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# The long-term impact of irradiation on functional connectivity in brain circuits involved in memory processes after pediatric posterior fossa tumor

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## ABSTRACT

**Purpose:** Memory is one of the main specific cognitive domains impaired with attention and processing speed after a pediatric brain tumor. This work explored the long-term impact of radiotherapy in children with posterior fossa tumor (PFT) on brain connectivity in neural circuits involved in memory using resting-state functional magnetic resonance imaging (rs-fMRI).

**Methods:** A total of 20 irradiated and 15 non-irradiated PFT survivors, and 21 healthy controls, prospectively included in the IMPALA study (NCT04324450), performed memory tests assessing episodic, procedural, and working memories and were subjected to an rs-fMRI. We manually contoured main structures involved in memory to explore connectivity at rest in a seed-to-voxel analysis. The groups were compared and differences in connectivity were correlated with behavioral scores and irradiation doses.

**Results:** The performance of all mnemonic tasks was lower in PFT survivors with a greater alteration in working and episodic memory in irradiated patients. Irradiated survivors had atypical connectivities in all memory circuits compared to controls and in cortico-caudate and cortico-cerebellar circuits compared to non-irradiated survivors. Non-irradiated survivors had only atypical connectivities in the cortico-cerebellar circuits compared to controls. In irradiated survivors, atypical connectivities in cortico-hippocampal circuits were linked with episodic memory scores and dose of irradiation to the left hippocampus and in cortico-striatal circuits with procedural memory scores and dose of irradiation to the striatum.

**Conclusion:** The results of this study highlight that irradiation has a long-term impact on brain connectivity in brain circuits involved in memory after pediatric PFT with a specific radiation-dose effect in supratentorial structures.

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## Introduction

Memory deficit is one of the main neurocognitive outcomes in pediatric posterior fossa tumor (PFT) survivors [1]. Impairments have been shown in declarative memory [2,3] depending mainly on the

hippocampus and cortico-hippocampal circuit, in working memory [4–6] depending mainly on the cerebellum and prefrontal areas, and in motor procedural memory [3,7] depending on the striatum and the cerebellum [8].

The respective role of the tumor, initial hydrocephalus, surgery,

chemotherapy, and radiotherapy (RT) on memory performance is not fully understood. Tumoral lesion surgery can alter and disrupt the cerebellum and the cortico-cerebellar circuit [9] leading to impairments of procedural and working memories. Moreover, radiation-induced damage to normal brain tissue can persistently affect cognition [10]. RT is an important part of malignant PFT treatment following surgery with a high irradiation dose (about 50 Gy) in the posterior fossa and varying doses to the striatal and hippocampal structures, including the craniospinal irradiation (CSI) dose (24–36 Gy) for medulloblastoma and the diffused dose from the clinical target volume that depends on the radiotherapy techniques used [11].

It is now well established that the irradiation dose to the hippocampus has a negative impact on episodic memory and that a sparing approach can preserve memory function [12–14]. However, the dose constraints are not yet established and the understanding of the underlying neuronal mechanisms, using neuroimaging techniques, is still a current challenge. Conventional and advanced magnetic resonance imaging (MRI) has shown, in a pediatric population, long-term morphologic, microstructural, vascular, and metabolic tissue changes after radiotherapy [15] but there is less data on functional connectivity, which may be a finer marker of cognitive outcome.

Resting-state fMRI (rs-fMRI), measure at rest, spontaneous fluctuation in neuronal activity between different brain regions by means of the blood-oxygen-level-dependent (BOLD) signal. In brain tumor survivors, hyperconnectivity, consistent with neurological injuries and disease, have been found in the executive control, default mode network (DMN), and salience networks compared to controls using this methods [16]. Moreover, in a recent study, Morrisson et al. showed significant network individual time variability in brain tumor patients compared to controls and found correlation between higher memory scores and higher global modularity and higher efficiency [17]. The authors concluded, in agreement with Anandarajah et al. that rs-fMRI can be a marker of long-term cognitive outcomes in pediatric brain tumors [18,19].

We used in this work a seed-to-voxel approach to analyze the connectivity difference at rest between a region of interest (seed) and all the other voxels in the brain in irradiated or non-irradiated PFT survivors and controls. This approach has already been successfully used to explore specific cortical-subcortical functional connectivity in a pediatric clinical population with neurodevelopmental disorders [20] or genetic disorders [21], and their links to behavioral performance. We used as seed, hippocampus, cerebellum and striatum to explore connectivity respectively (1) in the cortico-hippocampal circuits involved in episodic memory, (2) in the cortico-cerebellar circuits involved in working memory and the adaptative part of procedural learning, and (3) in the cortico-striatal circuits involved in the sequence learning part of procedural memory. The second aim was to explore how observed changes in connectivity were linked to neuropsychological scores in learning and memory, and to the irradiation dose received by the hippocampus, cerebellum, and striatum.

## Materials and methods

### Participants

Among the sixty participants included in the prospective IMPALA study on long-term memory outcomes in children, adolescent, and young adult pediatric PFT survivors ([ClinicalTrials.gov: NCT04324450](https://clinicaltrials.gov/ct2/show/study/NCT04324450)),

56 were included in the functional MRI analysis. One irradiated participant did not have MRI because of claustrophobia and three rs-fMRI images were not analyzable because of motion artifact (PFT + RT and PFT group) or dental lacing (PFT group). Participants were divided into three groups: 20 PFT survivors who had received treatment including focal or craniospinal irradiation (PFT + RT group), 15 PFT survivors treated without RT (PFT group), and 21 participants without any neurological or psychiatric history who were matched for sex, age, and manual laterality to the PFT + RT group (control group). All participants were subjected to a 3T MRI, and medical and neuropsychological tests assessing global efficiency (WISC V aged < 16 years [22]; WAIS IV aged > 16 years [23]) and the different memory systems. Written informed consent and parental consent (where applicable) was obtained. This study was approved by the local ethics boards. For more details, please refer to the published study protocol [24].

### Behavioral data

Episodic memory was assessed using the “Faces recognition” and “Word lists” subtests of the Children’s Memory Scale (CMS) for children aged < 16 years or the Wechsler Memory Scale – 3rd edition (MEM-III) for participants aged > 16 years.

Visuo-spatial working memory was assessed using the “Spatial span” subtest of the Wechsler Nonverbal Scale of Ability (WNV) for children aged < 16 years or MEM-III, and the auditory-verbal working memory using “Digit span” subtest of the Wechsler Intelligence Scales (WISC-V or WAIS-IV).

Perceptual-motor procedural learning was assessed using the serial reaction time task (SRTT) for sequence learning part [25] and using a non-conventional direction writing task for motor adaptation part [7]. More details about these two tasks were reported in a previous article on perceptual-motor procedural learning [7].

### Irradiation dose

For irradiated patients, irradiation doses were collected from the initial dosimetry plan when available. The right and left hippocampus, the right and left anterior and posterior cerebellum (taking the primary fissure as a separation), and the right and left caudate nucleus and putamen were retrospectively and manually delineated by NC and checked by an experienced radiation oncologist (AL) in accordance with European guidelines [26]. Mean irradiation doses for each structure were reported as well as the mean supratentorial irradiation dose.

### MRI acquisition

We collected anatomical T1-weighted images (3D-T1) and resting-state functional scans (rs-fMRI) using a Philips Achieva dStream 3.0 T MRI scanner equipped with a 32-channel head coil. Acquisition took place at the technical Platform MRI, ToNIC, Toulouse NeuroImaging Center, University of Toulouse, Inserm, UPS, France. The MRI parameters were as follows:

- 3D-T1: sagittal 3D turbo field echo sequence: TR = 7.4 ms; TE = 3.4 ms; TI = 657 ms; flip angle = 8°; FOV: 240 mm, matrix: voxel-size = 1.0 × 1.0 × 1.0 mm<sup>3</sup>, 180 slices;

- Rs-fMRI: echo planar images (EPI) sequence: TR/ TE = 1300 / 30 ms, flip angle = 90°, field of view (FOV) = 240 mm, matrix = 80 × 78, voxel size = 3.0 × 3.0 × 3.0 mm, 44 slices. Each scan session lasted 1.3 s and included 500 volumes. Resting-state data were acquired during a 10:55-minute period during which each subject was asked to stay awake, with their eyes opened, and not to think of anything in particular.

#### MRI analysis

##### Pre-processing

Rs-fMRI images were preprocessed using Conn software (<https://www.nitrc.org/projects/conn> [27]) including the following steps: realignment and unwarp, outlier detection using strict settings (97th percentiles in the normative sample, global signal z-value threshold 5, subject motion mm threshold 0.9), indirect segmentation and normalization, and smoothing with an 8 mm kernel. Blood-oxygen-level dependent (BOLD) time series were denoised using the aCompCor method (31–33) of the CONN toolbox, which consisted in regressing out from the functional time series the first two principal components of the time series extracted from white matter and cerebro-spinal fluid (CSF). The BOLD time series were finally band-pass filtered (0.008–0.09 Hz).

A visual check of all images after preprocessing was performed for each patient to ensure that the normalization step did not alter the location of anatomical structures. Distortions secondary to tumor and posterior fossa surgery in a number of patients in the irradiated and non-irradiated groups were too significant to allow acceptable normalization in the infratentorial regions. The results of the voxel-to-voxel and seed-to-voxel analyses therefore only considered the supratentorial voxels.

##### Voxel-to-voxel and network analyses

Prior to a specific analysis, we performed both a voxel-to-voxel analysis to highlight differences in local or regional connectivity between groups and a network analysis in well-known and robust functional resting networks, the DMN, using the Willard atlas (ref. <https://doi.org/10.1093/brain/awv278>). Details of methods and results are reported in the [Supplementary Data](#).

##### ROI delineation

Conventional automatic segmentation methods did not provide satisfactory segmentation, especially at the cerebellum level, in our clinical population of patients operated on for cerebellar tumors and retaining significant structural changes. EB manually delineated on the 3D-T1 10 regions of interest (ROI) using LifeX software (Version-6.73.8) (<https://aacrjournals.org/cancerres/article/78/16/4786/631693/LIFEX>): the right and left hippocampus, and the right and left anterior and posterior cerebellum using the primary fissure as a delimitation, and the right and left caudate nucleus and striatum. All ROI were double-checked by AL and GA.

##### Seed-to-voxel analysis

A seed-to-voxel analysis was performed using the 10 manually contoured ROI. Using SPM 12, ROI were realigned and normalized within each subject MNI space using the same individual matrices as the EPI sequence. The ROI were then imported into the Conn toolbox and a gray-matter mask was applied. This procedure allowed a group analysis based on the individual seeds of each participant.

#### Statistical analysis

Non-parametric tests were performed for group comparisons of the participants' characteristics and behavioral data.

Using a general linear model (GLM) analysis, we first analyzed the connectivity maps in each group. Then, we explored group differences between PFT + RT vs. control, PFT vs. control, and PFT + RT vs. PFT, including the following covariates: age and sex.

Connectivity Z-scores in clusters showing a statistical difference between patient and control groups were extracted and correlated using a non-parametric Spearman correlation on Jamovi software [28] with behavioral scores: episodic memory scores for clusters from the cortico-hippocampal circuits, working memory and motor adaptation scores for clusters from the cortico-cerebellar circuits, and specific learning score for clusters from the cortico-striatal circuits.

To investigate the impact of the mean irradiation dose on the 10 ROI, we performed a correlation between the connectivity Z-score showing a statistical difference between the PFT + RT and control groups, and the mean irradiation dose to the seed on which the network depended (e.g. a cluster from the cortico-right caudate nucleus network analysis with a mean irradiation dose to the right caudate nucleus).

The cluster-forming threshold  $P < 0.001$  and the cluster-extent threshold  $P\text{-FDR} < 0.05$  were applied to all analyses.

The figures were prepared with the BrainNet Viewer [29].

#### Results

Fifty-six participants, in average aged of 17.5 yo (SD = 5; R:7–26) were included in the rs-fMRI analysis: 20 in the PFT + RT group, 15 in the PFT group, and 21 in the control group. Patients in the PFT + RT group were in average 8 years and 9 months from the end of radiotherapy (SD = 3 years; R:5–15). The characteristics of participants included in the rs-fMRI analyses are summarized in [Table 1](#).

**Table 1**  
Participant characteristics.

	PFT + RT (n = 20)	PFT (n = 15)	Controls (n = 21)	P-value
<b>Demographic characteristics</b>				
Sex (Male/Female)	15/5 †	4/11 †	16/5	0.001
Maternal education level (number of years of study)	12.9 (2.24)	13.4 (3.44)	15.3 (2.55)	0.009
<b>Tumor diagnostic and treatment</b>				
Tumor type	1 ATRT 3 EP 16 MD	14 PA 1 MD		
Age at diagnosis (mean in years (SD))	8.50 (4.10)	5.80 (3.93)		0.094
Hydrocephalus requiring a shunt at diagnosis	15	13		0.961
Chemotherapy	17 †	1		< 0.001
Radiation type	4 focal 11 CSI (36 Gy) 5 CSI (23.4 Gy)			

† : Significant difference with the control group ( $p = 0.05$ ); ‡: significant difference with the PFT group ( $p = 0.05$ ). ATRT: Atypical Teratoid Rhabdoid Tumor; CSI: craniospinal irradiation; EP: ependymoma, MD: medulloblastoma; PA: pilocytic astrocytoma; PFT: posterior fossa tumor; PFT + RT: posterior fossa tumor treated with radiotherapy.



Memory performances were lower in all memory systems in the PFT + RT and PFT groups compared to healthy controls. Scores were significantly lower in PFT + RT compared to PFT group regarding episodic memory (verbal learning) and visual working memory. The performance of the participants is reported in Table 2.

The irradiation doses were available from the initial dosimetry treatment plans for 17 patients (Supplementary data). Three dosimetries were unavailable because they were calculated in obsolete treatment planning systems that did not allow dose retrieval by DICOM-RT export and analysis. Mean supratentorial doses were never null (31 Gy; SD = 12.66; R:6.00–44.49), combining the CSI dose when such an RT type was performed and the diffused dose of the posterior fossa or tumor bed boost. The characteristics of this sub-group did not differ from the PFT + RT group: 12 boys and 5 girls were included, 14 treated for a medulloblastoma (nine with a 36 Gy CSI and five with a 23.4 Gy CSI), two for an ependymoma and one for an ATRT, mean age at diagnosis was 3,6yo (SD = 4), mean age at study 17yo (SD = 5) and mean delay since the end of radiotherapy was 8yo (SD = 4).

Voxel-to-voxel and network analyses showed small differences between the groups in long-term functional connectivity. The detailed results are reported in the Supplementary Data. However, more specific study of the circuits involved in memory revealed between groups differences in long term connectivity.

In non-irradiated PFT survivors compared to control participants, atypical connectivities were found only in the left cortico-cerebellar circuits, with hyperconnectivity in patients compared to controls between the left posterior cerebellum and the frontal regions, and between the left anterior cerebellum and the motor cortex. No atypical connectivity was found in the supratentorial memory circuits.

In irradiated PFT survivors compared to control participants, atypical connectivities were found in the left cortico-hippocampal circuits (Fig. 1-A), in the right anterior cortico-cerebellar circuits (Fig. 2-A), and in the bilateral cortico-striatal circuits (Fig. 3-A and the Supplementary Data).

Difference of connectivities between irradiated and non-irradiated PFT survivors were fewer in number compare to the difference between irradiated PFT and controls, but they remained significant in cortico-cerebellar and in cortico-caudate circuits. We showed higher connectivities between bilateral caudate and motor regions in irradiated PFT survivors and lower connectivities between left caudate and precuneus. In cortico-cerebellar circuits, irradiated PFT survivors showed lower connectivities compared to non-irradiated participants within operculum, insula, cingulate gyrus and frontal regions.

The details of clusters of difference for each seed are reported in the Supplementary Data.

Memory performances were linked with atypical connectivities in irradiated patients only. Relationships were found with lower episodic memory scores and lower cortico-hippocampal connectivity (Fig. 1-B), and with a higher procedural learning score and higher cortico-striatal connectivity from the right caudate nucleus (Fig. 3-B). In cortico-cerebellar circuits, a correlation was found with higher verbal working memory scores and higher connectivity in the insula for the whole population of PFT + RT and controls (Figs. 2-B1), and with higher motor adaptation scores and higher connectivity in the precuneus for PFT + RT survivors (Figs. 2-B2); however, this correlation did not remain significant after correction for multiple correlations.

Irradiation dose to left hippocampus, left putamen, and bilateral caudate nucleus was linked with atypical connectivities in irradiated

Table 2  
Behavioral results.

	PFT + RT (n = 20)	PFT (n = 15)	Controls (n = 21)	p-value
<b>Neuropsychological assessment</b>				
Delay from treatment (mean in years (SD))	9.11 (3.21)	9.27 (2.74)		0.820
Age at the time of the study (mean in years (SD))	17.8 (5.22)	15.9 (5.12)	18.2 (5.22)	0.389
Handedness (Right/left)	15/5	11/4	18/3	0.722
ICARS score	8.95 (9.32) †	0.93 (1.44)	0.05 (0.22)	< 0.001
Full-scale intellectual quotient	83.5 (16.1) †	95.8 (16.4) †	119 (11.4)	< 0.001
<b>Episodic memory: mean scaled score (standard deviation)</b>				
<b>Visual anterograde long-term memory</b>				
Immediate recognition	7.20 (4.01)	9.13 (3.20)	9.67 (3.10)	0.060
Delayed recognition	7.45 (3.66) †	9.13 (3.09)	11.0 (3.19)	0.009
<b>Verbal anterograde long-term memory</b>				
Learning	8.65 (3.42) † ‡	12.2 (3.30)	13.7 (2.78)	< 0.001
Delayed recall	9.70 (3.42) †	11.5 (3.64)	13.8 (2.21)	0.001
Recognition	9.84 (2.41)	10.7 (2.63)	11.4 (1.43)	0.070
<b>Working memory: mean scaled score (standard deviation)</b>				
<b>Visual-spatial working memory</b>				
Direct span (percentile rank)	32.6 (33.0) † ‡	63.9 (28.2)	82.9 (15.2)	< 0.001
Reverse span (percentile rank)	37.5 (29.0)	51.9 (32.3)	52.1 (28.0)	0.221
<b>Auditory-verbal working memory</b>				
Digit span forward	7.25 (2.24) †	8.87 (2.36) †	11.4 (2.31)	< 0.001
Digit span backward	8.00 (3.20) †	9.13 (3.09) †	12.5 (1.99)	< 0.001
<b>Procedural learning: mean raw score (standard deviation)</b>				
<b>Sequence learning</b>				
Specific learning score	34.4 (74.7)	45.9 (67.8)	48.0 (33.3)	0.646
<b>Motor adaptation</b>				
Number of correct trials in the non-conventional writing direction	20.0 (5.12)	21.1 (3.02)	22.6 (2.79)	0.060

† : Statistically significant difference with the control group (p = 0.05); ‡ : statistically significant difference with the PFT group (p = 0.05). ICARS: International Cooperative Ataxia Rating Scale; PFT: posterior fossa tumor; PFT + RT: posterior fossa tumor treated with radiotherapy; SD: standard deviation; SRTT: serial reaction time task.

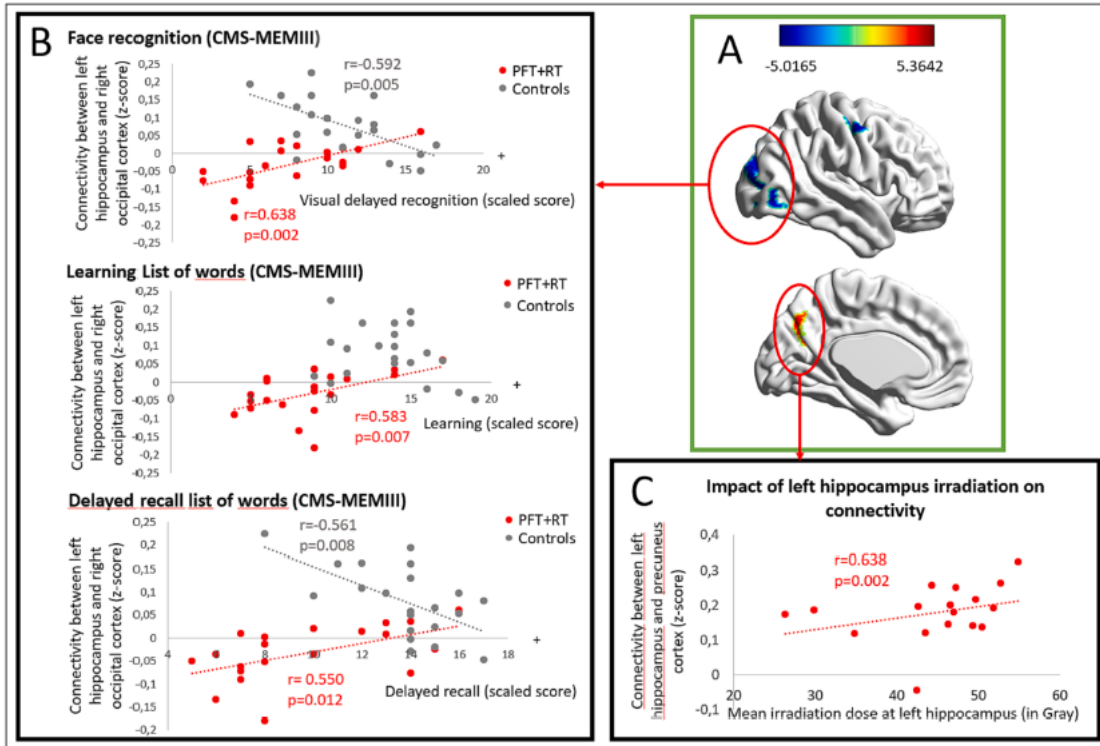


Fig. 1. Hypoconnectivity in the left cortico-hippocampal circuit in the PFT + RT group compared to the control group linked to lower episodic memory scores and hyperconnectivity linked to higher irradiation doses in the left hippocampus. A. Differences in left cortico-hippocampal connectivity between PFT + RT and controls. All analyses were thresholded by applying the cluster-forming threshold  $P < 0.001$  and the cluster-extent threshold  $P\text{-FDR} < 0.05$ . Sex and age were co-variables. Age and gender were taken as covariates. B. Spearman correlation between left cortico-hippocampal connectivity (z-score) and episodic memory scores. Only significant correlations were reported after the Bonferroni correction for multiple correlations (3 clusters:  $p = 0.05/3 = 0.017$ ). +: Higher cognitive score indicates better memory performance. C. Spearman correlation between left cortico-hippocampal connectivity (z-score) and the irradiation dose to the left hippocampus. Only significant correlations were reported after the Bonferroni correction for multiple correlations.

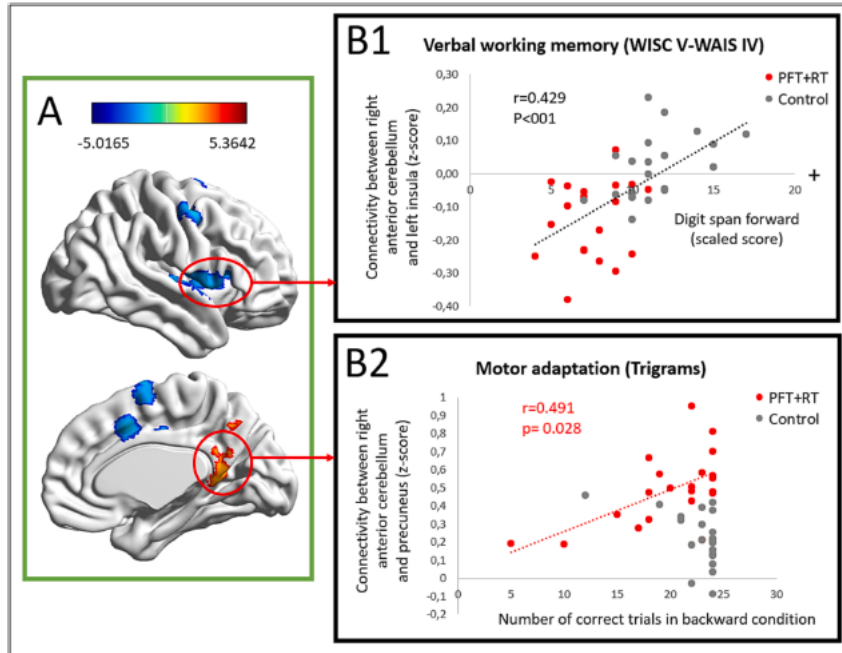


Fig. 2. Hypoconnectivity in the cortico-right anterior cerebellum circuit in the PFT + RT group compared to the control group linked to lower working memory scores and the effect of the irradiation dose to the right anterior cerebellum circuit in higher connectivity with frontal and temporal regions and hypoconnectivity in cingulate cortex. A. Differences in right anterior cerebellum connectivity between PFT + RT and controls. All analyses were thresholded by applying the cluster-forming threshold  $P < 0.001$  and the cluster-extent threshold  $P\text{-FDR} < 0.05$ . Sex and age were co-variables. Age and gender were taken as covariates. B1. Spearman correlation between right anterior cerebellum connectivity (z-score) and working memory scores. The black trend line reported is for participants in both the PFT + RT and control groups. Correlation in the PFT + RT and control groups was not significant after the Bonferroni correction for multiple correlations (7 clusters:  $p = 0.05/7 = 0.007$ ). +: Higher cognitive score indicates better memory performance. B2. Spearman correlation between right anterior cerebellum connectivity (z-score) and motor adaptation performances. Correlation did not remain statistically significant after the Bonferroni correction for multiple correlations (7 clusters:  $p = 0.05/7 = 0.007$ ).

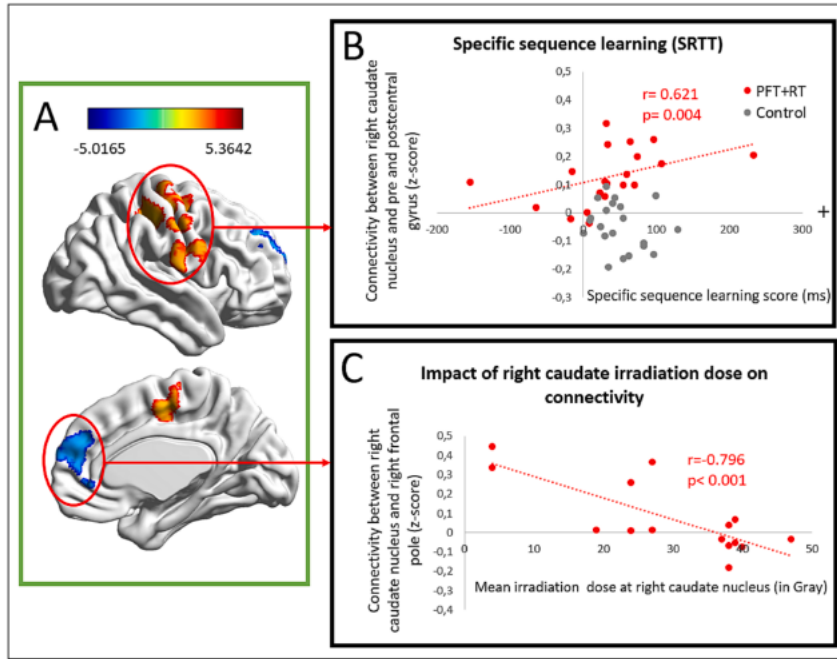


Fig. 3. Hyperconnectivity in the right cortico-caudate nucleus circuit from the right caudate nucleus in the PFT + RT group compared to the control group linked to lower sequence learning scores and hypoconnectivity linked to a higher irradiation dose in the right caudate nucleus. A. Differences in right cortico-striatal connectivity between PFT + RT and controls. All analyses were thresholded by applying the cluster-forming threshold  $p < 0.001$  and the cluster-extent threshold  $P-FDR < 0.05$ . Sex and age were co-variables. Age and gender were taken as covariates. B. Spearman correlation between right cortico-striatal connectivity (z-score) and sequence learning scores. Only significant correlations were reported after the Bonferroni correction for multiple correlations (5 clusters:  $p = 0.05/5 = 0.01$ ). +: Higher cognitive score indicates better memory performance. C. Spearman correlation between right cortico-striatal connectivity (z-score) and the irradiation dose at the right caudate nucleus. Only significant correlations were reported after the Bonferroni correction for multiple correlations.

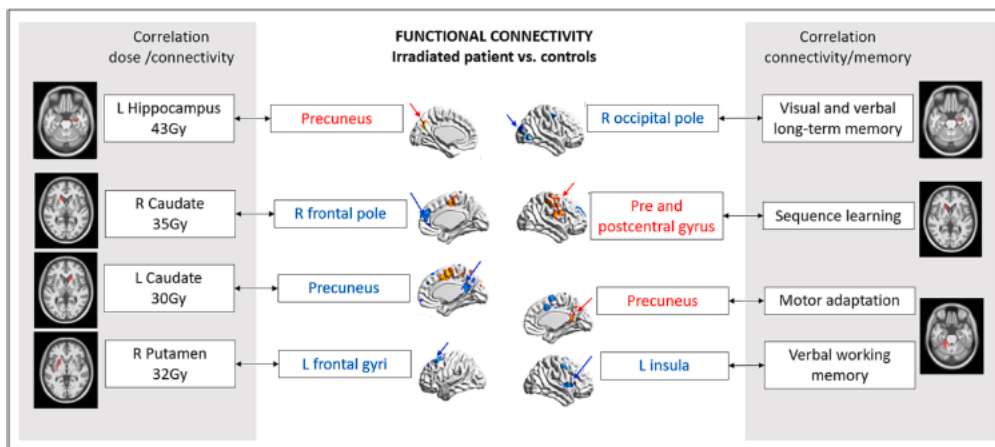


Fig. 4. Synthesis of main functional connectivity significant differences at rest in memory circuits in irradiated patients compared to controls and significant relationships with the mean dose of irradiation (left part) and memory performances (right part). Brain structures used as seed were represented in red in axial brain images on black background. Regions showing significant connectivity differences were represented in the central part of the figure, in blue when hypoconnectivity was found in irradiated group compared to control (suspected mechanism of disconnection), in red when hyperconnectivity was found in irradiated group compared to control (suspected compensatory). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



patients. Higher mean irradiation dose to the left hippocampus was linked to higher connectivity in the precuneal region (Fig. 1-C), while higher mean irradiation dose to the left putamen ( $r = -0.624$ ,  $p$ -value = 0.013; supplementary data), to the right (Fig. 3-C) and to the left caudate nucleus ( $r = -0.796$ ,  $p$ -value < 0.001; supplementary data) were correlated with lower connectivity in cortico-striatal circuits.

## Discussion

We showed that non-irradiated pediatric PFT survivors presented atypical connectivities only in cortico-cerebellar circuits probably as a consequence of the tumor and its surgery, and as a result of neuroplasticity. In other hand, irradiated pediatric PFT survivors showed atypical connectivities in the cortico-hippocampal, cortico-cerebellar, and cortico-striatal circuits suggesting an additional impact of adjuvant treatments (radiotherapy and/or chemotherapy) on long-term connectivity at rest in the supratentorial structures. Fig. 4 summarized results on connectivity and relationship with memory scores and irradiation doses in irradiated patients, specifying what can be consider as a dysfunction (in blue) of circuit or compensatory mechanisms (in red). We found no correlation with the irradiation dose to the cerebellum, probably because all patients received a homogeneous high-dose distribution in the posterior fossa.

Mostly unilateral circuits were atypical in this work. We hypothesized that, in non-irradiated participants, the predominant right lateralization of the tumor could have led to asymmetry because compensatory mechanisms have been set up in the contralateral region. In irradiated participants, tumors were mainly median, that cannot explain by itself a lateralization. As the irradiation dose were not higher in the left part of the brain (except for hippocampus) we assumed the left brain could be more sensitive to radiotherapy. Sensitivity to radiotherapy has already been shown in the left hippocampus [30,31], but data are missing for the other brain structures. These hypotheses need to be explored in larger sample size population to control for handedness and localization of the tumor.

These findings have important implications as they improve our understanding of how the tumor and its surgery in one hand, and the radiation therapy in the other hand, impact the long-term connectivity in brain circuits involved in the different memory processes. Although the hippocampal regions have well-known radiosensitivity with an impact on episodic memory [12], it seems important to also consider in the future the striatum as a potential organ at risk. The striatum has a central position in the brain, making it more susceptible than cortical regions to receive diffused radiation doses from the posterior fossa bed tumor boost and is susceptible to receive more irradiation dose when a sparing approach of hippocampus is done. The assessment of more functions of the striatum which is also involved in learning associations between stimuli [32], cognitive procedural memory [33], actions and rewards [34], and emotions [35] could improve our understanding of the impact of irradiation and should help to define constraints of dose [36].

This study has some limitations. Firstly, the small number of participants in each group limited the ability to perform statistical analyses including more covariates, such as the hydrocephalus, manual laterality, tumor site, tumor histology, age at treatment, delay from treatment, and chemotherapy. Especially, comparing patients with focal posterior fossa irradiation and various dose of CSI should have been of interest to better understand the impact of different dose of irradiation on the functional connectivity. However, this study validates a procedure that can be reproduced in a national multi-center study with a larger sample size [24]. Secondly, in the irradiated group, treatments were heterogeneous due to the variety of protocols used during the treatment period from 2005 to 2015. Thirdly, we used a time-consuming, but robust method involving manual delineation of each ROI for each participant, with double checking, and indirect segmentation and normalization in MNI space to enable group analyses. Improvement of automatic

segmentation techniques could make it possible to lighten this methodology in the future. Fourthly, the relationship between cognitive functions and rs-fMRI connectivity should be taken with caution, keeping in mind that only specific tasks performed during fMRI can demonstrate activation in specific brain areas. Lastly, we highlighted the relationship between both connectivity atypies and behavioral function and with the irradiation dose, but in different brain regions; therefore, we could not make the direct link between the irradiation dose and the function.

## Conclusion

These results highlighted that irradiation has a long-term impact on the cortico-subcortical circuits. In the future, these points are crucial to find ways to limit radiation toxicity to the normal brain tissue, but also to consider treatments to improve neuroplasticity and guide future interventional studies using transcranial magnetic stimulation.

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## Authorship

Conception: EB, PP, FT, JP, JD, JT, CD, YC, AL. Data collection: EB, LP, NC, AIB, MG, AD, AL. Data analysis: EB, PP, FT, GA, AS, MR, JP, LP, JD, JT, YC, AL. Data interpretation: EB, FT, JP, LP, JD, JT, YC, AL. Manuscript writing: All authors. Final approval of manuscript: All authors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2023.110073>.

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