HHS Public Access

Author manuscript

*Neuropsychology*. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

*Neuropsychology*. 2023 February ; 37(2): 204–217. doi:10.1037/neu0000882.

# Superior Verbal Learning and Memory in Pediatric Brain Tumor Survivors Treated with Proton Versus Photon Radiotherapy

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## Abstract

**Objective:** Radiotherapy for pediatric brain tumor has been associated with late cognitive effects. Compared to conventional photon radiotherapy (XRT), proton radiotherapy (PRT) delivers lower doses of radiation to healthy brain tissue. PRT has been associated with improved long-term cognitive outcomes compared to XRT. However, there is limited research comparing the effects of XRT and PRT on verbal memory.

**Methods:** Survivors of pediatric brain tumor treated with either XRT ($n$ = 29) or PRT ($n$ = 51) completed neuropsychological testing > 1 year following radiotherapy. Performance on neuropsychological measures was compared between treatment groups using analysis of covariance (ANCOVA). Chi-squared tests of independence were used to compare the frequency of encoding, retrieval, and intact memory profiles between treatment groups. Associations between memory performance and other neurobehavioral measures were examined using Pearson correlation.

**Results:** Overall, patients receiving PRT demonstrated superior verbal learning and recall compared to those treated with XRT. Encoding and retrieval deficits were more common in the XRT group than the PRT group, with encoding problems being most prevalent. The PRT group was more likely to engage in semantic clustering strategies, which predicted better encoding and

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We have no known conflict of interest to disclose.

retrieval. Encoding ability was associated with higher intellectual and adaptive functioning, and fewer parent-reported concerns about day-to-day attention and cognitive regulation.

**Conclusion:** Results suggest that PRT is associated with verbal memory sparing, driven by effective encoding and use of learning strategies. Future work may help to clarify underlying neural mechanisms associated with verbal memory decline, which will better inform treatment approaches.

## Keywords

Pediatric brain tumor; proton radiotherapy; verbal memory; late effects

Survival rates of pediatric brain tumor have improved considerably as more advanced treatments have become available in recent decades (Girardi et al., 2019). With many patients now surviving into adulthood, research has increasingly focused on long-term outcomes in this population (Ris, 2007). Adult survivors of pediatric brain tumor tend to have lower social attainment, academic achievement, and functional independence compared to same-age peers (King et al., 2017; Schulte et al., 2019; Warren et al., 2022). These negative outcomes may reflect treatment-related declines in cognitive functioning (Roth et al., 2020). Radiotherapy, in particular, has been associated with late effects on cognition that may appear months to years after treatment (de Ruiter et al., 2013; Robinson et al., 2013; Robinson et al., 2010). Moreover, severity of cognitive decline is related to individual patient factors, such as age at diagnosis, craniospinal radiation, radiation dose, tumor size and location, and socioeconomic variables (Antonini et al., 2017; Armstrong et al., 2010; Kahalley et al., 2019; Pulsifer et al., 2018; Raghubar et al., 2019).

Conventional photon (i.e., X-Ray) radiotherapy (XRT) deposits entry and exit doses of radiation to healthy brain tissue surrounding the tumor site. Conformal proton radiotherapy (PRT) has been shown to offer similar disease control to conventional XRT, while delivering a smaller entry dose and no exit dose to nearby healthy tissue (DeNunzio & Yock, 2020; Hoffman & Yock, 2009; Merchant, 2009; Merchant & Farr, 2014). Thus, PRT has emerged as a promising alternative to XRT to minimize damage to healthy brain tissue, and potentially improve long-term cognitive outcomes in these patients.

Accumulating evidence suggests that neurocognitive outcomes may be improved in patients treated with PRT versus XRT. Compared to patients receiving PRT, those treated with XRT are more likely to experience global intellectual impairment, as well as deficits in attention, executive functioning, and fine motor control (Baliga & Yock, 2019; Child et al., 2021; Gross et al., 2019; Warren et al., 2022). Craniospinal irradiation (CSI) has consistently emerged as a major risk factor for cognitive impairment, especially when delivered with XRT. However, patients receiving focal PRT tend to demonstrate neuropsychological outcomes similar to healthy controls (Antonini et al., 2017; Child et al., 2021; Pulsifer et al., 2018). Moreover, longitudinal research suggests that while IQ tends to decline over time following XRT and/or CSI, patients receiving focal PRT demonstrate largely stable intellectual functioning into late survivorship (Kahalley et al., 2019; Kahalley et al., 2020; Kahalley et al., 2016). Importantly, these studies identified processing speed as especially vulnerable to decline following any kind of radiotherapy. Finally, Yock et al. (2014) found

that reported quality of life was higher in survivors treated with PRT vs. XRT, with the PRT treatment group reporting no more physical symptoms than the normative population. Quality of life has also been found to improve over time following treatment with PRT (Kamran et al., 2018), and has been associated with cognitive outcomes (Kuhlthau et al., 2012).

Verbal memory impairment has been well-documented in survivors of pediatric brain tumor, but the nature of these difficulties is not well characterized. This may be due in part to the complexity of memory, which consists of neurologically distinct encoding and retrieval processes. Verbal list-learning tasks seek to independently measure these components by assessing immediate recall for a novel list of words over repeated trials. Recall and recognition memory are then assessed after a delay period. Poor initial learning, delayed recall, and recognition are the hallmark of encoding difficulty (Delis et al., 2000; Massman et al., 1992; Obermeit et al., 2015; Wright et al., 2009). Anterograde memory deficits following radiation treatment are thought to reflect poor encoding, possibly due to reduced neurogenesis of hippocampal stem cells (Gibson & Monje, 2012; Sekeres et al., 2018). On the other hand, impaired delayed recall and intact recognition is characteristic of a retrieval deficit (Delis et al., 2000; Massman et al., 1992; Obermeit et al., 2015; Wright et al., 2009). Retrieval problems may reflect impairment in attention and executive functioning; specifically, changes in white matter networks following CNS-directed radiation have been associated with declines in these abilities (Nieman et al., 2015; Reddick et al., 2014; Rueckriegel et al., 2015; Van Petten et al., 2004).

Various verbal memory deficits have been inconsistently reported following treatment for pediatric brain tumor. Nagel et al. (2006) found that medulloblastoma survivors treated with XRT+CSI demonstrated a mixed profile of both encoding and retrieval deficits on the California Verbal Learning Test for Children (CVLT-C), which was interpreted as evidence for both white matter and hippocampal change in this population. Another study using a similar sample of medulloblastoma survivors reported no statistically significant impairment on the CVLT-C, but a trend toward generally below-average performance on all subtests (Reeves et al., 2006). In a group of adult survivors of pediatric brain tumor, Jayakar et al. (2015) reported that on the CVLT-II, auditory attention (e.g., Trial 1 learning) was most significantly impacted in survivors compared to controls, and that this was associated with reduced hippocampal volume. These findings were largely driven by individuals who had been treated with radiation. Another study found that CVLT Total Recall (Trials 1–5) was significantly below average in survivors of pediatric brain tumor who had undergone surgery and radiation (Reddick et al., 2003), providing further evidence for encoding deficits in this population. Of note, different memory profiles have been reported in patients with different tumor characteristics (King et al., 2004; Micklewright et al., 2007). Inconsistent findings may also reflect different statistical approaches and selection of measures.

The majority of research exploring verbal memory outcomes in pediatric brain tumor has examined patients treated with conventional XRT. Thus, little is known about potential verbal memory sparing following PRT. Moreover, the degree to which memory difficulties are related to treatment versus the tumor itself is unclear; for example, verbal memory deficits have been demonstrated at time of diagnosis, prior to initiation of treatment

(Margelisch et al., 2015). Direct comparisons between different types of radiotherapy may help to elucidate these questions. Warren et al. (2022) reported significantly poorer verbal memory (i.e., delayed recall) but not verbal learning (i.e., total recall on learning trials) on the CVLT for survivors treated with XRT compared to PRT. Moreover, poor delayed recall predicted worse peer relations in this sample. Another study found that verbal learning and memory (i.e., CVLT total recall and delayed recall) were similar in XRT and PRT treatment groups, but were significantly worse in those who received CSI (Child et al., 2021). Using a different approach, Gross et al. (2019) found that XRT and PRT groups performed similarly on a story memory task; this may reflect the more contextual nature of story recall compared to verbal list-learning and memory. Of note, each of these studies limited group comparisons to one or two CVLT subscales, which precludes a more in-depth evaluation of encoding, retrieval, and learning strategies.

The current study examined long-term verbal learning and memory outcomes in a sample of pediatric brain tumor survivors treated with XRT or PRT. Specifically, this study aimed to 1) compare verbal list-learning performance in individuals treated with XRT versus PRT, 2) characterize learning and memory profiles in each treatment group, and 3) examine behavioral correlates of encoding and retrieval ability. In line with previous studies reporting cognitive sparing in PRT, we expected individuals treated with XRT to broadly show poorer verbal learning and recall, higher rates of encoding and retrieval deficits, and less effective use of learning strategies. Moreover, intellectual ability, adaptive functioning, and day-to-day attention and executive function were expected to be associated with encoding and retrieval abilities.

## Methods

### Transparency and Openness

We report below how sample size was determined, all data exclusions, all measures in the study, and we follow journal article reporting standards (Kazak, 2018). Data and analysis code are available upon request. Data were analyzed using MATLAB R2022a. This study's design and analysis were not pre-registered.

### Participants

Participants were recruited as part of an ongoing study examining long-term cognitive outcomes in survivors of pediatric brain tumor. All participants were a) treated with a single course of PRT or XRT for a primary brain tumor, b) had no evidence of active disease at enrollment, c) were at least 6 years of age at the time of evaluation, and d) were fluent in English or Spanish. Given our interest in long-term neurocognitive and social outcomes, patients diagnosed with brain stem glioma, high grade glioma, or atypical teratoid/rhabdoid tumors were not enrolled. No participants were receiving treatment for recurrence at the time of participation. In 2007, the standard of care at our institution shifted from XRT to PRT. Therefore, all XRT patients were treated between 2000 and 2007, while PRT patients were treated between 2007 and 2013. Eligible participants were identified via medical record review and were approached for enrollment between 2011 and 2018. An 87% participation

rate was achieved. Participation did not significantly differ with respect to radiation type, sex, race, or tumor histology (all $p > .05$).

Data were excluded for individuals who could not complete neuropsychological testing due to profound cognitive or visual impairment ($n = 5$), individuals who underwent testing but did not complete a verbal memory measure ($n = 2$), and individuals with questionable performance validity on testing ($n = 1$). This study reports on the outcomes of 80 patients (XRT $n = 29$, PRT $n = 51$), whose characteristics are reported in detail in Table 1. "Other" tumor types not shown in Table 1 included astrocytoma, craniopharyngioma, choroid plexus carcinoma, atypical choroid plexus tumor, dysembryoplastic neuroepithelial tumor (DNET), cerebral ganglioneuroblastoma, desmoplastic ganglioma, and high grade neoplasm with small blue cell features. Prescription medications were reported in 41 participants (16 XRT, 25 PRT), and denied in 33 participants (9 XRT, 24 PRT). Medication data were unavailable for 6 participants (4 XRT, 2 PRT participants). Medications reported included benzodiazepines, SSRIs/SNRIs, stimulants, non-stimulant ADHD medication, anticonvulsants, cognitive enhancers, corticosteroids, other hormonal treatments, muscle relaxants, prescription NSAIDs, and antiemetics. The number of individuals taking prescription medications did not differ significantly between groups ($p > .05$). Informed consent was obtained from adult patients or caregivers, and assent was obtained from patients under 18 years of age. This study was approved by the Institutional Review Board at [REDACTED FOR REVEW].

## Measures

All participants completed a battery of standardized neuropsychological tests. When possible, caregivers completed norm-referenced rating scales. Measures were administered in a standardized fashion by trained research assistants under the supervision of a neuropsychologist. Appropriate versions of each test were selected based on patient age; thus, all patients were within the normative age range for tests they were administered. All evaluations were conducted prior to the onset of the COVID-19 pandemic; therefore, standardized administration procedures were not impacted by enhanced safety precautions practiced during the pandemic.

Intellectual functioning was assessed using the Wechsler Intelligence Scale for Children (WISC-V or WISC-IV) or the Wechsler Adult Intelligence Scale (WAIS-IV). 27.5% of participants completed the WAIS-IV, while the remaining 72.5% completed the WISC-V or WISC-IV. This did not differ between XRT or PRT treatment groups. Domains assessed included Full-Scale IQ (FSIQ), Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). The WISC-V Processing Speed Index (PSI) was unavailable for one participant in the PRT group. Because the WISC-V does not generate a PRI score, the publisher (NCS Pearson) provided norms to calculate PRI scores to facilitate comparison across the WISC-IV, WISC-V, and WAIS-IV. Reliabilities for the WISC-V PRI ranged from 0.93 to 0.95 for ages 6–16 (Pearson, 2014). Everyday attention, executive functioning, and adaptive skills were assessed using caregiver-report forms of the Behavior Assessment System for Children (BASC-2) and the Behavior Rating Inventory of Executive Function (BRIEF). BASC-2

scores were not available for nine individuals (4 XRT, 5 PRT). BRIEF scores were not available for four individuals (1 XRT, 3 PRT).

Verbal learning and memory were assessed using the California Verbal Learning Test (CVLT-II/CVLT-C). This task requires the examinee to learn a list of words (i.e., "List A") over five consecutive learning trials. The CVLT-II List A includes 16 words belonging to four semantic categories, while the CVLT-C List A includes 15 words belonging to three semantic categories. Recall across all learning trials yields a summary score of encoding ability (i.e., Trial 1–5 Total), while Learning Slope reflects the degree of improvement from Trial 1 to Trial 5. List A learning trials are followed by a single learning trial of a distractor list (i.e., "List B"). Examinees are subsequently asked to recall as many words as possible from List A, both without and with semantic category cues (i.e., Short Delay Free Recall; Short Delay Cued Recall). This procedure is then repeated after a 20-minute delay (i.e., Long Delay Free Recall; Long Delay Cued Recall). The CVLT also provides insight into memory strategies employed by examinees across all learning and recall trials. The Serial Clustering score reflects the degree to which examinees recall words in the order they were presented, while the Semantic Clustering score measures how well examinees organize their responses by category. The Intrusion Score captures the number of erroneous responses made during all free recall trials. Lastly, examinees complete a recognition task (i.e., respond "yes" or "no") for target words from List A. Recognition discriminability (d') is calculated as the ratio of recognition hits to false positives.

Standardized scores (i.e., z-scores, T-scores, and standard scores) were computed using age norms for all measures. Z-scores (all CVLT scores except Trial 1–5 Total) have a mean of 0 and a standard deviation of 1. T-Scores (BASC-2, BRIEF, and CVLT Trial 1–5 scores) have a mean of 50 and a standard deviation of 10. Standard scores (WISC and WAIS scores) have a mean of 100 and a standard deviation of 15.

## Statistical Analyses

**Group Comparisons—**Demographic characteristics and treatment-related variables were compared between XRT and PRT groups using Welch's t-tests or chi-square tests of independence, as appropriate. Analysis of covariance was conducted to explore group differences in neuropsychological test measures. Covariates included time since radiation, which differed between treatment groups, and age at the time of evaluation, given the broad age range of the sample. Other demographic and treatment variables that did not differ between treatment groups were not included as covariates. Effect sizes are reported as $\eta^2$, with effects interpreted as small ($\eta^2 = .01$), medium ($\eta^2 = .06$), or large ($\eta^2 = .14$).

**CVLT Profile Analysis—**Each participant was assigned to a prototypical CVLT profile based on their pattern of performance: Encoding Deficit, Retrieval Deficit, Intact, or Other. An encoding deficit profile was defined as impairment across learning (i.e., Trial 1–5 Total Score), Long Delay Free Recall (LDFR), and Recognition Discriminability (d'). Individuals with impaired LDFR but intact d' were classified as having a retrieval deficit profile. Participants with intact learning, LDFR, and d' were classified as having an intact profile. Individuals not meeting any of these criteria were classified under "other." For the purpose

of classification, scores more than 1.33 standard deviations below the normative mean (i.e., below a standard score of 80 or the 9th percentile) were considered impaired, whereas scores above this threshold were considered intact (Guilmette et al., 2020). Chi-square tests of independence were performed to compare the observed frequency of each profile in XRT and PRT treatment groups.

**Encoding and Retrieval Deficit Scores—**For each participant, the T-score representing total recall on CVLT-II/CVLT-C Trials 1–5 was used as a measure of encoding ability, with lower scores representing poorer encoding. Retrieval deficit scores were calculated by comparing standardized performance (i.e., z-scores) for recognition vs. delayed free recall (i.e., d' – LDFR). More positive scores suggest a greater retrieval deficit (i.e., more improvement when provided with cues). Encoding and retrieval deficit scores were compared between treatment groups using ANCOVA, covarying for time since radiation and age at evaluation. Pearson correlations were used to examine associations between encoding and retrieval performance and learning strategies (i.e., serial clustering, semantic clustering). Finally, encoding and retrieval scores were correlated with relevant neuropsychological measures.

## Results

### Demographic and Clinical Characteristics

Demographic characteristics and treatment-related variables are presented in Table 1. XRT and PRT groups did not significantly differ with respect to sex, age at diagnosis, age at evaluation, handedness, race, maternal education, household size, or family income. They also did not differ with respect to tumor location or type, and total radiation dose. XRT and PRT groups had similar proportions of individuals with a history of craniospinal irradiation, craniotomy, shunting, or chemotherapy. Due to the institutional shift in standard of care at our institution from XRT to PRT in 2007, time since radiotherapy was longer in the XRT group (mean = 9.1 years) than the PRT group (mean = 6.5 years). The PRT group also had significantly higher physician-rated Karnofsky-Lansky scores at their first postoperative appointment (mean 85.4) than the XRT group (mean = 77.2), indicating fewer neurosurgical complications and higher functional status.

### Cognitive and Behavioral Group Comparisons

With respect to cognitive ability, individuals treated with PRT demonstrated higher performance across all IQ composite scores when covarying for age and time since radiation, including Full-Scale IQ ($t(76) = 3.99$, $p < .001$), Verbal Comprehension (VCI; $t(76)= 3.25$, $p = .002$), Perceptual Reasoning (PRI; $t(76) = 3.28$, $p = .002$), Working Memory (WMI; $t(76) = 3.14$, $p = .002$), and Processing Speed (PSI; $t(75) = 4.31$, $p < .001$). As previous studies have reported, Processing Speed (PSI) was most impacted in both treatment groups. For individuals receiving PRT, mean IQ composite scores were consistently within typical age expectations, with the lowest score (Processing Speed) falling only one standard deviation below the normative mean (PRT mean PSI = 85.1; normative mean PSI = 100). On the other hand, both Working Memory and Processing Speed were significantly below normative expectations in the XRT group (mean WMI = 78.7, mean

PSI = 68.8). PRT and XRT groups did not significantly differ (all $p \geq .101$) with respect to parent-reported adaptive functioning (BASC-2 Adaptive Composite), attention (BASC-2 Attention), behavioral regulation (BRIEF Behavior Regulation Composite), or cognitive regulation (BRIEF Metacognition Composite). Group comparisons for IQ and behavioral measures are presented in Table 2.

## Verbal Memory Analysis

Standardized CVLT scores for both groups are described in Figure 1 and Table 3. When accounting for age and time since radiation, the PRT group significantly outperformed the XRT group with respect to Trial 1–5 Total Recall ($t(76) = 2.61$, $p = .011$) and Trial 5 Recall ($t(76) = 2.53$, $p = .014$). However, groups did not significantly differ with respect to Trial 1 Recall or Learning Slope. Individuals treated with PRT consistently performed better across all recall conditions (Short Delay Free and Cued Recall, Long Delay Free and Cued Recall; $t(76) = [2.61 – 3.57]$, all $p \leq .011$). There was also a trend toward higher Recognition Discriminability in the PRT group that approached statistical significance ($t(76) = 1.97$, $p = .052$). Regarding learning strategies, treatment groups showed a similar degree of serial clustering, but the PRT group demonstrated significantly more semantic clustering than the XRT group ($t(76) = 2.29$, $p = .025$).

CVLT profile analysis revealed significant differences in the distribution of deficit profiles across XRT and PRT groups (omnibus $X^2(3) = 10.77$, $p = .013$). Specifically, individuals treated with XRT were more likely to present with either an encoding deficit profile ($X^2(1) = 4.51$, $p = .034$) or a retrieval deficit profile ($X^2(1) = 4.11$, $p = .043$), and were less likely to have an intact profile ($X^2(1) = 8.14$, $p = .004$). Deficit profile classifications for each treatment group are presented in Figure 2 and Table 4. Encoding scores (Trial 1–5 Total) and retrieval scores (d' - LDFR) were calculated for each patient. Distributions of encoding and retrieval scores for each deficit profile group (i.e., Encoding Deficit, Retrieval Deficit, Intact, Other) are shown in Figure 3. When covarying for age and time since radiation, encoding scores were significantly higher in the PRT group compared to the XRT group (XRT mean T = 38.2, PRT mean T = 47.5; $t(76) = 2.61$, $p = .011$), indicating better performance. On the other hand, retrieval scores did not significantly differ between treatment groups (XRT mean z = 0.29, PRT mean z = −0.09, $t(76) = -1.56$, $p = .124$).

Analysis of learning strategies revealed a significant negative association between semantic and serial clustering strategies ($r = -.51$, $p < .001$), such that individuals relying on serial clustering were less likely to use semantic clustering, and vice versa. Further, higher semantic clustering scores were associated with significantly better encoding ($r = .28$, $p = .011$) and retrieval ($r = -.26$, $p = .022$). On the other hand, use of serial clustering was not related to either encoding ($r = .02$, $p = .861$) or retrieval ($r = .02$, $p = .895$) scores. Thus, encoding and retrieval appear to be supported by semantic, but not serial clustering strategies.

Retrieval scores were not associated with any clinical or behavioral measures (all $p > .05$). However, encoding scores were significantly correlated with Full-Scale IQ, BASC-2 Adaptive Composite, BASC-2 Attention, and BRIEF Metacognition ($r = [-.36 - .56]$, all $p \leq .011$, Table 5). In all cases, higher encoding scores were associated with higher intellectual

and adaptive performance and fewer attention and executive concerns. Follow-up analyses revealed associations between encoding ability and almost all areas of cognitive regulation (BRIEF Metacognition), including initiation, working memory, planning/organization, and monitoring ($r$ = [−.31 - −.39]; all $p \leq .006$). Associations between encoding ability and adaptive functioning (BASC-2) were driven by leadership skills (r = .35, $p$ = .002) and functional communication ($r$ = .45, $p < .001$). Correlations between encoding and behavioral measures are shown in Table 5 and Figure 4.

## Discussion

Verbal memory deficits are among numerous cognitive late effects that have been reported in survivors of pediatric brain tumor who have undergone radiotherapy. However, the exact nature of these difficulties has not been described in detail. Moreover, it is unclear whether recent reports of cognitive sparing in PRT compared to XRT extend to verbal memory performance. To our knowledge, this is the first study to conduct an in-depth analysis of verbal learning and memory performance in survivors of pediatric brain tumor, and the first to compare these outcomes in proton vs. photon radiotherapy.

### Encoding and Retrieval Deficits Are Associated with XRT

This study offers additional evidence for both encoding and retrieval difficulty following radiotherapy, which has been inconsistently reported in the literature (Jayakar et al., 2015; Nagel et al., 2006; Reddick et al., 2003; Reeves et al., 2006). Individuals receiving XRT were more likely to show characteristic patterns of encoding or retrieval deficits, and were less likely to demonstrate intact learning and memory compared to the PRT group. Among patients who received PRT, the vast majority met criteria for an intact CVLT profile (71%). In contrast, intact performance was observed in only 38% of XRT patients, with 31% meeting criteria for an encoding deficit. Retrieval deficits were relatively uncommon in both groups (17% of XRT, 4% of PRT). Furthermore, average encoding performance significantly differed between treatments (i.e., impaired in XRT, intact in PRT). However, XRT and PRT groups both demonstrated minimal retrieval effects on average; this corroborates the finding that pure retrieval deficits were fairly uncommon, albeit more common following XRT than PRT.

Overall, these findings may be interpreted as a predominance of encoding deficits following radiotherapy, particularly XRT. Alternatively, retrieval deficits may be “masked” by poor encoding in individuals with a mixed profile. In other words, if encoding difficulty prevents new material from being learned, there is no opportunity to observe impairment in retrieval processes during later recall and recognition. Therefore, patients with a classic encoding deficit profile may or may not also struggle with retrieval processes. Conversely, patients with classic retrieval deficits may have low encoding scores; of the seven patients with identified retrieval deficit profiles, five showed below-average learning on Trials 1–5. However, their intact recognition suggests that their poor immediate recall reflects difficulty with retrieval rather than encoding.

### More Effective Strategy Use in PRT vs. XRT

Semantic clustering is typically thought to optimize learning and recall by imposing additional structure on target information and facilitating “deep learning” based on word meanings and associations (Craik & Lockhart, 1972; Stricker et al., 2002). For example, it is easier to recall four categories than 16 unrelated words; these categories then serve as a cue for retrieval of individual words. On the other hand, serial clustering (i.e., recalling words in the order they are presented) is considered a “shallow learning” strategy that is severely limited by auditory working memory. On average, the PRT group was more likely to rely on semantic clustering strategies than the XRT group. Moreover, across all patients, semantic clustering was associated with both improved encoding and retrieval performance. As expected, use of semantic clustering and serial clustering were negatively correlated, such that individuals who relied heavily on one strategy were unlikely to use the other.

On the other hand, serial clustering did not differ between groups, and did not predict encoding or retrieval scores. On closer examination, it became clear that individuals with high serial clustering showed low semantic clustering, as expected. However, individuals with low serial clustering belonged to two groups: one group who chose a more effective strategy (i.e., high semantic clustering), and one group who used no strategy (i.e., low semantic clustering). Thus, serial clustering does not predict memory performance, because poor performance may be associated with either low serial clustering (i.e., no strategy) or high serial clustering (i.e., suboptimal strategy).

### Encoding is Associated with Cognitive and Behavioral Measures

As discussed above, encoding deficits were especially prominent in patients receiving XRT, and were more common than retrieval deficits in both treatment groups. Moreover, encoding (but not retrieval) ability was uniquely associated with neurocognitive and behavioral outcomes, including intellectual functioning, adaptive skills, attention, and cognitive regulation. This may partially reflect a more distributed range of encoding scores than retrieval scores, as retrieval deficits were relatively uncommon (discussed above). Alternatively, it may be easier to compensate for retrieval deficits than encoding deficits in day-to-day life, with natural environmental cues and reminders facilitating successful retrieval. Strikingly, almost all areas of cognitive regulation were associated with encoding; this suggests that skills such as initiation, working memory, planning, and self-monitoring may improve learning by promoting focus and effective strategy use.

### Evidence of Intellectual Sparing in PRT

Consistent with the previous literature, this study found that all areas of intellectual functioning were significantly lower in patients who received XRT compared to PRT, with processing speed emerging as especially vulnerable in both groups (Antonini et al., 2017; Child et al., 2021; Gross et al., 2019; Kahalley et al., 2019; Kahalley et al., 2020). Individuals receiving PRT consistently performed within typical age expectations, while the XRT group demonstrated notable deficits with respect to working memory and processing speed. This corroborates previous research suggesting stable neurocognitive scores into late survivorship following PRT, but steady decline associated with XRT, especially with respect

to processing speed and working memory (Kahalley et al., 2019; Kahalley et al., 2020; Kahalley et al., 2016).

## Potential Neural Mechanisms of Verbal Memory Impairment

Further exploration of underlying neural mechanisms may help to elucidate the nature of verbal memory deficits in pediatric brain tumor survivors. The hippocampus plays an important role in encoding and consolidation of new memories (Eichenbaum, 2013; Squire, 1992); radiotherapy may specifically inhibit neurogenesis of hippocampal stem cells, which facilitate new declarative learning (Gibson & Monje, 2012). Prior studies have found that verbal learning and memory are associated with hippocampal radiation dose and hippocampal volume in survivors of pediatric brain tumor (Decker et al., 2017; Riggs et al., 2014; Sekeres et al., 2018). Therefore, hippocampal sparing in the delivery of whole-brain radiation may be beneficial in optimizing memory outcomes, when possible (Dye et al., 2015).

However, radiation has also been associated with widespread white matter toxicity (Nieman et al., 2015; Palmer et al., 2002; Reddick et al., 2000; Wang et al., 2009). Myelination is a critical component of brain network maturation, which continues throughout adolescence and early adulthood (Kwon et al., 2020; Stiles & Jernigan, 2010). Although not specifically implicated in memory, changes in white matter structure have been associated with broad declines in intellectual functioning (King et al., 2015; Mulhern et al., 2001; Mulhern et al., 1999; Rueckriegel et al., 2015), attention (Mulhern et al., 2004; Reddick et al., 2014; Reddick et al., 2003; Rueckriegel et al., 2015), working memory (Jacola et al., 2014; Law et al., 2011), and processing speed (Aukema et al., 2009; Palmer et al., 2012; Rueckriegel et al., 2015; Scantlebury et al., 2016). These deficits may impact learning and memory by limiting focus, reducing processing capacity, and interfering with effective use of memory strategies, which were associated with both encoding and retrieval performance in this study. In sum, it is unclear to what degree verbal memory deficits following radiotherapy reflect global cognitive decline associated with widespread white matter change, versus damage to specific memory structures.

## Limitations and Future Directions

The findings reported in this study are limited by the characteristics of this clinical sample, which may impact the generality of reported findings. Sample size was relatively small, particularly in the XRT treatment group, as XRT has been replaced by PRT as the standard of care at our institution. Moreover, our heterogenous sample may obscure differences in cognitive outcomes among specific tumor types. Due to limited sample size, comparisons between patients receiving focal and craniospinal irradiation (CSI) could not be conducted. The proportion of focal and CSI patients did not differ significantly between XRT and PRT groups. However, CSI is known to be a major risk factor for cognitive impairment, which would likely impact the findings reported in this study. Additionally, the XRT group was farther from completion of radiotherapy than the PRT group (9.1 years vs. 6.5 years), due to the availability of each treatment at different times (i.e., prior to 2007 vs. after 2007). Therefore, poorer outcomes in the XRT group may be partially due to additional time for late effects to emerge. However, both groups were considered to be in a similar stage of late

survivorship at the time of enrollment. Additionally, it is unknown whether patients in both groups were receiving similar rehabilitative therapies and/or school supports, which may have impacted cognitive and functional outcomes reported in this study.

Additional work is necessary to clarify the neural mechanisms underlying verbal memory deficits following radiotherapy, and how sparing may occur in PRT. Neuroimaging, which is ongoing by our team, may help to determine the roles of hippocampal and white matter damage in different memory processes, and how these roles depend on specific clinical characteristics. For example, it is unclear how memory profiles may differ for individuals treated with surgery alone, focal radiation outside the hippocampus, and whole-brain radiation including the hippocampus. Moreover, the cross-sectional design of this study cannot speak to the trajectory of memory decline. Future longitudinal studies will help to clarify whether verbal memory sparing in PRT reflects differences in pre-treatment effects, immediate post-treatment effects, and/or cumulative late effects. Finally, intervention studies may demonstrate whether cognitive rehabilitation targeting memory is beneficial for survivors of pediatric brain tumor who are at high risk of cognitive decline. These interventions teach compensatory memory strategies, and often involve working with families to accommodate patients' cognitive difficulties. This approach has been shown to improve adaptive outcomes by facilitating learning and recall in day-to-day situations (Camm et al., 2021; Resch et al., 2018).

## Conclusion

This study is, to our knowledge, the first to offer an in-depth characterization of verbal learning and memory profiles in survivors of pediatric brain tumor following radiotherapy, as well as the first to compare these outcomes following photon vs. proton radiotherapy. As anticipated, PRT was associated with a higher rate of intact verbal memory performance, while XRT was associated with both encoding and retrieval deficits. The PRT group also tended to use more effective strategies to support learning and recall. Encoding deficits were especially common, and predicted a range of neurocognitive, adaptive, and behavioral outcomes. Additional research is necessary to fully elucidate the neural mechanisms of verbal memory deficits in this population, as well as to characterize the trajectory of these abilities over time.

## Acknowledgments

Data and analysis code for this study are available upon request.

This study was not preregistered.

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## Key Points

This study compared verbal learning and memory in pediatric brain tumor survivors treated with photon (XRT) or proton (PRT) radiotherapy. Overall, patients treated with PRT were better at learning and recalling new verbal information, and memory performance was related to aspects of day-to-day functioning. Therefore, survivors of pediatric brain tumor may benefit from interventions to help improve their learning and memory. Future research may help to identify brain regions that play a role in verbal memory decline after radiotherapy.

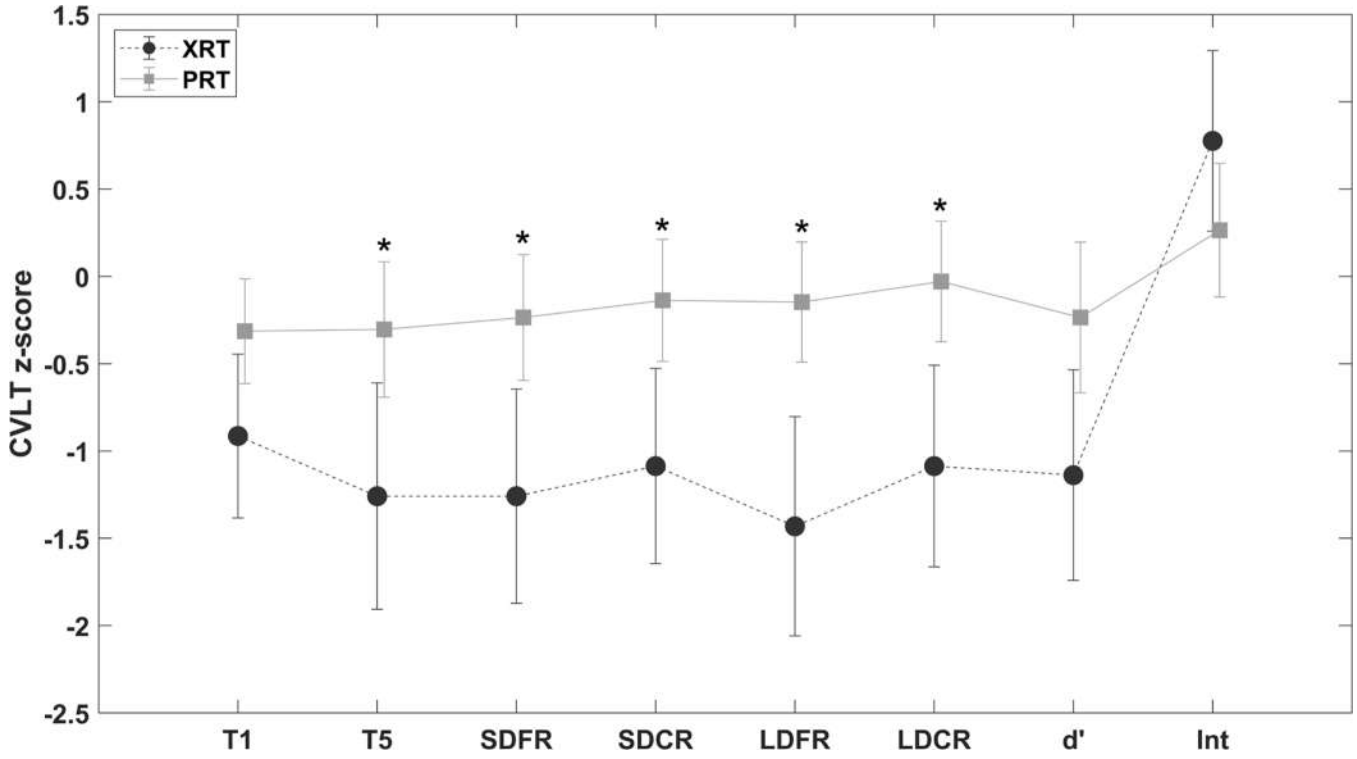


**Figure 1. CVLT Performance by Treatment Group**

*Note.* Mean standardized CVLT-II/CVLT-C scores are presented for each treatment group. Error bars represent 95% confidence intervals. Significant group differences are denoted by *. Intrusions are reverse scored, with a higher score representing poorer performance (i.e., more intrusion errors). T1 = Trial 1; T5 = Trial 5; SDFR = Short Delay Free Recall; SDCR = Short Delay Cued Recall; LDFR = Long Delay Free Recall; LDCR = Long Delay Cued Recall; d' = Recognition Discriminability; Int = Intrusion Errors.

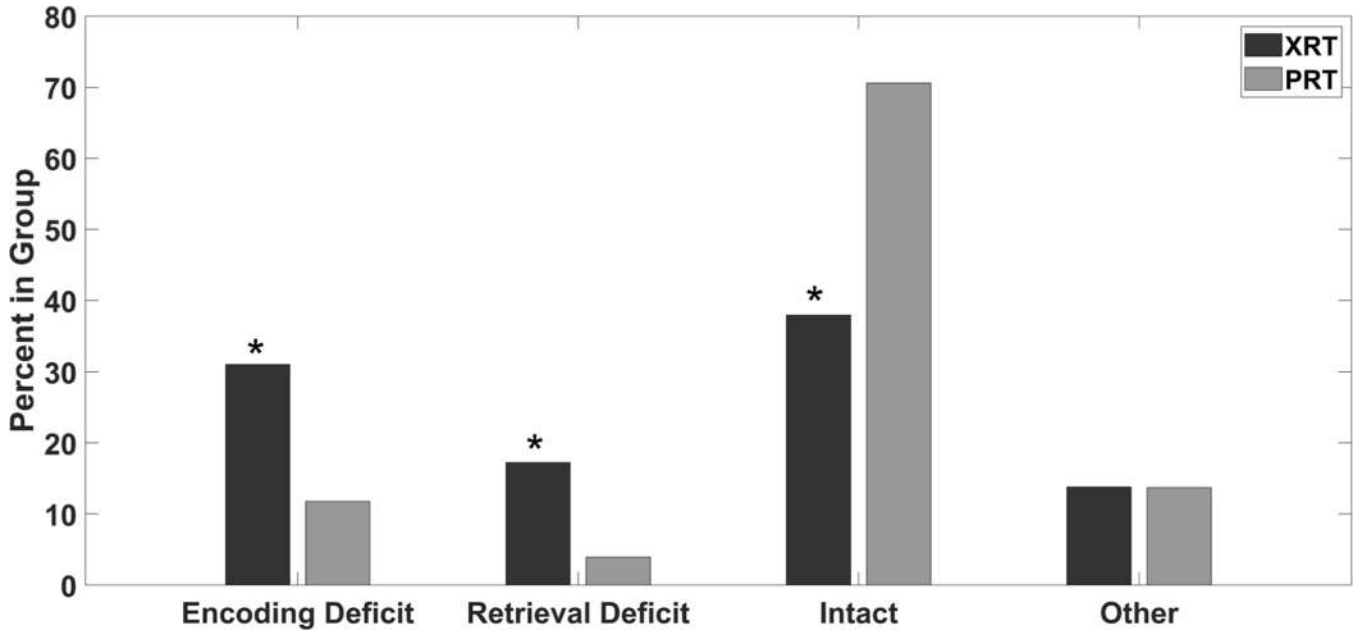


**Figure 2. CVLT Profile Classifications by Treatment Group**

*Note.* Bars show percentage of each treatment group classified within each memory profile on the CVLT-II/CVLT-C. Criteria for impairment was set at 1.33 standard deviations below the mean. An encoding deficit profile was defined as impairment on learning (T1–5), long delay free recall (LDFR), and recognition (d') scores. A retrieval deficit profile was defined as impaired LDFR and intact d'. Statistically significant group differences are denoted by *. The XRT group was significantly more likely than the PRT group to demonstrate encoding and retrieval deficit profiles, and less likely than the PRT group to be classified as intact. Detailed statistics are shown in Table

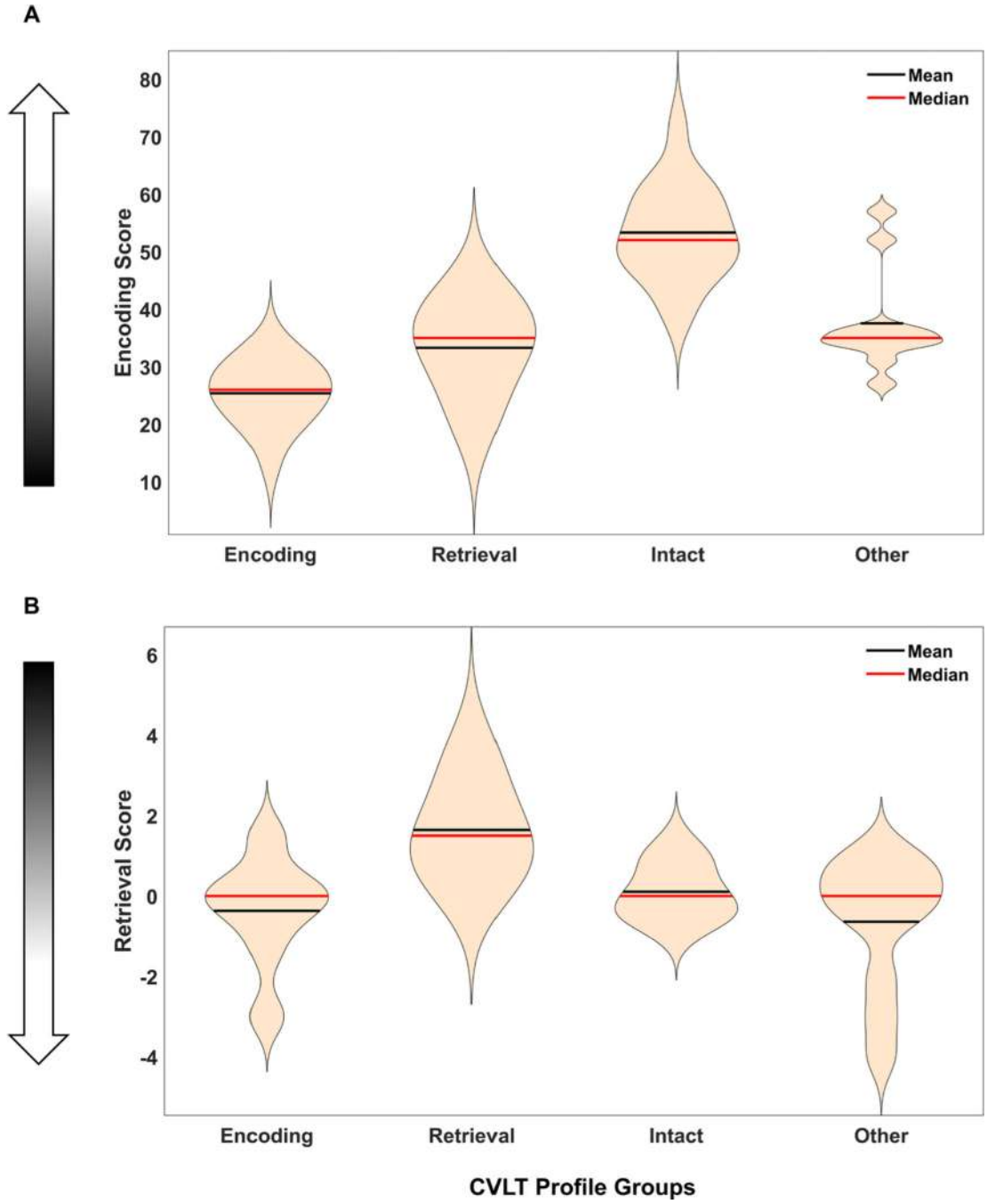


**Figure 3. Encoding and Retrieval Scores by Profile Classification**

*Note.* Violin plots describe distribution of encoding scores (top) and retrieval scores (bottom) for individuals classified into each memory profile. Mean (black line) and median (red line) scores are shown for each profile group. Arrows point from most impaired scores (black) to least impaired scores (white). Individuals classified as having an encoding deficit profile had the lowest encoding scores (i.e., poorer performance), while the intact profile group had the highest encoding scores (Panel A). Those classified as having a

retrieval deficit profile demonstrated the highest retrieval scores (i.e., greatest benefit from recognition cueing; Panel B).

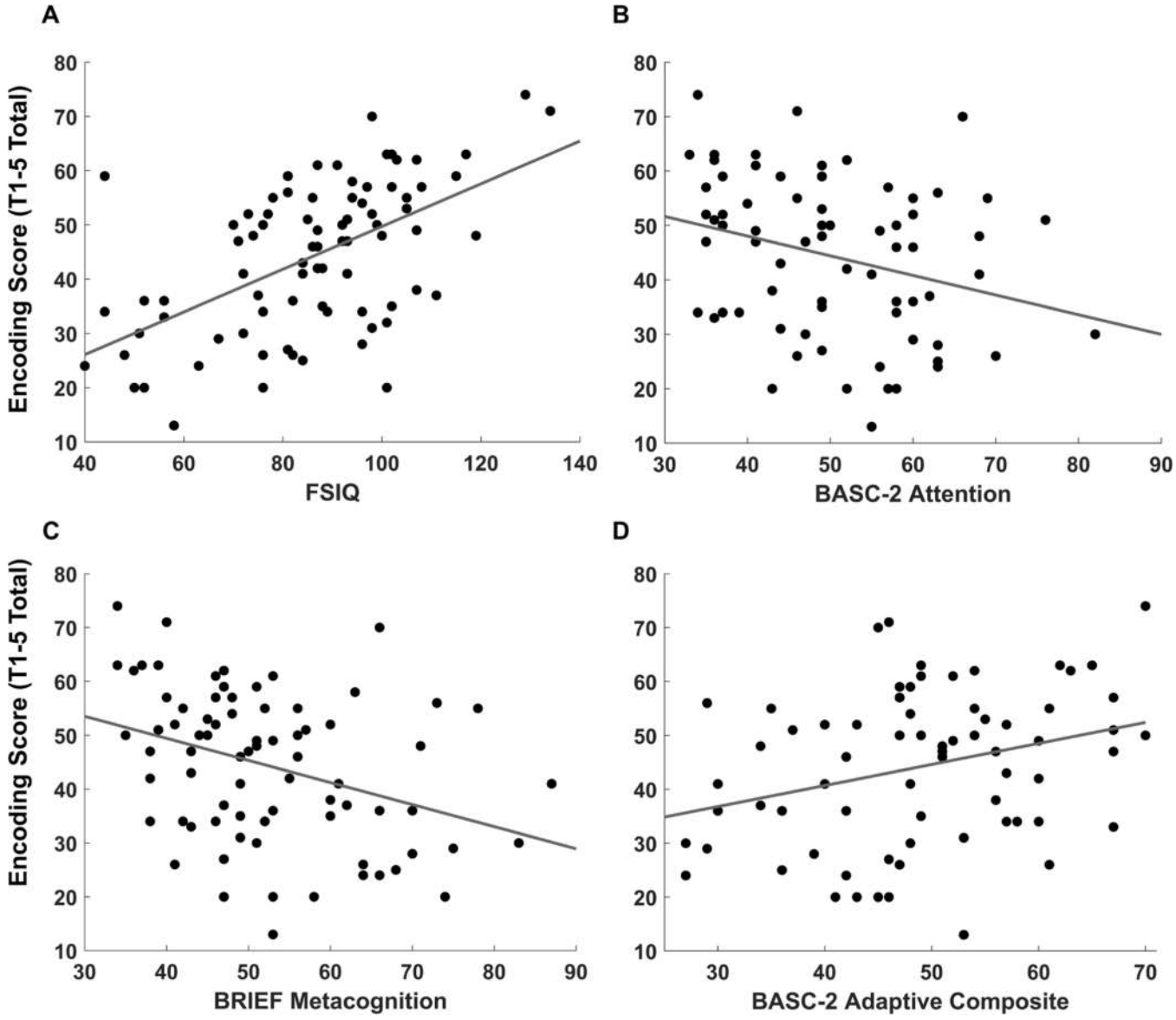


**Figure 4. Associations Between Encoding and Neurobehavioral Measure**

*Note.* Scatter plots depict statistically significant correlations between encoding ability (i.e., Trial 1–5 Total T-score) and standardized scores on neuropsychological measures. For FSIQ and BASC-2 Adaptive Composite Scores, higher scores indicate more intact performance. For BRIEF Metacognition and BASC-2 Attention Scores, higher scores indicate more parent-reported concerns. Better encoding ability is associated with higher intellectual and adaptive functioning, and fewer concerns about attention and cognitive regulation. All correlations are shown in Table 5. FSIQ = Full Scale IQ; BASC = Behavior Assessment System for Children; BRIEF = Behavior Rating Inventory of Executive Function

## Table 1

Clinical and Demographic Patient Characteristics

| | XRT (*n*=29) | | PRT (*n*=51) | | $X^2$ | *P* |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | |
| **Sex** | | | | | 1.07 | .301 |
| Male | 22 | 76 | 33 | 65 | | |
| Female | 7 | 24 | 18 | 35 | | |
| **Handedness** | | | | | 1.31 | .253 |
| Right | 27 | 93 | 43 | 84 | | |
| Left | 2 | 7 | 8 | 16 | | |
| **Race** | | | | | 0.64 | .724 |
| White | 24 | 83 | 41 | 80 | | |
| Black | 4 | 14 | 6 | 12 | | |
| Asian | 1 | 3 | 4 | 8 | | |
| **Ethnicity** | | | | | 0.02 | .879 |
| Hispanic/Latino | 9 | 31 | 15 | 29 | | |
| Not Hispanic/Latino | 20 | 69 | 36 | 71 | | |
| **Maternal Education** | | | | | 0.80 | .938 |
| <High school | 4 | 14 | 6 | 12 | | |
| High school | 13 | 45 | 21 | 41 | | |
| 4-year college degree | 7 | 24 | 17 | 33 | | |
| Advanced degree | 3 | 10 | 4 | 8 | | |
| Unknown | 2 | 7 | 3 | 6 | | |
| **Family Income ($)** | | | | | 0.53 | .912 |
| <40,000 | 9 | 31 | 18 | 35 | | |
| 40,000–79,999 | 6 | 21 | 9 | 18 | | |
| 80,000+ | 12 | 41 | 22 | 43 | | |
| Unknown | 2 | 7 | 2 | 4 | | |
| **Tumor location** | | | | | 1.33 | .515 |
| Supratentorial | 11 | 38 | 26 | 51 | | |
| Infratentorial | 17 | 59 | 24 | 47 | | |
| Both | 1 | 3 | 1 | 2 | | |
| **Tumor type** | | | | | 2.56 | .768 |
| Glioma | 5 | 17 | 8 | 16 | | |
| Medulloblastoma | 12 | 41 | 17 | 33 | | |
| PNET-NOS | 1 | 3 | 1 | 2 | | |
| Ependymoma | 5 | 17 | 6 | 12 | | |
| Germ cell | 3 | 10 | 10 | 20 | | |
| Other | 3 | 10 | 9 | 18 | | |
| **RT technique** | | | | | 0.24 | .624 |

| | XRT (*n*=29) | | PRT (*n*=51) | | $X^2$ | *P* |
|---|---|---|---|---|---|---|
| CSI | 17 | 59 | 27 | 53 | | |
| Focal | 12 | 41 | 24 | 47 | | |
| **Shunt** | | | | | 2.50 | .114 |
| Yes | 13 | 45 | 14 | 27 | | |
| No | 16 | 55 | 37 | 73 | | |
| **Chemotherapy** | | | | | 0.86 | .354 |
| Yes | 19 | 66 | 28 | 55 | | |
| No | 10 | 34 | 23 | 45 | | |

| | XRT (*n*=29) | | PRT (*n*=51) | | $\eta^2$ | t | *P* |
|---|---|---|---|---|---|---|---|
| | **Mean(SD)** | **[Min-Max]** | **Mean(SD)** | **[Min-Max]** | | | |
| Age at evaluation (years) | 16.2 (5.3) | [8.5–31.3] | 14.8 (4.1) | [8.8–23.7] | .03 | 1.16 | .253 |
| Age at diagnosis (years) | 6.3 (3.9) | [0.8–17.9] | 7.44 (4.2) | [1.1–16.1] | .02 | −1.21 | .232 |
| Time since RT (years) | 9.1 (2.9) | [3.9–15.3] | 6.5 (3.5) | [1.1–12.3] | .16 | 3.59 | **< .001** |
| Total tumor RT dose (cGy) | 5283 (558) | [3060–5940] | 5256 (365) | [4500–5940] | <.01 | 0.23 | .819 |
| Number of Craniotomies | 1.1 | [0–2] | 1.0 | [0–4] | <.01 | 0.42 | .674 |
| Karnofsky-Lansky score | 77.2 (14.5) | [50–100] | 85.4 (13.8) | [50–100] | .13 | −2.07 | **.047** |
| Household size | 4.1 (1.3) | [2–7] | 4.2 (1.2) | [2–8] | <.01 | −0.43 | .671 |

[1] **Bold text** indicates $p < .05$.

[2] Missing data include Karnofsky-Lansky score ($n = 11$ XRT, 5 PRT) and household size ($n = 1$ XRT, 5 PRT).

## Table 2

Neurobehavioral Scores for XRT and PRT Treatment Groups

| | XRT (*n*=29) | | PRT (*n*=51) | | $\eta^2$ | t | *P* |
|---|---|---|---|---|---|---|---|
| | ***Mean(SD)*** | ***Min-Max*** | ***Mean(SD)*** | ***Min-Max*** | | | |
| FSIQ | 74.0 (19.1) | 40 – 102 | 92.7 (16.8) | 48 – 134 | .16 | 3.99 | **<.001** |
| VCI | 81.7 (18.7) | 50 – 108 | 96.8 (16.4) | 59 – 136 | .12 | 3.25 | **.002** |
| PRI | 82.5 (19.2) | 45 – 115 | 97.6 (17.2) | 48 – 135 | .11 | 3.28 | **.002** |
| WMI | 78.7 (20.3) | 50 – 110 | 94.2 (15.6) | 51 – 135 | .11 | 3.14 | **.002** |
| PSI | 68.8 (13.4) | 50 – 92 | 85.1 (15.0) | 56 – 126 | .20 | 4.31 | **<.001** |
| BASC-2 Adaptive Composite | 45.9 (10.1) | 27 – 67 | 50.8 (11.1) | 27 – 70 | .04 | 1.66 | .101 |
| BASC-2 Attention | 52.8 (9.1) | 34 – 68 | 49.2 (12.3) | 33 – 82 | .01 | −0.89 | .378 |
| BRIEF Behavior Regulation | 49.3 (7.9) | 37 – 68 | 49.5 (11.6) | 36 – 88 | <.01 | 0.50 | .617 |
| BRIEF Metacognition | 54.6 (11.2) | 38 – 87 | 51.3 (12.5) | 34 – 83 | .01 | −0.96 | .342 |

[1]Unadjusted means are presented. FSIQ, VCI, PRI, WMI, and PSI are presented as standard scores. BASC-2 and BRIEF are presented as T-scores. *t*- and *p*-values are derived from ANCOVAs with time since radiation and age as covariates.

[2]**Bold text** indicates $p < .05$.

[2]Missing data include PSI (*n* = 1 XRT), BASC-2 (*n* = 4 XRT, 5 PRT), and BRIEF (*n* = 1 XRT, 3 PRT) .

## Table 3

CVLT Scores for XRT and PRT Treatment Groups

| | XRT (*n*=29) | | PRT (*n*=51) | | $\eta^2$ | t | *p* |
|---|---|---|---|---|---|---|---|
| | ***Mean(SD)*** | ***Min-Max*** | ***Mean(SD)*** | ***Min-Max*** | | | |
| Trial 1 | −0.91 (1.23) | −4.0 – 2.0 | −0.31 (1.07) | −2.5 – 3.0 | .08 | 1.83 | .072 |
| Trial 5 | −1.26 (1.70) | −4.5 – 1.0 | −0.30 (1.38) | −4.0 – 1.5 | .08 | 2.53 | **.014** |
| Total 1–5 | 38.21 (13.97) | 13 – 61 | 47.53 (12.82) | 20 – 74 | .08 | 2.61 | **.011** |
| SDFR | −1.26 (1.61) | −4.5 – 1.5 | −0.24 (1.28) | −3.5 – 1.5 | .14 | 2.61 | **.011** |
| SDCR | −1.09 (1.47) | −5.0 – 1.0 | −0.14 (1.24) | −4.0 – 2.0 | .09 | 2.74 | **.008** |
| LDFR | −1.43 (1.65) | −4.5 – 1.0 | −0.15 (1.22) | −3.0 – 1.5 | .06 | 3.57 | **.001** |
| LDCR | −1.09 (1.52) | −4.5 – 1.5 | −0.03 (1.23) | −3.5 – 2.0 | .02 | 3.04 | **.003** |
| Recognition d’ | −1.14 (1.59) | −5.0 – 1.0 | −0.23 (1.53) | −5.0 – 1.5 | .02 | 1.97 | .052 |
| Semantic Clustering | −0.36 (1.19) | −3.0 – 2.5 | 0.25 (1.20) | −2.0 – 3.5 | .05 | 2.29 | **.025** |
| Serial Clustering | −0.10 (1.18) | −1.5 – 3.5 | −0.28 (0.87) | −1.5 – 3 | .04 | −1.27 | .209 |
| Learning Slope | −0.62 (1.49) | −4.0 – 2.0 | −0.22 (1.32) | −3.0 – 3.0 | .07 | 1.31 | .194 |
| Intrusions | 0.78 (1.36) | −1.0 – 4.5 | 0.26 (1.36) | −1.0 – 5.0 | <.01 | −0.56 | .576 |

[1] Unadjusted means are presented. Total 1–5 is presented as a T-score. All other scores are presented as z-scores. *t*- and *p*-values are derived from ANCOVAs with time since radiation and age as covariates.

[2] **Bold text** indicates $p < .05$.

**Table 4**

CVLT Profile Classifications by Treatment Group

| | XRT (n=29) | | PRT (n=51) | | $X^2$ | *p* |
|---|---|---|---|---|---|---|
| | # | % | # | % | | |
| Encoding Deficit Profile | 9 | 31 | 6 | 12 | 4.51 | **.034** |
| Retrieval Deficit Profile | 5 | 17 | 2 | 4 | 4.11 | **.043** |
| Intact Profile | 11 | 38 | 36 | 71 | 8.14 | **.004** |
| Other Profile | 4 | 14 | 7 | 14 | <.001 | .993 |

[1]**Bold text** indicates $p < .05$.

## Table 5

Correlations Between Encoding Scores and Neurobehavioral Measures

| | Encoding Score (T1-5 Total) | |
|---|---|---|
| | ***r*** | ***p*** |
| FSIQ | .56 | **<.001** |
| BASC-2 Adaptive Skills Composite | .30 | **.011** |
| Adaptability | .17 | .162 |
| Social Skills | .13 | .277 |
| Leadership | .35 | **.002** |
| ADLs | .18 | .135 |
| Functional Communication | .45 | **<.001** |
| BASC-2 Attention | −.36 | **.002** |
| BRIEF Behavioral Regulation | −.16 | .156 |
| BRIEF Metacognition | −.35 | **.002** |
| Initiation | −.32 | **.005** |
| Working Memory | −.39 | **<.001** |
| Planning/Organization | −.34 | **.002** |
| Monitoring | −.31 | **.006** |
| Organization of Materials | −.20 | .077 |

[1] **Bold text** indicates $p < .05$.