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Original Article

Cognitive impairment following radiation to hippocampus and other brain structures in adults with primary brain tumours

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ABSTRACT

Background: Radiation therapy (RT) to the brain may result in cognitive impairment. The primary objective of the present study was to examine the relationship between RT dose to the hippocampus and learning and memory functions. Secondary objective was to examine relationships between doses to other brain structures and specific cognitive functions.

Methods: A cross-sectional analysis was undertaken in 78 primary brain tumour patients after RT. Cognitive function was assessed by neuropsychological tests. Test scores were standardized using normative data adjusted for age and level of education. Test-specific cognitive impairment was determined as a z-score ≤ -1.5. Radiation dose to brain structures and test-specific cognitive impairment outcomes were fitted to a logistic regression model.

Results: High RT dose to the left hippocampus was associated with impaired verbal learning and memory ($p = 0.04$). RT dose to the left hippocampus, left temporal lobe, left frontal lobe and total frontal lobe were associated with verbal fluency impairment ($p < 0.05$) and doses to the thalamus and the left frontal lobe with impaired executive functioning ($p \leq 0.03$). Finally, RT dose to the brain and thalamus were associated with impaired processing speed ($p \leq 0.05$).

Conclusion: The present study indicates that the hippocampus may be vulnerable to radiation and that high radiation doses to the left hippocampus may lead to significant verbal learning and memory impairment. High RT doses to the left hippocampus and other left side structures may result in impairments in verbal fluency, executive function, and processing speed. Validation of these findings are being undertaken in a prospective study.

Radiation therapy (RT) is fundamental in the treatment of primary brain tumours. RT contributes to improved local control and prolonged progression-free survival in patients with a broad range of tumour types [1–3]. Irradiation to the normal brain, including temporal and frontal regions may lead to cognitive impairments such as impaired attention, memory, language, and executive functioning [4]. Studies that have examined cognitive impairment in adult patients treated for brain tumours with RT have reported prevalence rates from 19% to 83% [5,36]. RT to the hippocampus, in particular, has been implicated in learning and memory impairments observed in brain tumour patients [6,7]. It has been suggested that equivalent doses of 2 Gy fractions (EQD_2) to 40% of the hippocampus greater than 7.3 Gy results in increased risk of cognitive impairment [8]. However, findings in this area are inconsistent [1,9,10]. Clarifying the nature and severity of impairment in adult RT-treated brain tumour patients, including region-specific effects, are important for optimal utilization of novel conformal RT technologies such as proton therapy [7,11]. The present study aimed to investigate dose–response relationships between RT to specific brain regions and cognitive performance in corresponding domains. Our primary hypothesis was that patients who had received high RT doses to the hippocampus would evidence poorer verbal learning and memory [12]. Furthermore, we wished to elucidate relationships between RT dose to other brain regions (the whole brain, thalamus, temporal and frontal lobes) and cognitive performance. The examined associations between specific brain structures and cognitive tests were all pre-defined.

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Methods

Study design and patients

In the present cross-sectional study, patients alive in January 2016 who had received RT for primary brain tumour grade I–III or medulloblastoma between 2006 and 2016 at Aarhus University Hospital (AUH), Denmark, were assessed with a comprehensive battery of standardized cognitive tests. The inclusion criteria were: a diagnosis of primary brain tumour grade I–III or medulloblastoma according to WHO 2016 guidelines [13]; age 18 years or older at the time of diagnosis; a Karnofsky performance status of 60–100; capable of undergoing cognitive testing; and progression-free survival after RT. Exclusion criteria were: diagnosis of glioblastoma and insufficient Danish language proficiency to complete cognitive tests (Table 1).

Table 1
Sociodemographic and clinical characteristics of participants.

Number of participants	78 (100%)
Age, median (range) in years	53.5 (20–79)
Gender, N (%)	
Male	47 (60%)
Female	31 (40%)
Education in years, median (range)	14 (7–20)
Employment, *N* (%)	
Full time (37 h)	22 (28%)
Part time (less than 37 h)	19 (24%)
Retired	20 (26%)
Not employed	17 (22%)
Karnofsky Performance Score mean (range)	90 (70–100)
Tumour type, *N* (%)	
Meningioma	21 (27%)
Pituitary adenoma	17 (22%)
Glioma grade II	18 (23%)
Glioma grade III	12 (15%)
Medulloblastoma	7 (9%)
Other rare brain tumors	3 (4%)
CTV, Median (range) in cm^3	46 (2–390)
Type of surgery, N (%)	
o None	3 (4%)
o Biopsy	11 (14%)
o Partial tumor resection	30 (39%)
o Gross tumor resection	34 (43%)
Number of surgery, *N* (%)	
o None	3 (4%)
o 1	45 (58%)
o 1+	30 (38%)
Location, *N* (%)	
o Left hemisphere	20 (26%)
o Right hemisphere	13(15%)
o Midline	12 (15%)
o Skull base (meningioma and pituitary tumors)	34 (44%)
Handedness	
o Right handed	4 (5%)
o Left handed	74 (95%)
Antiepileptic drug, *N* (%)	
o Yes	20 (26%)
o No	58 (74%)
Antidepressants, *N* (%)	
o Yes	9 (12%)
o No	69 (88%)
Chemotherapy, *N* (%)	
o None	59 (76%)
o Procarbazine, Lomustine and Vincristine	7 (9%)
o Temozolomide	2 (2%)
o Other	10 (13%)
Years since radiation therapy median (range)	4.6 (1–9)

Eligible participants were identified through the electronic medical record system and invited by letter to participate in the study.

Radiation therapy

RT consisted of 1.8–2.0 Gy per fraction with total doses ranging from 45 to 60 Gy. From 2006 to 2008, five patients were treated with three dimensional conformal RT (3D-CRT) and were set up by laser systems and skin marks supplied by portal imaging. After 2008, 64 patients received intensity-modulated radiation therapy (IMRT) and were set up with daily cone beam computed tomography. In most cases, static field IMRT technique was used. Nine patients received proton therapy at MD Anderson Cancer Center, Houston, Texas, Heidelberg Ion Beam Therapy Center, Germany or the Skandion Clinic, Uppsala, Sweden.

Radiation dose to brain structures

The following structures were delineated based on the treatment planning computerized tomography (CT) co-registered with contrast-enhanced 3D T1-weighted magnetic resonance imaging (MRI): whole brain (excluding clinical target volume [CTV] and brainstem), brainstem, hippocampus (left, right and total), temporal lobe (left, right and total), frontal lobe (left, right and total), thalamus, and CTV. The structures were contoured according to the European Particle Therapy Network (EPTN) International Neurological Contouring Atlas [14]; however, the hippocampus contours were based on the electronically available Radiation Therapy Oncology Group (RTOG) atlas [15], temporal and frontal lobes according to Sun et al. [16] and the thalamus according to the Sobotta atlas [17]. CTV included the resection cavity, the contrast-enhanced tumour on T1-weighted MRI, and the hyper intensive volume on T2/FLAIR MRI with 5–10 mm margin according to tumour grade [18]. All patients had been immobilized during the treatment plan scanning in supine position with a thermoplastic mask. All contouring was performed by one oncologist and reviewed by a neurosurgeon and a neuro-oncologist. Dose Volume Histograms (DVHs) were generated for the delineated structures. Doses were converted to biologically equivalent doses in 2 Gy fractions (EQD_2) assuming an α/β ratio of 3 Gy [19].

Cognitive testing

All participants underwent cognitive assessment with a battery of validated standardized cognitive tests covering the following cognitive domains: processing speed; attention and working memory; verbal learning and memory; verbal fluency; and executive functions. Standardized tests included the Trail Making Test – Parts A and B (TMT A & B) [20]; Hopkins Verbal Learning Test – Revised (HVLT-R) [12]; Controlled Oral Word Association Test (COWAT) – Animals and letter S [21]; Coding and Digit Span subtests from the Wechsler Adult Intelligence Scale – Version IV (WAIS-IV) [22]; Paced Auditory Serial Addition Test (PASAT) – the 3 s trial only [23]; and the Stroop Colour and Word Test [24]. Table 2 shows which domains the tests are designed to investigate. Cognitive assessments were all conducted by the same trained physician supervised by an expert neuropsychologist. Testing took approximately 60 min per participant and was undertaken at least one year after the completion of RT. Additionally, patients completed a questionnaire which took approximately 30 min [25]. The questionnaire included questions pertaining to their sociodemographic background, quality of life, self-reported cognition, fatigue, sleep quality, anxiety, depression and stress [25] (Tables 1 and 2).

Table 2
Mean *z*-score for each test compared to normative data.

Cognitive domain	Cognitive test	Mean (SD)	*p* value
Processing Speed	TMT-A	−0.20 (1.39)	0.22
	WAIS-IV Coding	−0.35 (1.00)	**<0.01***
Attention and working memory	PASAT	−0.80 (1.12)	**<0.01***
	WAIS-IV Digit Span	−0.03 (0.83)	0.72
Verbal learning and memory	HVLT-R Total	−0.64 (1.20)	**<0.01***
	HVLT-R Delayed	−0.97 (1.39)	**<0.01***
Verbal fluency	COWAT (Animals)	−0.25 (1.31)	0.10
	COWAT (Letter S)	−0.06 (1.17)	0.66
Executive function	TMT-B	−0.33 (1.48)	0.05
	Stroop Interference test	−0.58 (0.97)	**<0.01***

TMT-A; Trail-Making Test Part A. WAIS-IV Coding. PASAT; Paced Auditory Serial Addition Test, 3 s only. WAIS-IV Digit Span. HVLT-R; Hopkins Verbal Learning Test – revised total and delayed. COWAT; Controlled Oral Word Association, animals and letter S. TMT-B; Trail-Making Test Part B. Stroop inference test. Negative scores indicate poorer test performance. *Indicate significant findings by a 2-tailed *p* value < 0.05.

Statistics

Sample size was estimated based on findings from a previous publication that examined cognitive function in irradiated and non-irradiated brain tumour patients [25]. Power analysis was based on total recall of the HVLT-R [12]. With a 3:1 ratio between groups, a power of 80% and a two-sided p of 0.05, the study required 78 and 26 patients in the two groups respectively. The present analysis includes only the irradiated group.

All cognitive test outcomes were converted to *z*-scores using published normative data adjusted for age, and when available, education level. Descriptive statistics were generated for sociodemographic and clinical characteristics, as well as cognitive test scores. The presence of cognitive impairment was determined using cut-off criteria published by the International Cancer and Cognition Task Force (ICCTF) [26]. For each cognitive test, cognitive impairment was defined as a *z*-score ≤ -1.5, and patients were dichotomized according to their impairment status (impaired versus unimpaired). To determine statistically significant differences between the mean EDQ_2 of delineated structures in the two groups, independent samples *t*-tests were conducted.

In order to examine the effect of mean EDQ_2 to various brain structures and associations with impairment status, univariate logistic regression analyses were undertaken. Wald tests were used to test the statistical significance of each model, using two-tailed tests. *P*-values <0.05 were considered significant for all statistical tests. Only pre-determined associations between cognitive tests and specific brain structures were examined (Table 3 and Suppl. Table 1).

Results

Of the 121 patients who met the inclusion criteria, 81 (67%) consented to participate. Forty patients declined to participate; 10 due to insufficient resources or lack of time, and 30 gave no reason. Patients who declined did not differ from those agreeing to participate with respect to age, gender, and tumour type. Three patients were excluded from the current analysis; in 2 patients, a planning CT could not be obtained and 1 patient had only received one fraction of RT. Included participants were, on average, 54 years of age. Gliomas were the most common tumour type (45%), followed by meningioma (22.5%) and pituitary adenomas (22.5%). Overall, the median time since diagnosis was 6.6 years, while the median time since RT was 4.6 years. Table 1 shows detailed sociodemographic and clinical characteristics of the participants.

Patients had lower scores in the domains of processing speed, attention and working memory, verbal learning and memory and executive function compared with normative data (Table 2). Patients with skull base tumours (meningioma and pituitary adenomas) had marginally significant better cognitive scores compared to patients with parenchymal tumours (gliomas, medulloblastoma and other more rare tumours) (p = 0.05) and there was a non-statistical tendency of better scores with small CTV. There were no differences in HVLT-R scores on the following dichotomized parameters: median age, time since RT, or gender (Supplementary Table 1).

Two sample *t*-tests indicated that patients characterized as impaired on the HVLT-R (verbal learning and memory) had received significantly higher mean EDQ_2 to the left hippocampus compared to those characterized as unimpaired (p = 0.03). Similar differences in mean EDQ_2 could not be found for the right and the total hippocampus structures. Patients with impaired scores on the COWAT had received higher mean EDQ_2 to the left hippocampus ($p \leq 0.03$) and left frontal lobe ($p \leq 0.01$) compared to patients unimpaired on that task. For the total frontal lobe this was only the case for the COWAT animal subtest (p = 0.01). Patients with impaired TMT-B scores (executive function) had received higher mean EDQ_2 doses to the left frontal lobe (p = 0.01) and thalamus (p = 0.02) compared with unimpaired patients. There were no differences in mean EDQ_2 to temporal lobes between those impaired and those unimpaired on the cognitive tests assessing temporal lobe functions, nor to mean EDQ_2 to the right frontal lobe on tests assessing that region. Patients with impaired scores on the TMT-A, and Coding (processing speed), had received higher EDQ_2 to the brain ($p \leq 0.04$) and thalamus (plural p = 0.01) than those with unimpaired scores. Only two patients scored 1.5 SD below the normative mean on Digit Span, leading to exclusion of this test and 10% of the patients were too impaired to complete PASAT weakening the results from PASAT (Fig. 1 and Suppl. Table 2).

Binary logistic regression analyses revealed statistically significant associations between mean EDQ_2 to the left hippocampus, and performance on the HVLT-R (p = 0.04), COWAT animals (p = 0.03), and COWAT letter S subtests (p = 0.01), indicating that a higher EDQ_2 to the left hippocampus was associated with a greater likelihood of impaired verbal learning and memory and word fluency (Fig. 2). No associations between cognition and doses to the right and total hippocampus were found. High mean EDQ_2 to the temporal lobe was associated with a greater likelihood of impaired scores on COWAT animal (p = 0.04) and COWAT letter S (p = 0.01) (verbal fluency). No significant associations were found for right- and total temporal lobes. For the left frontal lobe, a higher mean EDQ_2 was associated with a greater likelihood of impaired scores on TMT-B (p = 0.01), COWAT animal (p < 0.01) and COWAT letter S (p = 0.01) (executive function and verbal fluency). Similarly, a higher mean EQD_2 to the total frontal lobe was associated with a greater likelihood of impaired scores on the COWAT animal (p = 0.02) (verbal fluency). No associations were found for the right frontal lobe. Higher EQD_2 to the whole brain and the thalamus were associated with a greater likelihood of impaired scores on the TMT-A ($p \leq 0.04$) and Coding ($p \leq 0.05$) (processing speed), as well as between doses to the thalamus and likelihood of impaired scores on the TMT-B (executive function) (p = 0.03). No dose-volume associations were found for delayed memory or attention and working memory (Fig. 2, Table 3, and Suppl. Table 3). Binary logistic regression analyses revealed no statistically significant associations between tumour size, type (skull base tumours verses parenchymal tumours), location (left, right, midline or skull base), handedness and any of the cognitive test scores (data not shown).

Table 3
Logistic regression, mean EQD_2 as a predictor of cognitive impairments versus unimpaired. Full table in Supplementary Table 3.

Structure	Test	*R* square	Slope (Standard error)	*P*-value	Odds ratio	Confidence interval: 95%
Hippocampus (left)	HVLT-R Total	0.083	−0.031 (0.015)	**0.04***	0.97	0.94–1.00
	COWAT (Animals)	0.109	−0.039 (0.018)	**0.03***	0.96	0.93–1.00
	COWAT (Letter S)	0.218	−0.065 (0.027)	**0.01***	0.94	0.89–0.99
Temporal lobe (left)	HVLT-R Total	0.059	−0.030 (0.017)	0.07	0.97	0.94–1.00
	COWAT (Animals)	0.090	−0.041 (0.020)	**0.04***	0.96	0.92–1.00
	COWAT (Letter S)	0.174	−0.062 (0.025)	**0.01***	0.94	0.90–0.99
Frontal lobe (total)	COWAT (Animals)	0.137	−0.057 (0.023)	**0.02***	0.95	0.90–0.99
	COWAT (Letter S)	0.021	−0.023 (0.026)	0.37	0.98	0.93–1.03
Frontal lobe (left)	STROOP_interference	0.066	−0.032 (0.018)	0.08	0.97	0.94–1.00
	TMT-B	0.156	−0.054 (0.022)	**0.01***	0.95	0.91–0.99
	COWAT (Animals)	0.221	−0.064 (0.021)	**0.002***	0.94	0.90–0.98
	COWAT (Letter S)	0.113	−0.047 (0.022)	**0.04***	0.96	0.91–1.00
Brain	TMT-A	0.119	−0.077 (0.037)	**0.04***	0.93	0.86–1.00
	WAIS-IV Coding	0.110	−0.075 (0.038)	**0.05***	0.93	0.86–1.00
Thalamus	TMT-A	0.150	−0.050 (0.022)	**0.03***	0.95	0.91–0.99
	TMT-B	0.130	−0.045 (0.020)	**0.03***	0.96	0.92–1.00
	WAIS-IV Coding	0.174	−0.056 (0.025)	**0.02***	0.95	0.90–0.99

HVLT-R; Hopkins Verbal Learning Test – revised. COWAT; Controlled Oral Word Association, animals and letter S. Stroop inference test. TMT-B; Trail-Making Test Part B. TMT-A; Trail-Making Test Part A. WAIS-IV Coding. Impaired is defined by a *z*-score < 1.5 standard deviation below the normative mean on a given test. *Indicate significant findings by a 2-tailed *p* value < 0.05.

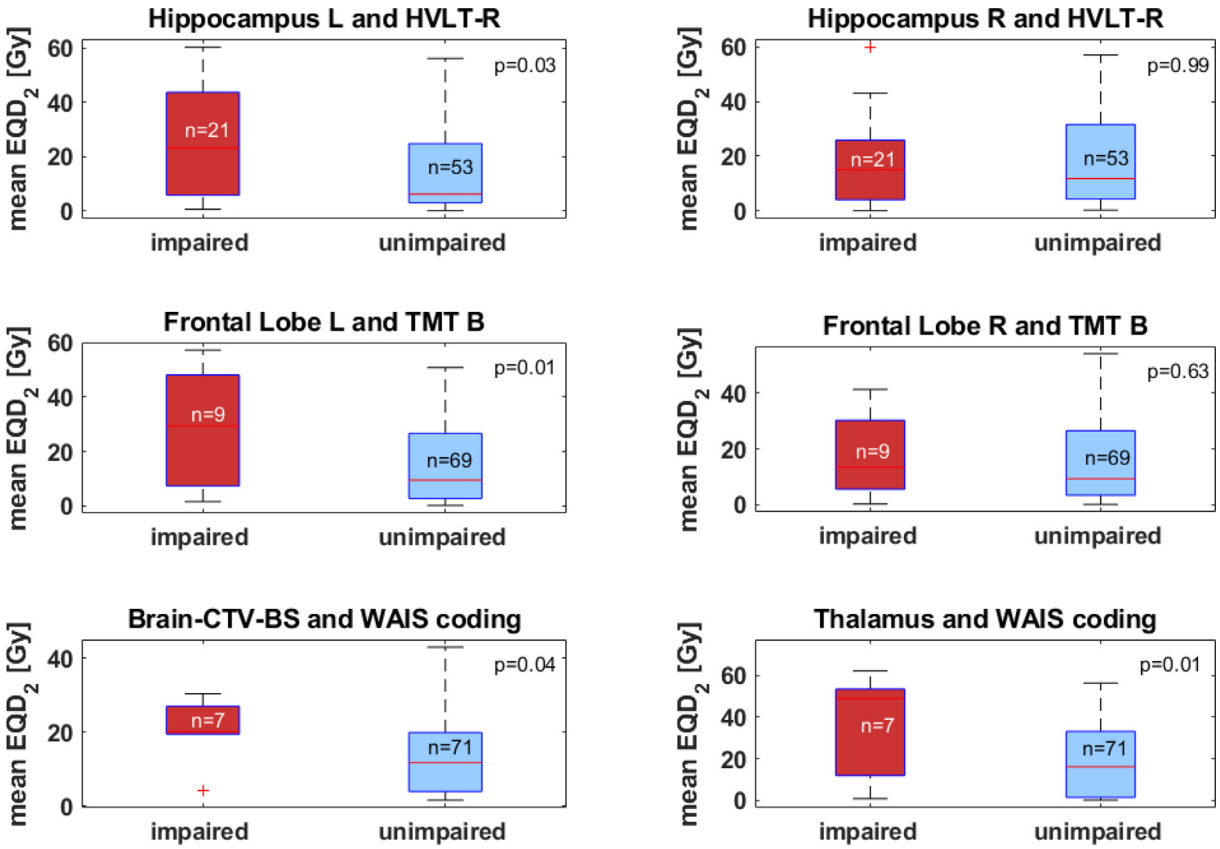

Fig. 1. Box plot for mean EQD_2 (biological equivalent doses in 2 Gy fractions) to hippocampus left and right, frontal lobe left and right, brain and thalamus and corresponding test dichotomized into impaired versus unimpaired. The horizontal line show the mean EQD_2 in each group. Impaired is defined by a *z*-score ≤ -1.5. For complete dataset see Supplementary Table 2.

Testing the receiver operating characteristics (ROC), it was not possible to verify the sensitivity to low radiation dose that was found by Gondi et al. [8] Assuming an α/β ratio of 2 and 3 Gy, the area under the curve (AUC) was 0.49 in both cases (Fig. 3).

Discussion

Overall, patients who had received RT for a brain tumour performed poorly on several cognitive tests when compared with normative data on the domains of processing speed, attention and

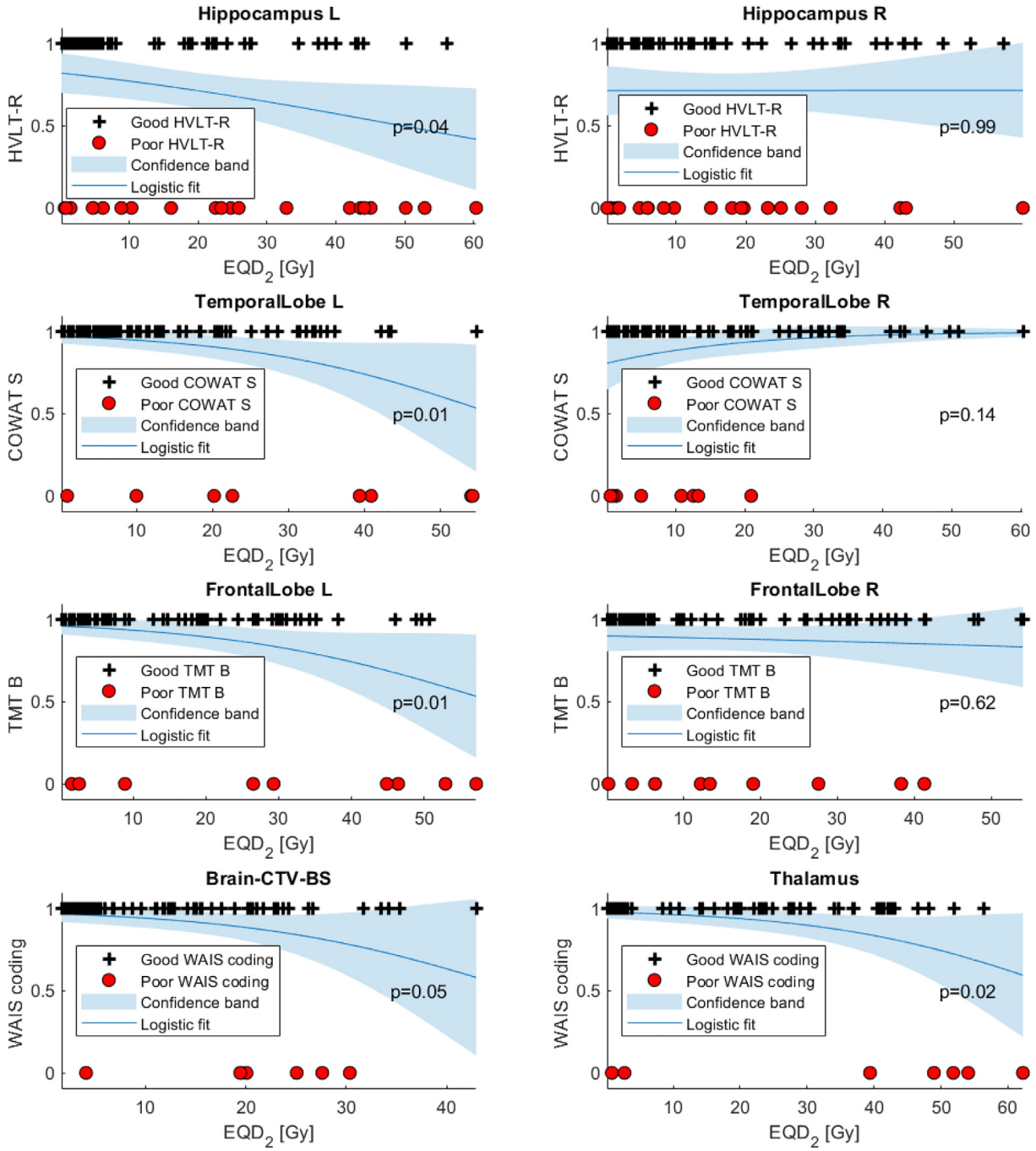

Fig. 2. Logistic regression analysis mean EQD_2 (biological equivalent doses in 2 Gy fractions) to hippocampus left (L) and right (R), frontal lobe left and right, brain and thalamus and corresponding test dichotomized into impaired versus unimpaired. The blue shade represent Confidence Interval of 95%. HVLT-R; Hopkins Verbal Learning Test – revised. COWAT; Controlled Oral Word Association, animals and letter S. TMT-B; Trail-Making Test Part B. WAIS-IV Coding. *Indicate significant findings by a 2-tailed *p* value. For complete data see Supplementary Table 3.

working memory, verbal learning and memory and executive function. High doses to the left hippocampus were associated with poorer performance on verbal learning and memory, and verbal fluency. This effect seemed to occur at any dose level and without a threshold. No associations between doses to the right hippocampus or total hippocampus and impairments to verbal learning and memory or verbal fluency were observed. Consistent with our primary hypothesis, the results point to the left hippocampus as an important risk structure following RT to the brain.

High RT doses to other left hemisphere regions of the brain and the thalamus were also found to be associated with poorer cognitive performance in related domains. Specifically, patients who had received higher RT doses to the left temporal lobe, left frontal lobe, thalamus and total brain were impaired on tests of verbal learning and memory, verbal fluency, executive function and processing speed. With respect to verbal fluency, a dose response relationship was observed for the left temporal lobe, left frontal lobe and total frontal lobe; for executive function, a dose response relationship was observed for the left frontal lobe and thalamus; and for process-

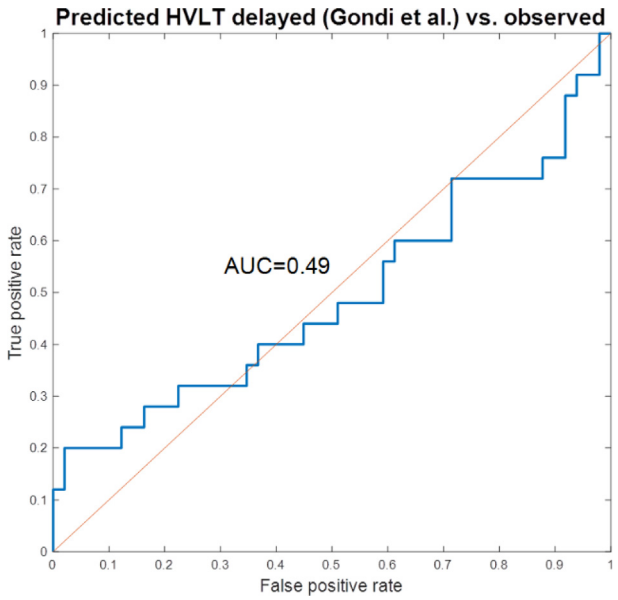

Fig. 3. ROC curve (receiver operating characteristic curve) based on Gondi's [8] results compared to ours, with the true positive (sensitivity) plotted in function of false positive (specificity) for different cut-off points. Each point represent a sensitivity/specificity pair corresponding to a particular threshold. AUC (area under the curve) = 0.49.

ing speed, a dose response relationship was observed for the brain and thalamus.

Studies on paediatric brain tumour patients are relatively clear in their conclusion on the detrimental effects of RT to hippocampus [27,28], whereas reports are inconsistent for adult patients [11,29–31]. Gondi found that in patients treated for benign or low-grade tumours, the hippocampus was sensitive to radiation even at very low EQD_2 doses; EQD_2 greater than 7.3 Gy to 40% of the total hippocampal volume increased the risk of impaired delayed memory recall [8]. However, the EORTC-22033 Low-Grade Glioma Trial could not replicate these findings [32]. Likewise we were unable to verify the dosimetric relation between total hippocampus and delayed recall. In contrast to the EORTC study that had only one patient below the 7.3 Gy threshold we had 30 out of 74 patients below this threshold making our study more balanced to validate a response in this low dose range. However, our results indicate that the dose–response relationship applies only for higher radiation doses. Okoukoni found a dose response relationship between the total hippocampus in the high dose range (53.4–60.9 Gy) and HVLT-R [33]. Peiffer found that greater doses to the total hippocampus and the right temporal lobe were predictors of poorer global cognitive outcomes [29]. Tabrizi and Brummelman could not establish a dose–response relationship for the hippocampus and cognitive function in patients treated with RT for benign brain tumours or pituitary adenoma [11,30]. Findings on cognitive effects related to other brain structures are heterogeneous with no established dose-volume relationships for frontal- or temporal lobes, thalamus or total brain in adult brain tumour patients [11,29–31]. These divergent findings may be related to differences in study design, patient characteristics, tumour type, included neuropsychological tests, and follow up time points. Equally important, the sample sizes in the majority of these studies were small.

Our finding that the thalamus was also susceptible to high doses of RT, with particular impacts on processing speed and executive functions, is not surprising. The thalamus plays an important role in the transmission of neural signals to the cerebral cortex from a number of brain areas and contributes to a broad range of basic cognitive functions including learning and memory and executive functions [34].

Habets et al. examined cognitive function prior to treatment in patients with diffuse glioma and found that tumour location in the left hemisphere was related to the highest risk of impaired cognitive function, and only tumour localization in the left hemisphere was associated with language functioning [35]. Furthermore, they observed the left frontal cortex to be related to performance on tests of verbal fluency and executive function [35]. They did not find any regions related to working memory capacity [35] which is similar to our findings. This underlines the importance of the left-hemispheric brain structures. It also emphasizes that the present study harbours a risk of overestimating the RT-induced effects on neurocognitive function since the tumour itself together with neurosurgical procedures may cause neurocognitive decline. In our study, we found that radiation dose was statistically significantly related to neurocognitive decline, and that there were marginally significant associations with tumour type and CTV. Tumour histology, localization, radiation volumes and doses are to some extend inter-related and these factors contribution to the decline in cognitive function following treatment for a brain tumour are not fully understood.

Our study has important strengths. A relatively high percentage of patients agreed to participate (67%), leading to a reasonably high sample size of 78 patients representing one of the largest studies in this area thus far. We used a recommended battery of cognitive tests that assess a broad spectrum of established cognitive domains [26], and testing was performed under standardized conditions with only one examiner. Some limitations should also be acknowledged. First, we do not have pre-treatment cognitive function of our patients which limits the conclusions of the study. Second, we aimed at a broad neurocognitive testing that included seven tests. Multiple testing carries a risk of Type 1 errors. To reduce this, we predefined our primary endpoint (HVLT-R) and made a strategy for data analysis that coupled specific neurocognitive tests to doses of respective related structures (Table 2). Finally, the heterogeneity of the study population could be a limitation. We aimed to include a cohort of patients that received radiation at various doses to critical brain structures to ensure that we had sufficient variability to capture important statistical associations and we excluded glioblastoma patients with expectancy of rapid progression and poor survival.

Conclusion

The present study suggests that the hippocampus is vulnerable to radiation and that high radiation doses to the left hippocampus may lead to significant verbal learning and memory impairment. High RT doses to the left hippocampus and other left side structures may result in impairments in verbal fluency, executive function, and processing speed; and radiation to the thalamus may lead to impairments in processing speed and executive function. These findings need further validation in larger-scale prospective studies with pre-treatment cognitive assessments. The Danish Neuro-Oncology Group is currently running two nation-wide prospective studies investigating cognitive function in brain tumour patients up to 10 years after photon and proton RT.

Conflict of interest

None.

Ethical statement

The Research Ethics Committee of Central Denmark Region approved this study (no. 1-10-72-367-15). The study has been conducted according to the Helsinki declarations.

ClinicalTrial.gov number: ID NCT04118426.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.03.023.

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