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Dose–volume metrics and their relation to memory performance in pediatric brain tumor patients:A preliminary study

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Abstract

Background: Advances in radiation treatment (RT), specifically volumetric planning with detailed dose and volumetric data for specific brain structures, have provided new opportunities to study neurobehavioral outcomes of RT in children treated for brain tumor. The present study examined the relationship between biophysical and physical dose metrics and neurocognitive ability, namely learning and memory, 2 years post-RT in pediatric brain tumor patients.

Procedure: The sample consisted of 26 pediatric patients with brain tumor, 14 of whom completed neuropsychological evaluations on average 24 months post-RT. Prescribed dose and dose–volume metrics for specific brain regions were calculated including physical metrics (i.e., mean dose and maximum dose) and biophysical metrics (i.e., integral biological effective dose and generalized equivalent uniform dose). We examined the associations between dose–volume metrics (whole brain, right and left hippocampus), and performance on measures of learning and memory (Children's Memory Scale).

Results: Biophysical dose metrics were highly correlated with the physical metric of mean dose but not with prescribed dose. Biophysical metrics and mean dose, but not prescribed dose, correlated with measures of learning and memory.

Conclusions: These preliminary findings call into question the value of prescribed dose for characterizing treatment intensity; they also suggest that biophysical dose has only a limited

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

advantage compared to physical dose when calculated for specific regions of the brain. We discuss the implications of the findings for evaluating and understanding the relation between RT and neurocognitive functioning.

Keywords

dosimetry; late effects; learning and memory; pediatric brain tumor; radiation

Brain and central nervous system tumors are among the most common childhood cancers.[1] Treatment advances have resulted in increased survival rates among pediatric brain tumor (PBT) patients; however, radiation therapy (RT) is associated with suboptimal cognitive, behavioral, and emotional outcomes.[2–5] Many survivors of PBT experience long-term impairments in cognitive abilities and decreased academic functioning, reducing the likelihood of vocational success. Therefore, research aimed at limiting cognitive morbidity is of paramount importance.

1 | NEUROPSYCHOLOGICAL LATE EFFECTS

The adverse effects of RT on the developing brain are well-documented. A mild decline in IQ among PBT patients is reported as early as 1 year and as late as 10 years post-treatment.[6,7] This decline in IQ reflects the failure of pediatric patients to make expected gains in their cognitive abilities relative to peers, rather than a loss of previously acquired skills.[8] Deficits in learning and memory are among the most common sequelae of RT, particularly among children with third ventricle tumors[9] and medulloblastoma.[10,11] Children with a brain tumor perform more poorly than comparative groups[9,12] and normative means[10] on tests of verbal and/or visual learning and memory.[9,10,13]

The hippocampus is a critical structure for memory.[14] Despite the established link between RT and hippocampal damage in animal models,[15,16] evidence is limited in humans but remains indicative of damage. Among children treated for infratentorial tumors, there is evidence for early decline in hippocampal volume with return to positive growth 2 years post-diagnosis,[17] however, hippocampal volume may remain reduced relative to healthy peers several years post-diagnosis.[18] Notably, memory performance of adult survivors of PBT is related to hippocampal volume but not whole brain or putamen volumes.[19] Findings from a recent study examining associations between hippocampal subfield volumes (cornus ammonis [CA] 1, CA2–3, dentate gyrus [DG]-CA4, stratum radiatum–lacunosum–moleculare [SRLM], and subiculum) and verbal short-term memory revealed smaller DG-CA4, CA1, CA2–3, and SRLM volumes in PBT survivors compared to healthy children; and positive correlations between verbal memory and DG-CA4, CA1, and SRLM volumes.[20]

2 | DOSIMETRY AND NEUROPSYCHOLOGICAL LATE EFFECTS

Although considerable evidence exists for a relationship between cognitive abilities and RT, previous research has relied primarily on prescribed dose (i.e., total dose to the target volume) or contrasts based on the volume of brain irradiated (i.e., whole brain vs. restricted field) to assess radiation exposure.[21,22] However, these broad-based metrics do not account for variability in RT procedures from one patient to the next, including variations in dose,

volume, and beam orientation, which are integral to minimizing damage to normal brain tissue and sparing critical brain structures. For example, prescribed dose does not account for dose–volume heterogeneity, commonly related to tissue late effects. Manipulation of these RT variables in treatment planning has made the use of prescribed dose an imprecise measure of RT.

Three dimensional (3D) conformal therapy and methods of dosimetry now allow for analysis using differential and cumulative dose–volume histograms (DVHs), derived from dosimetry calculated on a fine spatial scale. These analyses map the heterogeneous levels of dose throughout the brain, so that the dose delivered to the whole brain and specific structures can be assessed. In an attempt to better account for variability in the distribution of dose over treatment volume, Merchant and colleagues partitioned RT dose–volume data into three ranges (low, intermediate, and high) to represent the fractional volumes that received each dose in the total brain, supratentorial brain, and left and right temporal lobes.[23] They showed that IQ after RT was significantly correlated with dosimetry of the total and supratentorial brain volumes.

For further precision, information derived from 3D conformal therapy and dosimetry can be used to calculate radiobiologic indices, such as generalized equivalent uniform dose (gEUD) and integral biological effective dose (IBED). In addition to the physical RT dose, these indices model the actual biological effect resulting from dose. Radiobiological approaches to understanding long-term side effects of RT have shown that biological effects depend, for any given tissue, on the dose, volume, fractionation sizes, and alpha/beta ratio, where alpha and beta are the radiobiological cell survival parameters for the tissue within the treatment volume. *gEUD* refers to the absorbed dose that, when homogeneously delivered to a tumor, causes the same expected number of clonogens to survive as the actual nonhomogeneous absorbed dose distribution.[24] The underlying assumption is that homogeneous irradiation of a tumor with absorbed dose D, and any nonhomogeneous irradiations with EUD equal to D are equivalent in a biological sense. *IBED* is calculated using the linear quadratic model of cell survival.[25] Ultimately, the biological effect of RT, not the physical dose, is most relevant to late-effects research. Calculation of gEUD or IBED yields a single value and makes it possible to compare patients treated with the same dose, but with different dose volumes.

IBED has been the focus of limited research on neurobehavioral outcomes following RT (see Zureick[26] for limited use of gEUD). Reimers and colleagues reported a significant relationship between IBED to the isocenter of the treatment field and verbal IQ.[27] Ris and colleagues used IBED as a method for more precise modeling of neurobehavioral late effects in a sample of five children with PBT.[28] Decline in digit span performance from year 1 to year 2 post-RT significantly correlated with whole brain IBED but not prescribed dose. To our knowledge, no other studies have examined the relation between IBED and neuropsychological late effects. Although several studies have shown a relationship between prescribed dose and neurocognitive late effects, very few studies have employed more refined metrics to determine if any advantage is conferred in the study of late effects. General indices of dose may be satisfactory predictors of global cognitive abilities such as IQ, but more precise metrics may be better predictors of specific cognitive abilities such as learning and memory.

3 | THE PRESENT STUDY

The primary aims of the current study are twofold. First, this study extends Ris et al. by contrasting the values of prescribed dose and physical and biophysical metrics used to capture dose heterogeneity in brain tissue.[28] Second, this study directly assesses the associations among RT dose metrics and verbal and visual–spatial learning and memory. Because biophysical metrics of IBED and gEUD take into consideration individualized treatment variables, not accounted for by prescribed dose, we predicted that biophysical metrics would be more strongly associated with learning and memory performance than prescribed dose.

4 | METHODS

4.1 | Participants

This study is part of a longitudinal project on cognitive, behavioral, and social–emotional outcomes following PBT treated with or without RT. Participants were children and adolescents aged 3–17 years who recently underwent surgical resection of a brain tumor. They were recruited from neuro-oncology clinics at four urban medical centers. Detailed eligibility criteria are reviewed elsewhere.[4,29] Briefly, exclusion criteria include severe preexisting conditions or ineligible tumor types (e.g., glioblastoma multiforme), severe postsurgical complications, or history of neurofibromatosis type 1. Ultimately, 69 participants were enrolled in the study; 2 died prior to data collection and 4 dropped out, yielding 63 participants, 30 of whom were treated with RT. Only those receiving RT and for whom detailed dosimetric data were available are included in this study, yielding a sample of 26 patients diagnosed between the ages of 5 and 16 years. A summary of demographic and tumor-/treatment-related variables is presented in Table 1. The sample is predominantly male, with the majority of parents completing at least some college. The majority of participants had infratentorial tumors, were treated with craniospinal RT with a boost to the tumor bed, and received chemotherapy. Fourteen participants had neurocognitive data available at follow-up approximately 2 years postsurgery, so associations between dose metrics and memory are described for this subsample. Specifically, four participants dropped out, six were lost to follow-up, one died in the interim between baseline and follow-up evaluations, and one was not administered the memory measures. Participants with neuropsychological data did not differ from those without on demographic and tumor-related variables, including gender, parental education, age at surgery, tumor location, and prescribed dose (all P-values > 0.09).

4.2 | Dose reconstruction

Calculation of RT dose was performed throughout the brain volume using the results of the respective treatment planning systems. RT doses were calculated using the collapsed cone convolution super-position algorithm (Pinnacle, Tomotherapy Planning Station) or pencil beam algorithm (Brainscan, iPlanDose). The former provides excellent agreement between computed and measured doses under a wide variety of conditions, with almost all points within 3% of agreement,[30,31] and the latter provides equivalent agreement in homogenous media such as the brain.

4.3 | Contouring

Neuroanatomical structures including the right hippocampus, left hippocampus, and whole brain were delineated manually by a single author (M.L.) in all RT patients on 1.5T T1 magnetic resonance (MR) images (see Figure 1). As MR images were acquired over a period of time and locations, the scan parameters varied. Most images were standard post-contrast T1-weighted 2D sequences (2000 ms TR, 3 ms TE, 384 × 512), 5 mm slice thickness, acquired from base of skull to top of head; others were post-contrast T1-weighted FLAIR images (2000 ms TR, 27 ms TE, 512 × 512) or 3D T1-weighted SPGR sequences (4.2 ms TR, 1.9 ms TE, 256 × 256, 1.3–1.5 mm slice thickness).

Contouring was performed in MimVista (Mim Software Inc, Cleveland, OH) using the 2D brush tool and standard neuroanatomical atlases within MimVista. The hippocampi were generated following the methodology described by Gondi and colleagues.[32] Inter-rater reliability was assessed by comparing volumes of two contourers repeating contours 10 times on one patient on separate days. Mean volume differences were found to be 3.3%, with a maximum difference of 3.8%.

4.4 | Dose Metrics

4.4.1 | Prescribed dose—Refers to the total dose prescribed to the target volume. For patients receiving craniospinal RT with a boost to the tumor bed, the prescribed dose is the sum of these two doses.

4.4.2 | Physical dose metrics

Mean dose.: For a given structure, the mean dose is the average dose to that structure: Dose to a subvolume × volume of that subvolume / sum of all subvolumes.

Maximum dose.: This refers to the maximum dose of any subvolume in that structure for a given structure.

4.4.3 | Biophysical dose metrics

Generalized equivalent uniform dose (gEUD).: Equivalent uniform dose was first proposed to provide a metric for nonuniform tumor dose[33] and then extended to the more general form for nonuniform normal tissue dose.[24] It provides a single metric that attempts to reflect the biological effects to a structure resulting from a heterogeneous dose. It is calculated as

$$\mathrm{gEUD}=\left(\sum_{i}\upsilon_{i}\mathrm{D}_{i}{}^{a}\right)^{1/a}$$

Mathematically, gEUD is the quantity sum of all subvolume υ_i times the dose to that subvolume D_i to an exponent a, then taken to the inverse of a after summing. The value of a is generally negative for tumors and positive for normal tissues. A value of zero results in gEUD equaling the mean dose.

Integral biological effective dose (IBED): The calculation of IBED is a two-step process. In the first step, the heterogeneous dose distribution of a treatment volume is condensed to a dose–volume relation using a differential dose DVH. This step breaks the volume into many small subvolumes, sums the volumes in the dose increments, and presents the results in a DVH. In the second step, IBED is calculated from the DVH data.

Normal tissue response to RT can be modeled using linear (α) and quadratic (β) terms. Using the terms of the linear quadratic model of cell survival, IBED[30,31] is calculated as

$$\mathrm{IBED} = \sum \mathrm{n}\mathrm{d}_\mathrm{i}\left(1 + \frac{\mathrm{d}_\mathrm{i}}{\alpha/\beta}\right)\frac{\Delta \mathrm{v}_\mathrm{i}}{\mathrm{V}}$$

where n is the number of fractions delivered, d_i is the dose delivered to the ith element of the volume from the DVH, α / β is a measure of the early and late response for a particular tissue, Δv is the volume of the ith element, and V is the total volume of the treated volume. The α/β ratio was assumed to be constant for normal brain tissue with a value of 2.9(i).

4.5 | Measures

Subtests from the Children's Memory Scale (CMS)[34] assessed verbal and visual–spatial learning and memory. Subtest raw scores were converted to scaled scores.

Stories.—Children listened to two stories and after each they recalled the story verbatim immediately and following a 30 min delay.

Word Pairs.—Participants listened to a list of word pairs, and after each of the three learning trials, they repeated the list (i.e., immediate memory) as well as after a 30 min delay.

Faces.—Participants studied a series of faces; then another series of faces was presented immediately thereafter and 30 min later, and participants responded "yes" if the face was presented earlier and "no" if it was not.

Dot Locations.—Participants studied the location of blue dots inside a large grid, and then replicated this pattern using chips on a blank grid. Participants had three trials to learn the locations, before being asked to recall them after a 30 min delay.

4.6 | Procedure

Participants were recruited during neuro-oncology follow-up visits, and parents provided informed consent in accordance with institutional review boards. Patient charts and RT treatment plans were reviewed by a radiation oncology physicist blind to the results of memory testing (M.L.) to record treatment data. Total doses to the tumor site and craniospinal axis were recorded. For volumes other than craniospinal axis treatment, the planning data were reviewed and the planning target volumes and doses were recorded. The memory tests included in the study were collected during follow-up evaluations that occurred approximately 24 months following surgical resection.

4.7 | Statistical analyses

Due to the nonnormal distributions of the dosimetric variables, Spearman's rho rather than Pearson's r examined the strength and direction of the relationship between dosimetry variables for the whole brain and right and left hippocampi. Spearman's rho examined relationships between dose metrics for brain regions and memory performance. One-sample *t*-tests compared the sample mean on memory measures to the normative mean scaled score of 10.

5 | RESULTS

5.1 | Correlations among dose metrics

Table 2 presents the correlation matrix for RT dose metrics. Prescribed dose was not significantly correlated with other metrics, with the exception of maximum dose delivered to the whole brain and right hippocampus. For whole brain and hippocampal metrics, mean dose, IBED, and gEUD were highly correlated; maximum dose also correlated with other dose metrics in the hippocampi alone.

5.2 | Memory performance among PBT patients

Table 3 presents descriptive statistics for the memory tests. Mean performance for the study sample was significantly lower than the standardization mean on delayed recall of Faces ($t = -3.29$, $P < 0.01$; but not immediate recall, $t = -2.05$, $P < 0.07$) and Word Pair learning ($t = -3.12$, $P < 0.01$; but not delayed recall, $t < 1$). Significant differences were not observed for Dot Locations learning or delayed recall (t's < 1); and immediate and delayed recall for Stories ($t < 1$, $t = 1.37$, $P < 0.20$, respectively).

5.3 | Correlations among dose metrics and memory performance

Table 4 presents the correlation matrix relating dose metrics to memory performance. Memory measures were not correlated with prescribed dose. Conversely, Word Pair delayed recall was significantly associated with whole brain and right hippocampus mean dose, IBED, and gEUD; and left hippocampus gEUD, though correlations with IBED and mean dose were large ($r > -0.50$) and marginally significant. Additionally, Dot Locations learning and recall was associated with whole brain IBED, gEUD, and mean dose ($r < -0.56$).

6 | DISCUSSION

The current study examined the relationship between physical and biophysical RT dose metrics and their relationship to learning and memory outcomes 2 years post-RT in a sample of PBT patients. This study addressed a number of unique aspects of dosimetry and its relationship to neurocognitive outcome including: (1) the relative value of prescribed dose in characterizing RT exposure in pediatric patients and its association with neurocognitive outcome; (2) the relationship between different measures of physical and biophysical dose; and (3) the relative value of using physical dose versus biophysical dose to predict neurocognitive outcome.

Prescribed dose is the most commonly employed metric in neurocognitive late-effects research examining treatment intensity as a predictor of cognitive decline. In our sample, prescribed dose was not significantly correlated with more refined physical or biophysical dose metrics. Moreover, prescribed dose was not significantly correlated with memory performance, thereby replicating and extending the findings of Ris and colleagues, which focused specifically on brief attention and working memory.[28] Taken together, prescribed dose in pediatric samples with heterogeneous tumor types may be less meaningful as a marker than biophysical metrics, potentially because it does not reflect the volume of brain irradiated.

Biophysical metrics and the physical metric of mean dose were highly correlated. To the extent that dose is homogeneous, biophysical metrics and mean dose behave similarly. Homogeneity of dose is more likely in smaller brain structures, such as the hippocampus, relative to larger structures. In calculating biophysical metrics, lower dosage volumes are minimized and higher volumes are maximized given that higher doses often produce significant biological effects and lower doses result in no or subclinical effects. Our findings reveal near perfect correlations between biophysical metrics and mean dose in the hippocampus, with somewhat decreased association between whole brain metrics. Thus, biophysical metrics do not appear to offer any unique information over and above that accounted for by physical metrics in this sample, particularly for smaller brain structures. Our findings likely reflect the fact that more than half of the sample treated with RT received craniospinal RT plus a posterior fossa boost, resulting in increased homogeneity of dose to brain structures.

Given that biophysical metrics and mean dose were highly correlated, it is not surprising that both were predictive of learning and memory; and considerably more so than prescribed and maximum doses. As a group, our sample performed in the average range on measures of verbal and visual memory, with the exception of Word Pair learning and delayed recall of Faces, which fell in the low average to average range but significantly below the normative mean. Learning and memory outcomes following RT are mixed, with PBT patients demonstrating significantly worse verbal learning and memory than controls,[28,35] stable or improved verbal and visual memory over time[36]; or decline in verbal memory but not visual memory[26] or vice versa.[37]

Both verbal and visual memory measures were sensitive to the effects of RT. Word Pair delayed recall, which is commonly associated with hippocampal functioning, was similarly correlated with whole brain and hippocampal dose metrics. Although we observed more statistically significant correlations with the right than left hippocampus, the magnitude of the correlations were similar. Functional imaging studies from the adult literature indicate that successful verbal associative encoding requires activation of the left hippocampus as well as the left inferior frontal gyrus.[38] While the left hippocampus appears to be necessary for verbal associative learning, it may not be sufficient, as there is evidence for bilateral recruitment.[39,40] Significant correlations with the right hippocampus may suggest the presence of a compen-satory mechanism supporting average range performance, as is often the case when involvement of the adjacent hemispheric homologue is implicated.[41–43]

Dot Locations learning and recall were significantly correlated with whole brain dose metrics, though not specifically to the right or left hippocampus. These findings may reflect the notion that memory is a distributed process, particularly visual memory which is thought to be less lateralized than verbal memory, likely reflecting the broader distribution of the visual–perceptual system. Although the hippocampus is susceptible to damage in PBT patients, white matter is also at considerable risk.[11,44] In patients with TBI, visual memory performance was associated with wide spread reductions in grey and white matter volume of several cortical and subcortical structures, implicating the alteration of multiple systems subserving attentional and memory processing.[45]

Our findings must be considered in the light of the methodological limitations. First, the sample is small, which limits the generalizability of the findings, statistical power to detect significant effects, and robustness of observed relationships. Second, a number of participants received craniospinal RT with a boost to the tumor bed, thereby reducing dose heterogeneity and variation between biophysical and physical metrics. Third, this sample is notable for diagnostic heterogeneity. Although memory problems are commonly reported in children with infratentorial and midline tumors, the small sample precludes accounting for tumor location. Fourth, the study employed a variety of memory measures, with the exception of the commonly used list learning task.

With advances in radiation oncology, we are able to better explore relationships between RT and neurocognitive outcome. The current study suggests that prescribed dose in a heterogeneous sample does not correlate with physical and biophysical metrics or predict memory outcomes. In contrast, measures of dosimetry derived from physical and biophysical properties correlate in a predictable way and are predictive of memory, although biophysical metrics hold no clear advantage over mean dose. Understanding the effects of RT dosimetry on cognitive function is essential to develop new ways to target and administer RT in children with brain tumors. In fact, although mean dose does not account for the multidimensionality of individualized RT protocols, it is highly correlated with more precise metrics that take into account a number of individualized variables. Given the small sample size, replication of these findings is needed in a larger, more homogeneous sample.

Abbreviations:

CA	cornus ammonis
DG	dentate gyrus
DVH	dose-volume histogram
gEUD	generalized equivalent uniform dose
IBED	integral biological effective dose
MR	magnetic resonance
PBT	pediatric brain tumor
RT	radiation treatment

SRLM stratum radiatum–lacunosum–moleculare

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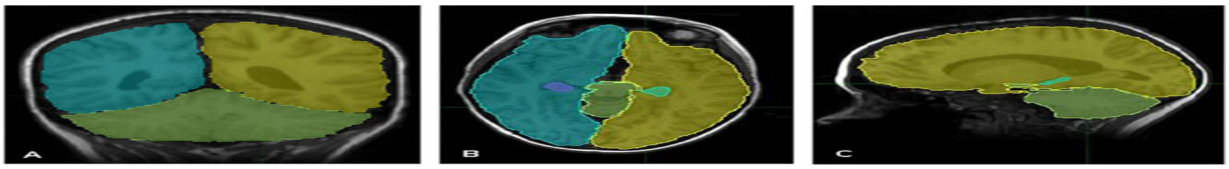

FIGURE 1.

Examples of slice contours oriented within the A) coronal B) axial, and C) sagittal planes. Each cerebral hemisphere is traced along with the hippocampi and cerebellum

TABLE 1

Demographic and tumor-related variables

Variable	
Gender (Male; n)	21
Age at surgery [Mean (SD)]	10.66 (3.87)
Age at follow-up (T2) [Mean (SD)]	12.60 (3.45)
Number of months post-surgery at follow-up [Mean (SD)]	24.83 (10.92)
Education of primary caregiver (n)	
Some high school	2
High school graduate	4
Some college	6
College graduate	7
Graduate degree	4
Type of tumor (n)	
Medulloblastoma/PNET	12
Astrocytoma	3
Germ cell	3
Ependymoma	2
Optic nerve glioma	2
Other (e.g., atypical teratoid-rhabdoid, bithalamic, and brainstem glioma)	4
Location of tumor (n)	
Supratentorial	10
Optic chiasm	3
Extrafrontal	2
Fronto-parietal/temporal	2
Other (pineal, sella)	3
Infratentorial	16
Posterior fossa	13
Other (multifocal, fourth ventricle)	3
Shunt placement	
Yes(n)	2
Chemotherapy	
Yes(n)	16
Type of radiation (n)	
Focal	9
Nonfocal	1
Craniospinal + Boost	16
Prescribed Dose (cGy) [Mean (SD)]	5210.77 (603.52)

Note: Missing data–chemotherapy (0); shunt placement (3); education of primary caregiver (3); follow-Up (12).

TABLE 2

Correlations among radiation metrics (N = 26)

	Prescribed dose	IBED	gEUD	Mean	Max
Whole brain					
IBED	−0.076	1.00	0.812**	0.973**	−0.281
gEUD	0.382	-	1.00	0.835**	0.109
Mean	−0.036	-	-	1.00	−0.238
Max	0.795**	-	-	-	1.00
Right hippocampus					
IBED	0.151	1.00	0.984**	0.991**	0.580**
gEUD	0.231	-	1.00	0.994**	0.670**
Mean	0.207	-	-	1.00	0.631**
Max	0.493*	-	-	-	1.00
Left hippocampus					
IBED	−0.035	1.00	0.984**	0.990**	0.666**
gEUD	0.058	-	1.00	0.996**	0.733**
Mean	0.028	-	-	1.00	0.709**
Max	0.319	-	-	-	1.00

Note: Nonparametric (Spearman's rho) correlations are reported.

*=$P < 0.05$;

**=$P < 0.01$.

TABLE 3

Performance on memory subtests (n = *14*)

	M	*SD*	Range
Dot Locations			
Learning	9.43	3.61	3–16
Delay	10.42	3.13	3–14
Faces			
Immediate	8.07	3.52	1–13
Delay *	7.79	2.52	3–12
Stories			
Immediate	10.36	2.65	6–15
Delay	10.86	2.35	7–15
Word Pair			
Learning *	8.29	2.05	5–12
Delay	9.36	3.00	4–16

Note

* $=P < 0.01$ for one-sample *t*-test (normative mean of 10).

TABLE 4

Correlations among radiation metrics and memory subtests (time 2 scores; n = 14)

	Stories		Faces		Word Pair		Dot Loc	
	Imm.	**Delay**	**Imm.**	**Delay**	**Learn.**	**Delay**	**Learn.**	**Delay**
Prescribed dose								
	0.159	0.142	−0.061	−0.235	0.227	−0.409	−0.140	−0.243
Whole brain								
IBED	−0.292	−0.328	−0.095	−0.461	−0.161	−0.606*	−0.561*	−0.582*
gEUD	−0.292	−0.323	−0.071	−0.476	−0.099	−0.648*	−0.632*	−0.636*
Mean	−0.268	−0.289	−0.007	−0.408	−0.167	−0.575*	−0.603*	−0.580*
Max	0.087	0.100	0.115	−0.028	−0.002	−0.391	−0.177	−0.218
Right hippocampus								
IBED	−0.190	−0.104	−0.032	−0.278	−0.018	−0.571*	−0.327	−0.286
gEUD	−0.125	−0.069	−0.027	−0.259	0.000	−0.551*	−0.382	−0.373
Mean	−0.181	−0.124	−0.020	−0.248	−0.023	−0.590*	−0.375	−0.389
Max	0.130	0.143	−0.011	−0.093	0.030	−0.417	−0.036	−0.237
Left hippocampus								
IBED	−0.145	−0.172	−0.135	−0.525	−0.101	−0.528	−0.279	−0.242
gEUD	−0.125	−0.181	−0.124	−0.505	−0.105	−0.566*	−0.340	−0.373
Mean	−0.116	−0.154	−0.097	−0.498	−0.066	−0.519	−0.326	−0.304
Max	0.292	0.205	−0.127	−0.336	−0.076	−0.411	0.050	−0.189

Note: Nonparametric (Spearman's rho) correlations are reported.

*$= P < 0.05$.