Neuro-Oncology Practice
9(3), 208–218, 2022 | https://doi.org/10.1093/nop/npac011 | Advance Access date 19 February 2022

Radiation dose to circumscribed brain regions and neurocognitive function in patients with meningioma

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Abstract

Background. Although radiation (RT) is standard treatment for many brain tumors, it may contribute to neurocognitive decline. The objective of this study was to investigate associations between RT dose to circumscribed brain regions and specific neurocognitive domains in patients with meningioma.

Methods. We undertook a retrospective study of 40 patients with meningioma who received RT and underwent an in-depth clinical neurocognitive assessment. Radiation dosimetry characteristics were delineated based on treatment planning computerized tomography co-registered with contrast-enhanced 3DT1-weighted magnetic resonance imaging. Principal components analysis was applied to organize neurocognitive test scores into factors, and multivariate multiple linear regression models were undertaken to examine if RT dose to circumscribed brain regions is associated with specific neurocognitive outcomes.

Results. Radiation dose to brain regions was associated with neurocognitive functions across a number of domains. High dose to the parietal-occipital region was associated with slower visuomotor processing speed (mean dose, $\beta = -1.100$, $P = .017$; dose to 50% of the region [D50], $\beta = -0.697$, $P = .049$). In contrast, high dose to the dorsal frontal region was associated with faster visuomotor processing speed (mean dose, $\beta = 0.001$, $P = .036$).

Conclusions. These findings suggest that RT delivered to brain regions (ie, parietal-occipital areas) may contribute to poor neurocognitive outcomes. Given that modern radiotherapy techniques allow for precise targeting of dose delivered to brain regions, prospective trials examining relations between dose and neurocognitive functions are warranted to confirm these preliminary results.

Keywords

meningioma | neurocognition | radiation dosimetry | radiation-induced cognitive decline

Radiation therapy (RT) is fundamental in the treatment of many primary brain tumors, yet RT may lead to neurocognitive decline due to the RT of healthy brain tissue, negatively affecting the tissue and plasticity and repair processes.[1,2] Neurocognitive decline can significantly impact patient quality of life.[3] In the absence of curative treatment, quality of life is

recognized as one of the most important outcomes following brain tumor treatment.[4] The neurotoxic effects of RT must be carefully weighed against the benefits for tumor control to aid in treatment planning. Yet, the risk for RT-induced neurocognitive decline is not clear in adults. This is particularly problematic for patients with high survival rates such as those with meningioma[5] given that the risk of developing irreversible neurocognitive decline may increase over time.[1,6]

Recent improvements in RT treatment planning allow for precise targeting and quantification of dose delivered to specific regions. There is, however, limited research investigating which brain regions are important to avoid in adults with primary brain tumors. Although several studies have examined the biological vulnerability (eg, atrophy and white matter damage) of specific brain structures exposed to RT,[7–9] few studies have used volumetric RT dosimetry to examine how individual neurocognitive domains are differentially affected by RT dose to these brain regions. Most of this research has investigated the effects of RT on the hippocampus and resultant memory decline,[10–12] given the central role of the hippocampus in memory function.[13] Moreover, the hippocampus is an active site of adult neurogenesis which is hypothesized to be vulnerable to RT.[14,15] In those studies, high dose to the left hippocampus was associated with worse verbal memory.[10,12,16] Other neurocognitive domains such as processing speed, attention, and executive function are, however, also affected by RT.[16–18] The radiosensitivity of brain regions associated with these neurocognitive domains is under-characterized. We are aware of only two studies that have investigated these in adults.[16,19] To this end, data suggest that high RT dose to other brain regions (eg, frontal lobe) is associated with poor neurocognitive outcome. What remains unclear is whether RT to circumscribed brain regions is associated, in a dose-dependent manner, with poor neurocognitive outcomes in specific domains. It is important to complement advances in our understanding of the biological vulnerability of brain structures to RT with additional research examining brain regions that are associated with poor clinical (ie, neurocognitive) outcomes when exposed to RT.

The current study expands upon this literature in the following ways. First, we investigated the association between RT dose to pre-specified brain regions and neurocognitive domains in a homogenous sample of patients with non-parenchymal brain tumor (ie, meningioma). Meningioma lacks the confounding factors that have clouded previous research investigating the impact of RT on neurocognition as they are not treated with chemotherapy and patients have long progression-free survival and life expectancies. Radiation is standard of care for patients with meningioma that are not safely amenable to surgery, or after incomplete surgical resection.[20] Here, we examined volumetric RT dosimetry to explore whether interindividual differences in RT dose to circumscribed brain regions influence specific neurocognitive domains. We hypothesized that high doses of RT directed at certain brain regions would be associated with poor memory, processing speed, attention, and executive function. In particular, we expected that high dose delivered to the left hippocampus would be associated with worse verbal memory, as has already been shown.[10,12,16] In addition, we hypothesized that high RT doses delivered to the dorsal frontal lobe would be associated with worse performance on tests of executive function.[16,21] Little is known about RT dose delivered to ventral frontal, subcortical, cerebellar, and parietal-occipital regions and associated neurocognitive function. We hypothesized that high RT dose to frontal and subcortical regions would be associated with poor processing speed and attention, given that these neurocognitive processes are distributed in nature and rely on a complex network of cortical and white matter structures located in frontal-subcortical regions.[22] We also hypothesized that high dose to cerebellar regions would be associated with worse executive function and visuomotor processing, given the involvement of the cerebellum in facilitating these processes.[23] Finally, we expected that high dose to parietal-occipital areas would be associated with worse visuomotor ability given the involvement of these regions in visuospatial and motor functions.[24] Increased understanding of the associations between RT to brain regions and specific neurocognitive domains could elucidate neurocognitive risk following RT and help guide RT treatment planning.

Methods

Participants and Procedure

We undertook a retrospective study of patients who underwent neurocognitive assessment at the Princess Margaret Cancer Centre in Toronto, Canada between 2006 and 2021. Eligibility criteria included radiographically presumed or confirmed diagnosis of meningioma, age ≥18 years, and sufficient English proficiency to undergo neurocognitive testing. Participants were excluded if they had a prior history of psychiatric or neurological disorder, or invalid neurocognitive test results. Test validity was examined when participants were found to perform above cutoff scores on two embedded validity measures: the Reliable Digits Span[25] and the Trail Making Test Part A.[26] For this study, we included only patients who received RT.

Tumor and treatment-related information were retrieved from electronic medical records. A chart review was conducted to obtain neurocognitive testing data. Tests were administered by trained personnel supervised by a licensed neuropsychologist (K.E.). Radiation dosimetry characteristics for each brain region were delineated from RT treatment planning software (described later). This study was approved by both the University Health Network and the University of Toronto research ethics boards.

Materials

Neurocognitive assessment.—In-depth neurocognitive testing was conducted for clinical purposes. Test descriptions, acronyms, and references are provided in Supplementary Table 1. In brief, we included the CVLT-II LDFR, FAS, RCFT-DR, TMT Parts A and B, WAIS-III and WAIS-IV Arithmetic, Digit Symbol Coding, Digit Span Forward and Backward, Symbol Search, and WCST. Neurocognitive test scores were standardized using normative data, accounting for patient age, gender, and

level of education when appropriate, and converted into *z*-scores (M = 0, SD = 1). Higher scores indicate better performance on neurocognitive tests.

Radiation dosimetry.—Treatment planning computerized tomography was co-registered with contrast-enhanced 3D T1-weighted magnetic resonance imaging on Pinnacle or RayStation planning system software. We segmented the brain into broad regions (cerebellum, dorsal frontal, hippocampus, parietal-occipital, subcortical, temporal, and ventral frontal) that were manually contoured in the treatment planning system according to standardized contouring anatomy modules[27–32] (for specific anatomical regions of interest [ROI] boundaries, see Supplementary Figure 1 and Supplementary Table 2). Tumor and surgical beds (ie, the contoured gross tumor volume [GTV]) were excluded from ROI contours; brain tissue surrounding the tumor and surgical beds were included in ROI contours. The contouring was performed by a single observer (A.S.) and reviewed by a radiation oncologist (D.S.T.). The clinical RT dose plans were used to calculate dose volume histograms for each of the delineated structures. Mean dose and dose received by 50% (D50) of each of these segmented brain regions for all participants were recorded and defined as dosimetric endpoints of interest.

Statistical Analyses

Demographic and medical characteristics were reported descriptively. Principal components analysis (PCA) was applied to organize neurocognitive test performance into factors in order to reduce the number of variables entered into the regression model. Based on PCA results, test *z*-scores were averaged to create one score for each factor. These factors were then entered into multivariate multiple regression models.

To determine if multivariate multiple regression analyses were appropriate, correlation analyses were undertaken to examine the relationship amongst neurocognitive factors. Multivariate multiple linear regression models were then used to determine if RT dose to ROI were associated with neurocognitive performance. In these models, neurocognitive performance was a latent variable composed of an aggregate of neurocognitive tests based on the factors identified by PCA. We first evaluated a baseline model (Model 1) to determine which variables to retain in Model 2. Model 1 included demographic (ie, age, sex, and education) and medical (ie, time since RT, surgery, antiepileptic medications, tumor laterality, tumor location [frontal vs other], and tumor volume) variables. Surgery and tumor location were confounding variables and were therefore entered into separate models (Model 1a and 1b, respectively). Model 1a is represented below.

Model 1a: $\text{Outcome} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Sex} + \beta_3 \text{Education} + \beta_4 \text{Time Since RT} + \beta_5 \text{Surgery} + \beta_6 \text{Antiepileptic Medications} + \beta_7 \text{Tumor Laterality} + \beta_8 \text{Tumor Volume}.$

Radiation dose delivered to individual brain regions (ie, cerebellum, dorsal frontal, hippocampus, parietal-occipital, subcortical, and ventral frontal) was then evaluated in Model 2, with mean dose and D50 entered into separate models (Model 2a and 2b, respectively). These models provided an omnibus test for each of the predictor variables regressed onto all four neurocognitive factors at once, controlling for demographic and medical variables that contribute to neurocognitive performance (ie, significant variables identified in Model 1). Correlation between ROI dosimetric measures were reported using Pearson's correlation coefficient. Dose to temporal lobes was not included due to the high correlation with dose to hippocampi ($r = .9$, $P < .001$; see Supplementary Figure 2). Dose to GTV was included in this model to control for dose administered to the tumor itself. Dose to ROI were added to the model together in order to estimate their impact on neurocognition when all other predictor variables were held constant. Model 2a is represented below (note, all ROI's represent mean dose in Model 2a).

Model 2a: $\text{Outcome} = \beta_0 + \beta_1 \text{Education} + \beta_2 \text{Tumor Location} + \beta_3 \text{GTV Dose} + \beta_4 \text{Cerebellum Dose} + \beta_5 \text{Dorsal Frontal Dose} + \beta_6 \text{Hippocampi Dose} + \beta_7 \text{Parietal-Occipital Dose} + \beta_8 \text{Subcortical Dose} + \beta_9 \text{Ventral Frontal Dose}.$

Post hoc tests evaluating the effect of significant ROI dose predictor variables on neurocognitive factors were then conducted. To determine which models were appropriate for post hoc investigation (ie, the model that contains only significant ROI or the model that controls for all ROI a better fit for the data), fit indices of the models with significant ROI predictor variables were compared with fit indices of the models with all ROI predictors. Models with better fit indices were selected for post hoc analyses. If model fit indices did not significantly differ, the more parsimonious model was selected for post hoc analyses. Statistical significance was defined at a *P*-value of <.05. *P*-values are two-sided and reported as unadjusted values. As this was an exploratory study testing the association between numerous ROI's and neurocognitive tests, there was an increased risk of family-wise type I errors. To reduce this risk, we used a hierarchical procedure to data analysis by investigating all four neurocognitive factors with a single test (ie, an overall omnibus measure). Post hoc analyses were only conducted with significant omnibus tests, thereby reducing the likelihood of type 1 errors.

To further explore these results, we examined the effect of dosimetry to brain regions and associations with performance on individual tests. Linear regressions were employed to generate models about the relationship between RT dose to circumscribed brain regions and performance on each neurocognitive test, while controlling for significant demographic and medical factors. In these exploratory analyses, *P*-values were adjusted for multiple comparisons using the false discovery rate (FDR) method[33] to account for the number of ROI dose variables and individual neurocognitive tests examined. This is known as a *Q*-value; a threshold of <.05 was used for statistical significance.

In all models, estimates of normality were analyzed. Variables that fell outside of the −1/1 range for skewness were log transformed. Continuous independent variables (Continuous independent variables included age, education, time since RT, tumor volume, and ROI dose.) were centered around their mean, whereas categorical independent

variables (Categorical independent variables included sex, surgery, antiepileptic medications, tumor laterality, and tumor location.) were effect-coded before being entered into the model. All analyses were performed using SPSS version 26 and R version 1.2.5042.

Results

Of 73 eligible participants who completed neurocognitive assessment, 10 were excluded due to prior history of neurological disease, 1 was excluded due to being <18 years of age at time of diagnosis, 1 was excluded due to prior history of comorbid neurological and psychiatric disease, and 1 was excluded due to non-credible neurocognitive test performance. We did include two (2.74%) participants who performed below cutoff scores on embedded validity measures, which is lower than the base-rate of validity test failure in clinical populations.[34] Notably, both participants were older adults, and there is an increased risk of misinterpreting genuine neurocognitive impairment as invalid performance among older adults.[35] As such, both participants were retained in our sample. Eighteen participants were excluded because they did not receive RT, and two were excluded because their RT treatment plans were irretrievable. The final sample consisted of 40 participants (52% male). Our sample had an average age of 49.55 (SD = 11.02) years and education of 15.78 (SD = 4.41) years. The average duration of time from RT to neurocognitive assessment was 23.79 (SD = 32.85) months. All participants received fractionated photon RT. Participant demographic and medical characteristics are shown in Table 1.

Table 1. Participant Demographic and Medical Characteristics

Characteristic	Mean (SD)	Range
Age at diagnosis[a]	49.55 (11.02)	29-74
Age at assessment[a]	55.85 (10.62)	36-80
Time between diagnosis and assessment[b]	80.68 (80.33)	2-445
Time between RT and assessment[b]	23.79 (32.85)	0-93
Education[a]	15.78 (4.41)	5-26
Tumor volume (cm^3)	22.89 (18.42)	1-77
Radiation prescription dose (median [SD])	5468.02 (530.52)	5000-7000
ROI mean radiation dose		
Cerebellum	1221.39 (968.20)	16-4291
Dorsal frontal	1367.42 (1179.77)	56-4462
Hippocampi	1922.84 (1234.17)	32-3932
Parietal-occipital	936.23 (871.60)	123-3142
Subcortical	1665.60 (1017.30)	63-3936
Ventral frontal	2128.76 (1556.01)	22-4832
ROI D50 radiation dose		
Cerebellum	1082.25 (944.67)	16-4485
Dorsal frontal	1123.65 (1402.60)	43-4951
Hippocampi	1593.30 (1238.04)	31-4130
Parietal-occipital	776.12 (843.27)	58-3003
Subcortical	1467.12 (1105.28)	54-4365
Ventral frontal	2097.50 (1682.50)	21-5371
Radiation fractions	28.12 (2.90)	25-35
	N (%)	
Sex (male)	21 (52.50)	
Marital status (married)	26 (65.00)	
Surgery (yes)	29 (72.50)	
Antiepileptic medication (yes)	9 (22.50)	
Tumor grade		
I	16 (40.00)	
II	12 (30.00)	
Unresected	11 (27.50)	
Unknown	1 (2.50)	
Tumor location		
Frontal	13 (32.50)	
Suprasellar	11 (27.50)	
Temporal	9 (22.50)	
Occipital	3 (7.50)	
Parietal	3 (7.50)	
Multiple locations	1 (2.50)	
Tumor laterality		
Left	18 (45.00)	
Right	17 (42.50)	
Midline	5 (12.50)	
Radiation technique		
3DCRT	2 (5.00)	
IMRT	28 (70.00)	
VMAT	10 (25.00)	

Abbreviations: 3DCRT, three-dimensional conformal RT therapy; assessment, neurocognitive assessment; IMRT, intensity-modulated RT therapy (ie, step-and-shoot); VMAT, volumetric modulated arc therapy.
[a]Years.
[b]Months.

Principal Components Analysis

PCA undertaken with neurocognitive test scores suggested that the data loaded onto four factors. This four-factor solution explained 79.18% of the total variance (KMO = .46). The four factors were interpreted as follow: (a) visuomotor processing speed (ie, TMT A and B, WAIS Digit Symbol Coding, and WAIS Symbol Search); (b) executive function (ie, FAS, WAIS Arithmetic, and WCST Errors); (c) memory (ie, CVLT-II LDFR and RCFT-DR); and (d) attention/working memory (ie, WAIS digit span backward and forward). See Supplementary Table 3 for more details.

Multivariate Multiple Regression Analyses

All neurocognitive factors were moderately correlated (r's = .30-.52, all $P < .05$), with the exception of visuomotor processing speed and memory ($r(37) = .30$, $P = .056$; see Supplementary Figure 3). Thus, multivariate multiple regression analyses were appropriate.

The results of the multivariate multiple regression analysis investigating demographic and medical characteristics revealed that education and tumor location significantly contributed to overall neurocognitive performance. That is, patients with lower levels of education and frontal tumors exhibited worse performance on neurocognitive tests (see Table 2, Model 1a and 1b). Therefore, education and tumor

Table 2. Multivariate Multiple Linear Regression Models

	Test Statistic	*F*-value	df	*P*-value
Model 1a				
Intercept	0.242	2.071	4, 26	.114
Age	0.024	0.158	4, 26	.958
Education	0.516	6.934	4, 26	.001*
Sex	0.282	2.552	4, 26	.063
AED	0.142	1.077	4, 26	.388
Surgery	0.219	1.821	4, 26	.155
Time since radiation	0.184	1.463	4, 26	.242
Laterality	0.165	1.282	4, 26	.303
Tumor volume	0.077	0.544	4, 26	.705
Model 1b				
Intercept	0.309	2.903	4, 26	.041*
Age	0.023	0.155	4, 26	.959
Education	0.457	5.479	4, 26	.002*
Sex	0.309	2.912	4, 26	.060
AED	0.168	1.311	4, 26	.292
Time since radiation	0.128	0.951	4, 26	.451
Laterality	0.146	1.113	4, 26	.372
Location	0.307	2.879	4, 26	.042*
Tumor volume	0.076	0.536	4, 26	.710
Model 2a				
Intercept	0.504	6.609	4, 26	.001*
Education	0.491	6.273	4, 26	.001*
Tumor location	0.210	1.732	4, 26	.173
GTV	0.132	0.989	4, 26	.431
Cerebellum	0.292	2.676	4, 26	.054
Dorsal frontal	0.341	3.361	4, 26	.024*
Hippocampi	0.157	1.210	4, 26	.330
Parietal-occipital	0.367	3.767	4, 26	.015*
Subcortical	0.100	0.720	4, 26	.586
Ventral frontal	0.274	2.459	4, 26	.071
Model 2b				
Intercept	0.352	4.074	4, 28	.009*
Education	0.245	2.441	4, 28	.068
Tumor location	0.246	1.280	4, 28	.300
GTV	0.150	1.322	4, 28	.284
Cerebellum	0.167	1.508	4, 28	.225
Dorsal frontal	0.289	3.050	4, 28	.032*
Hippocampi	0.140	1.274	4, 28	.302
Parietal-occipital	0.369	4.387	4, 28	.006*
Subcortical	0.049	0.390	4, 28	.814
Ventral frontal	0.122	1.041	4, 28	.402

Overall neurocognitive performance was the outcome variable in these models. Model 1 included demographic factors (age, education, and sex) and medical variables (antiepileptic medications, surgery, time since RT, tumor laterality, and tumor location). Surgery and tumor location were confounding variables and were entered separately into the model (Model 1a and Model 1b, respectively). Model 2 included significant variables from Model 1 (ie, education and tumor location), dose to GTV, and dose to individual brain regions. Model 2a included mean dose, and Model 2b included D50.
Abbreviations: df, degrees of freedom (numerator, denominator).
*Significant *P*-values (<.05).

location were retained in Model 2. Mean dose and D50 for each ROI were then added to separate models (see Table 2, Model 2a and 2b, respectively). As a whole, neurocognitive performance was positively influenced by mean dose to the dorsal frontal region ($F(4,626) = 3.361$, $P < .05$; higher dose to the dorsal frontal region was associated with better neurocognitive performance), negatively influenced by mean dose to the parietal-occipital region ($F(4,26) = 3.767$, $P < .05$; higher dose to the parietal-occipital region was associated with worse neurocognitive performance), positively influenced by D50 to the dorsal frontal region ($F(4,28) = 3.050$, $P < .05$; higher dose to the dorsal frontal region was associated with better neurocognitive performance), and negatively influenced by D50 to the parietal-occipital region ($F(4,28) = 4.387$, $P < .05$; higher dose to the parietal-occipital region was associated with worse neurocognitive performance). Neurocognitive performance was not significantly associated with mean dose or D50 to the cerebellum, hippocampi, subcortical, or ventral frontal regions.

Post hoc regression analyses with significant ROI's identified in Model 2a and 2b were conducted (see Table 3, Model 3a and 3b). Significant ROI predictor variables (ie, dorsal frontal and parietal-occipital) from Model 2a and 2b were retained in Model 3a and 3b, respectively. Fit indices of these models were compared with fit indices of the models with all ROI predictors (ie, Model 2a to Model 3a, $F(16,116) = 1.065$, $P = .396$; Model 2b to Model 3b, $F(16,116) = 0.546$, $P = .917$), suggesting that the models containing only dorsal frontal and parietal-occipital regions fit as well as the model with all ROI's. Thus, it was determined that the parsimonious models (ie, Model 3a and 3b) were more appropriate for post hoc investigation. These models indicated that visuomotor processing speed was significantly influenced by mean dose predictor variables ($F(5,33) = 5.079$, $P < .01$*, adjusted $R^2 = .349$). Specifically, greater levels of education ($\beta = 0.274$) was associated with better visuomotor processing speed, high mean dose to the dorsal frontal region was associated with better visuomotor processing speed ($\beta = 0.001$), and high mean dose to the parietal-occipital region ($\beta = -1.100$) was associated with worse visuomotor processing speed. Executive function was also significant ($F(5,33) = 3.396$, $P < .05$*, adjusted $R^2 = .240$). Specifically, greater levels of education was associated with better executive function ($\beta = 0.116$); mean dose variables were not significantly associated with executive function. Memory ($F(5,33) = 1.319$, $P = .280$, adjusted $R^2 = .040$) and attention/working memory ($F(5,33) = 0.776$, $P = .574$, adjusted $R^2 = .030$) were not influenced by mean dose predictor variables.

Visuomotor processing speed was also significantly influenced by D50 predictor variables ($F(5,33) = 5.064$, $P < .01$*, adjusted $R^2 = .348$). Similar to the mean dose model, greater levels of education ($\beta = 0.266$) was associated with better visuomotor processing speed, and high D50 to the parietal-occipital region ($\beta = -0.697$) was associated with worse visuomotor processing speed. Executive function was also significant ($F(5,33) = 3.453$, $P < .05$*, adjusted $R^2 = .244$). Specifically, greater levels of education ($\beta = 0.114$) was associated with better executive function, whereas frontal tumor location ($\beta = -0.377$) was associated with worse executive function; D50 variables were not

Table 3. Post Hoc Multivariate Multiple Linear Regression Model

	β	SE	*t*-value	*P*-value
Model 3a				
Visuomotor processing speed ($F(5, 33) = 5.079$, $P < .01$*, adjusted $R^2 = .349$)[a]				
Intercept	−1.100	0.295	−3.728	.001*
Education	0.274	0.062	4.407	.000*
Tumor location	−0.389	0.370	−1.051	.301
GTV	−0.001	0.001	−1.794	.082
Dorsal frontal	0.001	0.000	2.190	.036*
Parietal-occipital	−1.100	0.437	−2.516	.017*
Executive function ($F(5, 33) = 3.396$, $P < .05$*, adjusted $R2 = .240$)				
Intercept	−0.623	0.165	−3.786	.001*
Education	0.116	0.035	3.347	.002*
Tumor location	−0.378	0.200	−1.892	.067
GTV	0.000	0.000	−0.267	.791
Dorsal frontal	0.000	0.000	0.560	.579
Parietal-occipital	−0.076	0.206	−0.366	.717
Memory ($F(5,33) = 1.319$, $P = .280$, adjusted $R^2 = .040$)				
Attention/working memory ($F(5,33) = 0.776$, $P = .574$, adjusted $R^2 = .030$)				
Model 3b				
Visuomotor processing speed ($F(5,33) = 5.064$, $P < .01$*, adjusted $R^2 = .348$)				
Intercept	−1.029	0.300	−3.431	.002*
Education	0.266	0.066	4.043	.000*
Tumor location	−0.183	0.346	−0.527	.601
GTV	−0.001	0.001	−0.988	.330
Dorsal frontal	0.459	0.347	1.321	.196
Parietal-occipital	−0.697	0.346	−2.013	.049*
Executive function ($F(5,33) = 3.453$, $P < .05$*, adjusted $R^2 = .244$				
Intercept	−0.622	0.162	−3.836	.001*
Education	0.114	0.036	3.192	.003*
Tumor location	−0.377	0.187	−2.013	.048*
GTV	0.000	0.000	−0.239	.812
Dorsal frontal	0.123	0.188	0.654	.517
Parietal-occipital	−0.121	0.187	−0.648	.521
Memory ($F(5,33) = 1.089$, $P = .385$, adjusted $R^2 = .011$)				
Attention/working memory ($F(5,33) = 0.619$, $P = .686$, adjusted $R^2 = .053$)				

Neurocognitive factors were the outcome variables. Model 3a represents mean dose and Model 3b represents dose to 50% of the region (D50). Only the visuomotor processing speed and executive function factors were significant, and thus individual ROI's are presented. Memory and attention/working memory factors were not significant and thus ROI's cannot be interpreted and are not presented. Surgical resection (Y/N) was not related to our outcomes and therefore not included in Model 2. Analyses excluding the 11 participants who did not have surgery are provided in Supplementary Table 4. The pattern of results tended to be consistent with the findings above.

Abbreviations: SE, standard error; GTV, gross tumor volume.

*Significant *P*-values (<.05).

[a]Adjusted R^2 values of <.13 represent weak associations, ≥.13 and <.26 represent moderate associations, and ≥.26 represent substantial associations.[54]

significantly associated with executive function. Memory ($F(5,33) = 1.089$, $P = .385$, adjusted $R^2 = .011$) and attention/working memory ($F(5,33) = 0.619$, $P = .686$, adjusted $R^2 = .053$) were not influenced by D50 predictor variables.

We subsequently explored associations between RT dose to brain regions and performance on individual neurocognitive tests after adjusting for education and tumor location. Due to the large number of comparisons, only significant predictors are presented in Table 4 (see Supplementary Table 5 for the full table). Notably, high mean dose to the left hippocampus was associated with worse CVLT-II LDFR scores (β = −0.001), although this did not remain significant after FDR correction. High mean dose to the parietal-occipital region was significantly associated with worse TMT B (β = −5.208). High mean dose to the dorsal frontal region was associated with better TMT B (β = 0.004). High mean dose to the ventral frontal region was associated with worse TMT B (β = −0.003). In addition, high mean dose to the parietal-occipital region was significantly associated with worse TMT A (β = −2.272), high mean dose to the dorsal frontal region was associated with better WAIS digit span forward (β = 0.001), high mean dose to the cerebellum was associated with better WAIS digit span backward and forward (backward β = 0.458 and forward β = 0.616), high mean dose to the hippocampi was associated with worse WAIS digit span backward (β = −0.001), and high D50 to the parietal-occipital region was associated with worse TMTA (β = −1.415) and TMTB (β = −2.091), although these associations did not remain significant after FDR correction.

Discussion

In this study, we examined volumetric RT dosimetry to explore whether interindividual differences in RT dose to particular brain regions are associated with specific neurocognitive domains in patients with meningioma. Our results suggest that in addition to known associations between increased RT dose to the left hippocampus and worse verbal memory demonstrated in the literature, RT delivered to other brain regions may contribute to poorer neurocognitive outcomes in respective domains. In particular, we found that high dose to the parietal-occipital region was associated with slower visuomotor processing speed. Unexpectedly, we found that high dose to the dorsal frontal region was associated with better visuomotor processing speed. These findings add to the scant literature which posits that neurocognitive decline associated with RT is not limited to memory, but includes other domains including visuomotor processing speed.[16–18]

Of the demographic and medical variables examined, education and tumor location were significantly associated with neurocognition; patients with lower levels of education and frontal tumors exhibited worse neurocognitive performance. The finding that education was related to neurocognition may be related to the concept of cognitive reserve; individuals with higher levels of education are better able to compensate for the effects of brain injury, and can sustain greater brain damage before demonstrating

Table 4. ROI's Predicting Performance on Individual Tests

	Individual Test	β	SE	*t*-value	*P*-value	*Q*-value
Mean dose	CVLT-II LDFR					
	Intercept	−0.073	0.216	−0.338	.737	
	Education	0.033	0.050	0.649	.521	
	Tumor location	0.317	0.224	1.416	.166	
	Left hippocampus	−0.001	0.000	−1.685	.047*	.320
	TMT A					
	Intercept	−1.219	0.361	−3.380	.002*	
	Education	0.234	0.076	3.078	.004*	
	Tumor location	−0.514	0.477	−1.079	.289	
	Parietal-occipital	−2.272	0.711	−3.195	.003*	.050
	TMT B					
	Intercept	−2.608	0.651	−4.007	.000*	
	Education	0.475	0.159	2.990	.006*	
	Tumor location	−1.926	0.832	−2.316	.028*	
	Dorsal frontal	0.004	0.001	3.388	.002*	.045*
	Parietal-occipital	−5.208	1.271	−4.097	.000*	.000*
	Ventral frontal	−0.003	0.001	−3.385	.002*	.045*
	WAIS digit span backward					
	Intercept	−0.627	0.167	−3.751	.001*	
	Education	0.086	0.032	2.716	.012*	
	Tumor location	0.028	0.217	0.130	.898	
	Cerebellum	0.458	0.203	2.254	.033*	.316
	Hippocampi	−0.001	0.000	−2.268	.032*	.316
	WAIS digit span forward					
	Intercept	−0.675	0.223	−3.020	.006*	
	Education	0.030	0.042	0.721	.477	
	Tumor location	−0.398	0.290	−1.372	.182	
	Cerebellum	0.616	0.272	2.265	.032*	.316
	Dorsal frontal	0.001	0.000	2.151	.041*	.320
D50	TMT A					
	Intercept	−1.113	0.358	−3.113	.004*	
	Education	0.231	0.077	2.977	.006*	
	Tumor location	−0.285	0.431	−0.661	.514	
	Parietal-occipital	−1.415	0.484	−2.925	.007*	.469
	TMT B					
	Intercept	−2.114	0.759	−2.783	.010*	
	Education	0.433	0.191	2.272	.031*	
	Tumor location	−0.623	0.871	−0.715	.481	
	Parietal-occipital	−2.091	1.018	−2.054	.049*	.582

This table displays the effect of each ROI on individual neurocognitive tests. Due to the number of contrasts, only significant results are presented here. All analyses can be found in Supplementary Table 4. Neurocognitive scores were the outcome variables.
Abbreviations: SE, standard error; *Q*-value, *P*-values adjusted for multiple comparisons using the FDR method; D50, dose to 50% of the target region volume; CVLT-II LDFR, California Verbal Learning Test Second Edition Long Delay Free Recall; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; WAIS, Wechsler Adult Intelligence Scale.
*Significant *P*-values or *Q*-values (<.05).

functional deficits.[36] Consistent with the literature,[37] frontal tumors were associated with executive dysfunction suggesting that the effect of meningioma on neurocognition may be, at least in part, due to the tumor itself. Because of our relatively small sample size, we had limited power to detect effects related to age, sex, surgery, antiepileptic

medication, and tumor laterality on neurocognition, all of which have been associated with neurocognitive performance in meningioma samples.[38,39] The contribution of non-RT factors is important considering that the etiology of neurocognitive decline in patients with brain tumor is multifactorial.

Consistent with our hypothesis, high dose to the left hippocampus was associated with worse verbal memory in our exploratory analyses. Although this finding did not remain significant after FDR corrections, likely due to our relatively small sample and the large number of contrasts, it is notable when considered together with the growing literature and consistent findings that high dose to the left hippocampus is associated with worse verbal memory.[10–12,16,19] Results of hippocampal-sparing RT trials suggest that conformal avoidance of the hippocampus during whole brain RT preserves memory function.[11,12] However, hippocampal-sparing approaches may lead to increased dose exposure to other brain areas,[40] which are also vulnerable to RT-induced damage.[1,7,21] This could contribute to dysfunction in other neurocognitive domains, which we have shown are also susceptible to RT toxicity.

Here, high mean dose and D50 to parietal-occipital regions was associated with worse visuomotor processing speed after controlling for education and tumor location, suggesting that increased RT delivered to this region may contribute to poor neurocognitive outcomes. Associations between parietal-occipital regions and visuomotor ability (eg, transformation of visual information into commands for directing attention and guiding motor output) are well-established.[24] In addition, high D50 to the parietal-occipital region was associated with poor executive function. The parietal lobe is integral in a widely distributed functional network, the frontoparietal control network, which may be particularly sensitive to RT.[41] This network is believed to play a critical role in the control over and coordination of multiple functional networks (for a full review, see Marek and Dosenbach[42]) including higher order neurocognitive functions such as executive function. Collectively, these findings suggest that RT may not only interfere with focal brain regions such as hippocampal function, but likely also disrupt the efficiency of other brain regions that are fundamental to functional networks.[43] This supports our hypothesis that neurocognitive processes that are distributed in nature and rely on a complex network of cortical and white matter structures are also sensitive to RT, and is consistent with the finding that the most common neurotoxic effect of RT is not focal necrosis but diffuse cerebral injury.[44]

It is important to underscore that multiple mechanisms are likely to be involved with RT-induced neurocognitive decline, including decreased hippocampal neurogenesis, damage to oligodendrocytes that underlie myelin production, white matter damage, and vascular injury.[1–3] As a result, brain regions including the hippocampus, dorsolateral prefrontal cortex, and corpus callosum are more vulnerable to RT toxicity.[7,10,21] The parietal-occipital ROI in this study contained the corpus callosum, which is particularly sensitive to RT-induced injury[45] even after low-dose RT exposure[8] as this structure may have a lower threshold to functional damage due to its role in the interconnectivity and relaying of information across brain structures.[46] Alterations in corpus callosum microstructure have been shown to correlate with neurocognitive decline in other neurological disorders such as traumatic brain injury. For example, damage to the genu, which connects the frontal cortices, has been associated with executive dysfunction, whereas damage to the splenium, which connects the parietal-occipital lobes, has been associated with attention and visuomotor dysfunction.[47] Damage to the corpus callosum has also been associated with poorer attention and processing speed after RT in individuals with primary brain tumors.[45] Our finding that RT primarily affects frontal and parietal-occipital brain regions and associated neurocognitive domains (ie, visuomotor processing speed) is consistent with this pathophysiological data. Dose delivered to ventral frontal, cerebellum, and subcortical regions were not associated with neurocognitive outcomes.

In contrast with our prediction that high RT doses would be associated with poorer neurocognitive scores, we found that high dose to the dorsal frontal region was associated with better visuomotor processing speed. Broad estimations of dorsal frontal lobe functions include activation, initiation, switching, monitoring, and inhibitory processes,[48] which are measured by tests in this neurocognitive factor. Improvements in neurocognition following RT have been demonstrated in previous studies[49,50] and may reflect region-specific benefits of tumor control (ie, the neurocognitive benefit of tumor control might outweigh RT-induced damage in the frontal lobe whereas RT-induced damage to hippocampal neurogenesis, eg, might outweigh the effect of the tumor on neurocognition). It is also possible that the effects of other medical treatments (eg, neurosurgery) known to have a beneficial impact on neurocognition in this population[39] may be mediating this finding. More research investigating this finding is necessary to understand these preliminary associations between high RT dose and better neurocognition.

Among the tests that comprised the visuomotor processing speed factor, performance on the TMT A and B were associated with RT dose to frontal and parietal-occipital regions. This is consistent with previous studies investigating associations between brain structures and neurocognition in adult brain tumor samples,[16,19] which also found that TMT performance is associated with RT dose. In a study of 57 primary brain tumor survivors (mixed histopathology), TMT B controlling for performance on TMT A (ie, TMT B-A; which provides a measure of executive functions controlling for speed) was associated with RT dose to left precentral gyrus, left temporal, and cerebellum structures. Another study investigated 78 patients with primary brain tumor (mixed histopathology), finding that TMT A scores were associated with dose to the whole brain, and TMT B scores were associated with RT dose to the left frontal lobe and thalamus. This is consistent with the literature, which suggests that the TMT is one of the most sensitive indicators of brain dysfunction.[51] Performance on this test, however, requires intact neurocognitive functioning across multiple domains; it does not specifically assess visuomotor processing speed. Performance on the TMT B requires several neurocognitive processes, including task switching, planning, general attention, processing speed, visual search, and motor ability. Thus, there are many reasons why an individual may receive a poor score. In addition to the TMT A and B, exploratory analyses

revealed that high RT dose to other brain regions were associated with performance on other neurocognitive tests. Specifically, high dose to the hippocampi was associated with worse working memory, although this did not remain significant after FDR correction. Surprisingly, our exploratory analyses also revealed that high RT doses to certain brain regions were associated with better performance on related neurocognitive tests. Here, high dose the cerebellum was associated with better attention and working memory, and high dose to the dorsal frontal region was associated with better attention, although these variables did not remain significant after FDR correction. Nevertheless, these positive associations may indicate the region-specific benefits of tumor control, or may be driven by the effects of other medical treatments such as neurosurgery. More research investigating these contrasting findings is necessary to understand the variability in these exploratory results.

In addition to the small sample size, there are limitations to this study that warrant caution in interpreting these results. This was a cross-sectional study with variability in the timing of neurocognitive assessment relative to diagnosis and initiation of RT. Although time since RT was not significant in our model, early and late effects of RT may be caused by different pathophysiological mechanisms, with the early phase mediated by demyelination, and the late phase caused by vascular injury including damage to cerebral blood vessels.[1–3] We also did not have pretreatment baseline neurocognitive data, which limits conclusions related to neurocognitive decline as a result of RT toxicity. Further, we partitioned the brain into large regions based on clinical imaging and it is possible that the specific impact of RT on neurocognition was not captured. Previous groups[16] investigating the impact of RT on hippocampal function have found an association between left hippocampus and verbal memory, but that association was no longer significant when both hippocampi were entered into the model together. While our exploratory findings replicated this, this might also be true for other ROI and neurocognitive domains. For example, the dorsal frontal ROI in this study was large, and previous research has shown that performance on executive tasks is dependent on isolating different brain regions within the frontal lobes (eg, left vs right dorsal frontal regions).[48] This broad segmentation of the dorsal frontal lobe, considered together with the distribution of tumor location (ie, 32% of the sample had frontal tumors), could potentially contribute to bias and outliers in our sample. Future studies would benefit from further investigation into frontal and parietal-occipital regions using larger samples, brain imaging technology that is sensitive to measuring disruption in functional networks such as functional MRI, and more systematic neurocognitive testing (eg, baseline neurocognitive testing, immediately following RT, and several months/years following RT).

An increased understanding of the effect of RT on neurocognition is necessary in light of recent improvements in RT treatment planning, which allow for the precise targeting and quantification of dose delivered to specific regions (ie, delivery of dose distributions that are conformal to the tumor while sparing nearby critical structures). To our knowledge, this is the first study to report the association between RT dose to circumscribed brain regions and associated neurocognitive domains in adults with meningioma. This research can be used to inform RT treatment planning and cognitive rehabilitation support as it identifies other brain regions that may increase risk of poor neurocognitive outcome beyond the few structures that are currently considered during routine clinical radiotherapy planning (eg, hippocampi).[52] We found that high RT dose to parietal-occipital brain areas in particular may lead to increased neurocognitive risk. Specifically, high dose to the parietal-occipital area may lead to slower visuomotor processing speed, with the TMT A and B being particularly sensitive to these effects. Cognitive rehabilitation services targeting slowed visuomotor processing speed (eg, compensatory strategy training[53]) can be made available for these patients to address the neurocognitive effects of RT. Future prospective longitudinal studies examining relations between dose and neurocognitive functions are warranted to confirm these preliminary results.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Practice*.

Funding

This work was supported in part by an award from the Strategic Training in Transdisciplinary Radiation Science for the 21st Century [A.S.]; the Princess Margaret Cancer Foundation; and the Ontario Ministry of Health and Long Term Care (OMOHLTC). The views expressed do not necessarily reflect those of the OMOHLTC.

Acknowledgements

The authors would like to thank Nadine Richard for providing us with Supplementary Figure 1.

Conflict of interest statement. The authors have no conflicts of interest to report.

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