484.

Bobinski, M., de Leon, M. J., Wegiel, J., DeSanti, S., Convit, A., Saint Louis, L. A., … Wisniewski, H. M. (2000). The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. *Neuroscience*, *95*(3), 721–725.

Catani, M., Allin, M. P. G., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., & Jones, D. K. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(43), 17163–17168.

Chakraborti, A., Allen, A., Allen, B., Rosi, S., & Fike, J. R. (2012). Cranial irradiation alters dendritic spine density and morphology in the hippocampus. *PLoS ONE*, *7*(7),

Chakravarty, M. M., Steadman, P., van Eede, M. C., Calcott, R. D., Gu, V., Shaw, P., … Lerch, J. P. (2013). Performing label-fusion-based segmentation using multiple automatically generated templates. *Human Brain Mapping*, *34*(10), 2635–2654.

Cheng, H., Li, W., Gong, L., Xuan, H., Huang, Z., Zhao, H., … Wang, K. (2017). Altered resting-state hippocampal functional networks associated with chemotherapy-induced prospective memory impairment in breast cancer survivors. *Scientific Reports*, *7*,

Christie, L.-A., Acharya, M. M., Parihar, V. K., Nguyen, A., Martirosian, V., & Limoli, C. L. (2012). Impaired Cognitive Function and Hippocampal Neurogenesis following Cancer Chemotherapy. *American Association for Cancer Research*, *18*(7), 1954–1965.

Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Fragniere, A., Tyers, P., … Bussey, T. J. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science (New York, N.Y.)*, *325*(5937), 210–213.

Cohen. (1997). *CMS: Children's Memory Scale: Manual*. San Antonio, TX: Psychological Corporation.

Daugherty, A. M., Bender, A. R., Raz, N., & Ofen, N. (2016). Age differences in hippocampal subfield volumes from childhood to late adulthood. *Hippocampus*, *26*(2), 220–228.

de Blank, P. M. K., Berman, J. I., & Fisher, M. J. (2016). Systemic Chemotherapy and White Matter Integrity in Tracts Associated with Cognition Among Children With Neurofibromatosis Type 1. *Pediatric Blood & Cancer*, *63*(5), 818–824.

de Flores, R., La Joie, R., Landeau, B., Perrotin, A., Mézenge, F., de La Sayette, V., … Chételat, G. (2015). Effects of age and Alzheimer's disease on hippocampal subfields: comparison between manual and FreeSurfer volumetry. *Human Brain Mapping*, *36*(2), 463–474.

de Guzman, A. E., Gazdzinski, L. M., Alsop, R. J., Stewart, J. M., Jaffray, D. A., Wong, C. S., & Nieman, B. J. (2015). Treatment age, dose and sex determine neuroanatomical outcome in irradiated juvenile mice. *Radiation Research*, *183*(5), 541–549.

DeMaster, D., Pathman, T., Lee, J. K., & Ghetti, S. (2014). Structural development of the hippocampus and episodic memory: developmental differences along the anterior/posterior axis. *Cerebral Cortex*, *24*(11), 3036–3045.

de Toledo-Morrell, L., Dickerson, B., Sullivan, M. P., Spanovic, C., Wilson, R., & Bennett, D. A. (2000). Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus*, *10*(2), 136–142.

Deprez, S., Amant, F., Smeets, A., Peeters, R., Leemans, A., Van Hecke, W., … Sunaert, S. (2012). Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *30*(3), 274–281.

Duvernoy, H. M. (2005). *The Human Hippocampus*. Berlin/Heidelberg: Springer-Verlag.

Eldridge, L. L., Engel, S. A., Zeineh, M. M., Bookheimer, S. Y., & Knowlton, B. J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(13), 3280–3286.

Free, S. L., Bergin, P. S., Fish, D. R., Cook, M. J., Shorvon, S. D., & Stevens, J. M. (1995). Methods for normalization of hippocampal volumes measured with MR. *American Journal of Neuroradiology*, *16*(4), 637–643.

Frodl, T. (2010). Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *Journal of Psychiatric Research*, *44*(13), 799–807.

Gemmell, E., Bosomworth, H., Allan, L., Hall, R., Khundakar, A., Oakley, A. E., … Kalaria, R. N. (2012). Hippocampal neuronal atrophy and cognitive function in delayed poststroke and aging-related dementias. *Stroke; a Journal of Cerebral Circulation*, *43*(3), 808–814.

Gilbert, P. E., & Kesner, R. P. (2003). Localization of Function Within the Dorsal Hippocampus: The Role of the CA3 Subregion in Paired-Associate Learning. *Behavioral Neuroscience*, *117*(6), 1385–1394.

Gilbert, P. E., Kesner, R. P., & Lee, I. (2001). Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. *Hippocampus*, *11*(6), 626–636.

Giménez, M., Junqué, C., Narberhaus, A., Caldú, X., Salgado-Pineda, P., Bargalló, N., … Botet, F. (2004). Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. *NeuroImage*, *23*(3), 869–877.

Gleissner, U., Sassen, R., Lendt, M., Clusmann, H., Elger, C. E., & Helmstaedter, C. (2002). Pre- and postoperative verbal memory in pediatric patients with temporal lobe epilepsy. *Epilepsy Research*, *51*(3), 287–296.

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., … Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus*, *16*(8), 664–672.

Hatanpaa, K. J., Raisanen, J. M., Herndon, E., Burns, D. K., Foong, C., Habib, A. A., & White, C. L. (2014). Hippocampal sclerosis in dementia, epilepsy, and ischemic injury: differential vulnerability of hippocampal subfields. *Journal of Neuropathology and Experimental Neurology*, *73*(2), 136–142.

Hellström, N. A. K., Björk-Eriksson, T., Blomgren, K., & Kuhn, H. G. (2009). Differential recovery of neural stem cells in the subventricular zone and dentate gyrus after ionizing radiation. *Stem Cells (Dayton, Ohio)*, *27*(3), 634–641.

Isaacs, E. B., Lucas, A., Chong, W. K., Wood, S. J., Johnson, C. L., Marshall, C., … Gadian, D. G. (2000). Hippocampal volume and everyday memory in children of very low birth weight. *Pediatric Research*, *47*(6), 713–720.

Jabès, A., Lavenex, P. B., Amaral, D. G., & Lavenex, P. (2011). Postnatal development of the hippocampal formation: a stereological study in macaque monkeys. *The Journal of Comparative Neurology*, *519*(6), 1051–1070.

Jenkinson, M., Pechaud, M., & Smith, S. (2005). MR-Based Estimation of Brain, Skull and Scalp Surfaces In Presented at the *Int. Conf. on Human Brain Mapping (HBM), Toronto, Canada*

Kerchner, G. A., Deutsch, G. K., Zeineh, M., Dougherty, R. F., Saranathan, M., & Rutt, B. K. (2012). Hippocampal CA1 apical neuropil atrophy and memory performance in Alzheimer's disease. *NeuroImage*, *63*(1), 194–202.

Kesler, S., Janelsins, M., Koovakkattu, D., Palesh, O., Mustian, K., Morrow, G., & Dhabhar, F. S. (2013). Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. *Brain, Behavior, and Immunity*, *30*, (0), S109–S116.

Krogsrud, S. K., Tamnes, C. K., Fjell, A. M., Amlien, I., Grydeland, H., Sulutvedt, U., … Walhovd, K. B. (2014). Development of hippocampal subfield volumes from 4 to 22 years. *Human Brain Mapping*, *35*(11), 5646–5657.

Lavenex, P., & Banta Lavenex, P. (2013). Building hippocampal circuits to learn and remember: insights into the development of human memory. *Behavioural Brain Research*, *254*, 8–21.

Lee, J. K., Ekstrom, A. D., & Ghetti, S. (2014). Volume of hippocampal subfields and episodic memory in childhood and adolescence. *NeuroImage*, *94*, 162–171.

Leunen, D., Caroff, X., Chmura, S., Fohlen, M., Delalande, O., & Jambaqué, I. (2009). Verbal and spatial learning after temporal lobe excisions in children: An adaptation of the Grober and Buschke procedure. *Epilepsy & Behavior*, *16*(3), 534–538.

Llorens-Martín, M., Jurado-Arjona, J., Avila, J., & Hernández, F. (2015). Novel connection between newborn granule neurons and the hippocampal CA2 field. *Experimental Neurology*, *263*, 285–292.

Loken, C., Gruner, D., Groer, L., Peltier, R., Bunn, N., Craig, M. … Zon, (2010). SciNet: Lessons Learned from Building a Power-efficient Top-20 System and Data Centre. *Journal of Physics: Conference Series*, *256*(1), 012026.

Mabbott, D. J., Monsalves, E., Spiegler, B. J., Bartels, U., Janzen, L., Guger, S., … Bouffet, E. (2011). Longitudinal evaluation of neurocognitive function after treatment for central nervous system germ cell tumors in childhood. *Cancer*, *117*(23), 5402–5411.

MacMaster, F. P., Mirza, Y., Szeszko, P. R., Kmiecik, L. E., Easter, P. C., Taormina, S. P., … Rosenberg, D. R. (2008). Amygdala and Hippocampal Volumes in Familial Early Onset Major Depressive Disorder. *Biological Psychiatry*, *63*(4), 385–390.

Madsen, T. M., Kristjansen, P. E. G., Bolwig, T. G., & Wörtwein, G. (2003). Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. *Neuroscience*, *119*(3), 635–642.

Monje, M. L., Mizumatsu, S., Fike, J. R., & Palmer, T. D. (2002). Irradiation induces neural precursor-cell dysfunction. *Nature Medicine*, *8*(9), 955–962.

Monje, M. L., Vogel, H., Masek, M., Ligon, K. L., Fisher, P. G., & Palmer, T. D. (2007). Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies. *Annals of Neurology*, *62*(5), 515–520.

Monje, M., Thomason, M. E., Rigolo, L., Wang, Y., Waber, D. P., Sallan, S. E., & Golby, A. J. (2013). Functional and structural differences in the hippocampus associated with memory deficits in adult survivors of acute lymphoblastic leukemia. *Pediatric Blood & Cancer*, *60*(2), 293–300.

Moxon-Emre, I., Bouffet, E., Taylor, M. D., Laperriere, N., Sharpe, M. B., Laughlin, S., … Mabbott, D. J. (2016). Vulnerability of white matter to insult during childhood: evidence from patients treated for medulloblastoma. *Journal of Neurosurgery. Pediatrics*, *18*(1), 29–40.

Mueller, S., Chao, L., Berman, B., & Weiner, M. (2011). Evidence for functional specialization of hippocampal subfields detected by MR subfield volumetry on high resolution images at 4T. *NeuroImage*, *56*(3), 851–857.

Nagel, B. J., Delis, D. C., Palmer, S. L., Reeves, C., Gajjar, A., & Mulhern, R. K. (2006). Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology*, *20*(1), 105–112.

Nagel, B. J., Herting, M. M., Maxwell, E. C., Bruno, R., & Fair, D. (2013). Hemispheric lateralization of verbal and spatial working memory during adolescence. *Brain and Cognition*, *82*(1), 58–68.

Nagel, B. J., Palmer, S. L., Reddick, W. E., Glass, J. O., Helton, K. J., Wu, S., … Mulhern, R. K. (2004). Abnormal Hippocampal Development in Children with Medulloblastoma Treated with Risk-Adapted Irradiation. *American Journal of Neuroradiology*, *25*(9), 1575–1582.

Naylor, A. S., Bull, C., Nilsson, M. K. L., Zhu, C., Björk-Eriksson, T., Eriksson, P. S., … Kuhn, H. G. (2008). Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(38), 14632–14637.

Nokia, M. S., Anderson, M. L., & Shors, T. J. (2012). Chemotherapy disrupts learning, neurogenesis and theta activity in the adult brain. *The European Journal of Neuroscience*, *36*(11), 3521–3530.

Parihar, V. K., & Limoli, C. L. (2013). Cranial irradiation compromises neuronal architecture in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(31), 12822–12827.

Pereira, J. B., Junqué, C., Bartrés-Faz, D., Ramírez-Ruiz, B., Marti, M.-J., & Tolosa, E. (2013). Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. *Hippocampus*, *23*(8), 720–728.

Pereira, J. B., Valls-Pedret, C., Ros, E., Palacios, E., Falcón, C., Bargalló, N., … Junque, C. (2014). Regional vulnerability of hippocampal subfields to aging measured by structural and diffusion MRI: Effects of Age on Volume, Md, and Fa in Hippocampal Subfields. *Hippocampus*, *24*(4), 403–414.

Pipitone, J., Park, M. T. M., Winterburn, J., Lett, T. A., Lerch, J. P., Pruessner, J. C. … Alzheimer's Disease Neuroimaging Initiative. (2014). Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates. *NeuroImage*, *101*, 494–512.

Qiu, L. R., Germann, J., Spring, S., Alm, C., Vousden, D. A., Palmert, M. R., & Lerch, J. P. (2013). Hippocampal volumes differ across the mouse estrous cycle, can change within 24 hours, and associate with cognitive strategies. *NeuroImage*, *83*, 593–598.

R Core Team (2013). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for statistical computing.

Raber, J., Rola, R., LeFevour, A., Morhardt, D., Curley, J., Mizumatsu, S., … Fike, J. R. (2004). Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiation Research*, *162*(1), 39–47.

Riggins, T., Blankenship, S. L., Mulligan, E., Rice, K., & Redcay, E. (2015). Developmental Differences in Relations Between Episodic Memory and Hippocampal Subregion Volume During Early Childhood. *Child Development*, *86*(6), 1710–1718.

Riggs, L., Bouffet, E., Laughlin, S., Laperriere, N., Liu, F., Skocic, J., … Mabbott, D. J. (2014). Changes to memory structures in children treated for posterior fossa tumors. *Journal of the International Neuropsychological Society: JINS*, *20*(2), 168–180.

Riggs, L., Piscione, J., Laughlin, S., Cunningham, T., Timmons, B. W., Courneya, K. S., … Mabbott, D. J. (2016). Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. *Neuro-Oncology*, *19*(3), 440–450.

Saling, M. M., (2009). Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. *Brain: A Journal of Neurology*, *132*(Pt 3), 570–582.

Saling, M. M., Berkovic, S. F., O'shea, M. F., Kalnins, R. M., Darby, D. G., & Bladin, P. F. (1993). Lateralization of verbal memory and unilateral hippocampal sclerosis: evidence of task-specific effects. *Journal of Clinical and Experimental Neuropsychology*, *15*(4), 608–618.

Scharfman, H. E., & Myers, C. E. (2013). Hilar mossy cells of the dentate gyrus: a historical perspective. *Frontiers in Neural Circuits*, *6*, 106.

Schlichting, M. L., Mack, M. L., Guarino, K. F., & Preston, A. R. (2016). Comparison of semi-automated hippocampal subfield segmentation methods in a pediatric sample. *bioRxiv*. doi:10.1101/064303

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155.

Sun, A.-M., Li, C.-G., Han, Y.-Q., Liu, Q.-L., Xia, Q., & Yuan, Y.-W. (2013). X-ray irradiation promotes apoptosis of hippocampal neurons through up-regulation of Cdk5 and p25. *Cancer Cell International*, *13*, 47.

Tamnes, C. K., Walhovd, K. B., Engvig, A., Grydeland, H., Krogsrud, S. K., Østby, Y., … Fjell, A. M. (2014). Regional hippocampal volumes and development predict learning and memory. *Developmental Neuroscience*, *36*(3–4), 161–174.

van der Beek, E. M., Wiegant, V. M., Schouten, W. G. P., van Eerdenburg, F. J. C. M., Loijens, L. W. S., van der Plas, C., … Lucassen, P. J. (2004). Neuronal number, volume, and apoptosis of the left dentate gyrus of chronically stressed pigs correlate negatively with basal saliva cortisol levels. *Hippocampus*, *14*(6), 688–700.

Van Leemput, K., Bakkour, A., Benner, T., Wiggins, G., Wald, L. L., Augustinack, J., … Fischl, B. (2009). Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. *Hippocampus*, *19*(6), 549–557.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394–1413.

Willment, K. C., & Golby, A. (2013). Hemispheric lateralization interrupted: material-specific memory deficits in temporal lobe epilepsy. *Frontiers in Human Neuroscience*, *7*,

Winterburn, J. L., Pruessner, J. C., Chavez, S., Schira, M. M., Lobaugh, N. J., Voineskos, A. N., & Chakravarty, M. M. (2013). A novel in vivo atlas of human hippocampal subfields using high-resolution 3 T magnetic resonance imaging. *NeuroImage*, *74*, 254–265.

Wiskott, L., Rasch, M. J., & Kempermann, G. (2006). A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. *Hippocampus*, *16*(3), 329–343.

Wisse, L. E. M., Biessels, G. J., & Geerlings, M. I. (2014). A Critical Appraisal of the Hippocampal Subfield Segmentation Package in FreeSurfer. *Frontiers in Aging Neuroscience*, *6*, 261.

Wisse, L. E. M., Kuijf, H. J., Honingh, A. M., Wang, H., Pluta, J. B., Das, S. R., … Geerlings, M. I. (2016). Automated hippocampal subfield segmentation at 7 tesla MRI. *AJNR. American Journal of Neuroradiology*, *37*(6), 1050–1057.

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus*, *21*(9), 968–979.

Yassa, M. A., & Stark, C. E. L. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences*, *34*(10), 515–525.

Yee, L. T. S., Hannula, D. E., Tranel, D., & Cohen, N. J. (2014). Short-term retention of relational memory in amnesia revisited: accurate performance depends on hippocampal integrity. *Frontiers in Human Neuroscience*, *8*, 16.

Yushkevich, P. A., Pluta, J. B., Wang, H., Xie, L., Ding, S.-L., Gertje, E. C., … Wolk, D. A. (2015). Automated Volumetry and Regional Thickness Analysis of Hippocampal Subfields and Medial Temporal Cortical Structures in Mild Cognitive Impairment. *Human Brain Mapping*, *36*(1), 258–287.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science*, *299*(5606), 577–580.

SUPPORTING INFORMATION

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