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## A prospective behavioral and imaging study exploring the impact on long-term memory of radiotherapy delivered for a brain tumor in childhood and adolescence

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### ABSTRACT

**Background:** Posterior fossa tumors represent two thirds of brain tumors in children. Although progress in treatment has improved survival rates over the past few years, long-term memory impairments in survivors are frequent and have an impact on academic achievement. The hippocampi, cerebellum and cerebellar-cortical networks play a role in several memory systems. They are affected not only by the location of the tumor itself and its surgical removal, but also by the supratentorial effects of complementary treatments, particularly radiotherapy. The IMPALA study will investigate the impact of irradiation doses on brain structures involved in memory, especially the hippocampi and cerebellum.

**Methods/design:** In this single-center prospective behavioral and neuro-imaging study, 90 participants will be enrolled in three groups. The first two groups will include patients who underwent surgery for a posterior fossa brain tumor in childhood, who are considered to be cured, and who completed treatment at least 5 years earlier, either with radiotherapy (aggressive brain tumor; Group 1) or without (low-grade brain tumor; Group 2). Group 3 will include control participants matched with Group 1 for age, sex, and handedness. All participants will perform an extensive battery of neuropsychological tests, including an assessment of the main memory systems, and undergo multimodal 3 T MRI. The irradiation dose to the different brain structures involved in memory will be collected from the initial radiotherapy dosimetry.

**Discussion:** This study will provide long-term neuropsychological data about four different memory systems (working memory, episodic memory, semantic memory, and procedural memory) and the cognitive functions (attention, language, executive functions) that can interfere with them, in order to better characterize memory

**Abbreviations:** pCASL, pseudocontinuous arterial spin labeling; 3DT1, T1-weighted imaging; CMS, Children's Memory Scale; DFA, discriminating factor analysis; DTI, diffusion tensor imaging; IQ, intellectual quotient; MEM-III, Wechsler Memory Scale; NTCP, normal tissue complication probability; PFT, posterior fossa tumor; rs-fMRI, resting-state functional magnetic resonance imaging; SRTT, serial reaction time task; TCP, tumor control probability; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children.

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deficits among the survivors of brain tumors. We will investigate the correlations between neuropsychological and neuroimaging data on the structural (3DT1), microstructural (DTI), functional (rs-fMRI), vascular (ASL) and metabolic (spectroscopy) impact of the tumor and irradiation dose. This study will thus inform the setting of dose constraints to spare regions linked to the development of cognitive and memory functions.

*Trial registration:* ClinicalTrials.gov: NCT04324450, registered March 27, 2020, updated January 25th, 2021. Retrospectively registered, <https://www.clinicaltrials.gov/ct2/show/NCT04324450>.

## Background

Two thirds of central nervous system tumors, the most common solid neoplasm in children, occur in the posterior fossa. The most frequent posterior fossa tumors (PFTs) are medulloblastomas (40%), astrocytomas (30%), and ependymomas (10%). Their treatment depends on the histological type of the tumor: surgery only for astrocytomas, surgery and focal radiotherapy for ependymomas, and a combination of surgery, craniospinal radiotherapy and chemotherapy for medulloblastomas, depending on risk factors and age.

Research has focused on the long-term neuropsychological consequences of the management of PFTs, pointing to radiation therapy as a risk factor for cognitive impairment. Studies have mainly involved the assessment of general cognitive function (e.g. intellectual quotient, IQ) [1] and, more rarely, core cognitive functions, such as processing speed, attention, memory, and executive functions [2]. Few have so far focused on the memory systems impacted by PFT treatment [3–5].

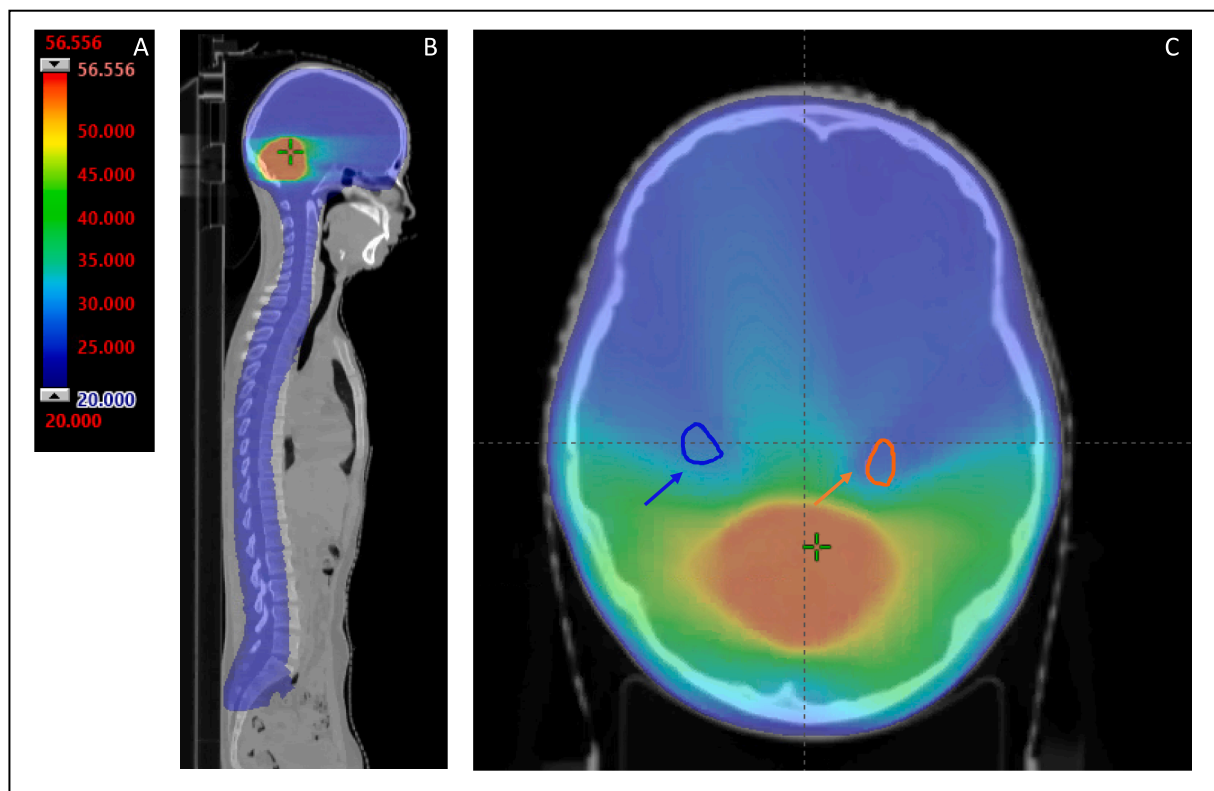
The cerebellum plays a central role in working memory and procedural memory, both of which are involved in motor [6] and cognitive learning, as it allows for the automation and procedural retention required in reading (automation of grapheme–phoneme conversion) and arithmetic (mental calculation) [7]. Whereas there is a growing body of literature on the impact of a PFT and its irradiation on working memory

[8,9], very few studies have looked at the procedural memory system [10,11].

Supratentorial structures involved in declarative memory, such as the mediotemporal lobe and hippocampi, are either partially (lower part, owing to proximity to target volume or tumor bed for boost radiotherapy) or fully (craniospinal irradiation for medulloblastomas) irradiated (Fig. 1).

In radiotherapy, a tumor control probability (TCP) and a normal tissue complication probability (NTCP) are calculated for each tumor. NTCP levels are well established in adults and children for the chiasma and inner ear. The impact of radiotherapy on brain structures [12] and on brain volumes has been reported in several studies, with reductions in whole-brain gray matter [13], cerebellar [14,15] or hippocampal volumes [16] correlated with the irradiation dose and with neuropsychological outcomes. However, despite extensive literature linking hippocampal irradiation to cognitive impairment and recommendations for avoiding hippocampal disease, there are no clearly established NTCP levels for the hippocampus and cerebellum in children [17–19].

Progress in external radiotherapy, in the shape of intensity-modulated radiotherapy and, within the near future, intensity-modulated proton therapy, will increase the possibility of saving normal tissue near the tumor irradiation bed, providing the dose constraints are known, thereby limiting the functional impact on learning



**Fig. 1.** Patient treated with postoperative prophylactic craniospinal irradiation, followed by a boost to the tumor bed for a medulloblastoma. A: dose range; B: sagittal view of the dose distribution; C: axial view of the dose distribution. The cerebellum and left and right hippocampi were delineated on the coregistered pre-radiotherapy MRI. The hippocampi are visible on the axial slice (C: left hippocampus outlined in orange, right hippocampus outlined in blue). The healthy cerebellum and both hippocampi received a full dose of craniospinal irradiation, and an additional diffuse dose delivered by the boost.

and memory outcomes (see Figs. 2 and 3).

The IMPALA (Imaging Memory after Pediatric cancer in Children, Adolescents and Young Adults) study is designed to improve current understanding of the long-term structural, microstructural, functional, vascular and metabolic impact of radiotherapy, especially in cerebellar and hippocampal regions, and its behavioral impact on the different memory systems, by adopting a multimodal MRI approach and administering an extensive battery of memory tests.

## Methods

### Study objectives

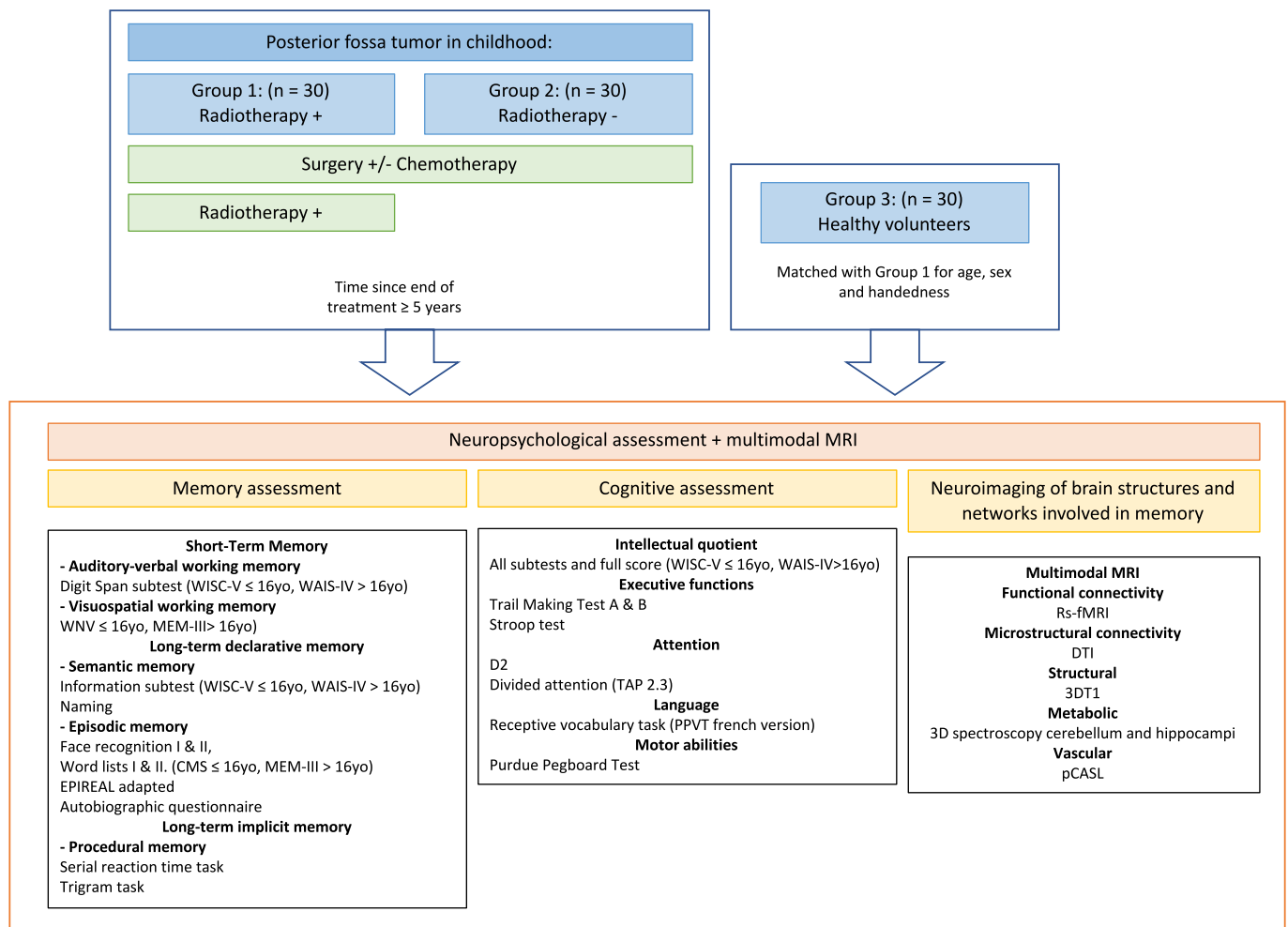
The primary objective is to explore the impact of irradiation on declarative episodic memory and its neuronal substrate, depending on the radiation dose to the episodic memory structures (mediotemporal lobes and hippocampi), in patients cured of PFTs who underwent radiotherapy, comparing them with cured patients who underwent surgery and/or chemotherapy but no irradiation and with typically developing children (control group) matched for sex, age and handedness. Our hypothesis is that irradiation of the mediotemporal lobes and hippocampi may modify their structure and connectivity, and have an impact on the development of declarative episodic memory.

Secondary objectives are as follows:

- Characterize the neuropsychological memory profiles of children, adolescents and young adults cured of a PFT, depending on the treatment they received (with or without irradiation). We hypothesize that patients with PFT may have more frequent impairment of procedural memory and working memory than controls, and patients treated by radiotherapy may have a more pronounced deficit in these memory systems, associated with a declarative memory impairment;
- Describe the possible correlations between participants' neuropsychological memory scores and MRI markers of the integrity of structures and networks involved in episodic memory (mediotemporal lobes, hippocampi, and episodic memory network) and procedural memory (striatum, cerebellum and cerebello-cortical and striatocortical networks);
- Study the possible links in children treated by radiotherapy between the characteristics of radiotherapy performed in childhood and neuropsychological scores, and between structural and functional modifications in the brain structures and networks associated with the hippocampus and cerebellum, in order to define NTCPs for the cerebellum and hippocampus.

### Study setting

IMPALA is a single-center prospective study.



**Fig. 2.** Population, neuropsychological tests and MRI sequences used. Abbreviations: pCASL: pseudocontinuous arterial spin labeling; 3DT1: three dimensional T1 weighted imaging; CMS: Children's Memory Scale; DTI: diffusion tensor imaging; PPVT: Peabody Picture Vocabulary Test; MEM-III: Wechsler Memory Scale; rs-fMRI: resting-state functional magnetic resonance imaging; SRTT: serial reaction time task; TAP: Test Battery for Attentional Performance; WAIS-IV: Wechsler Adult Intelligence Scale; WISC-V: Wechsler Intelligence Scale for Children; WNV: Wechsler Nonverbal scale of ability.

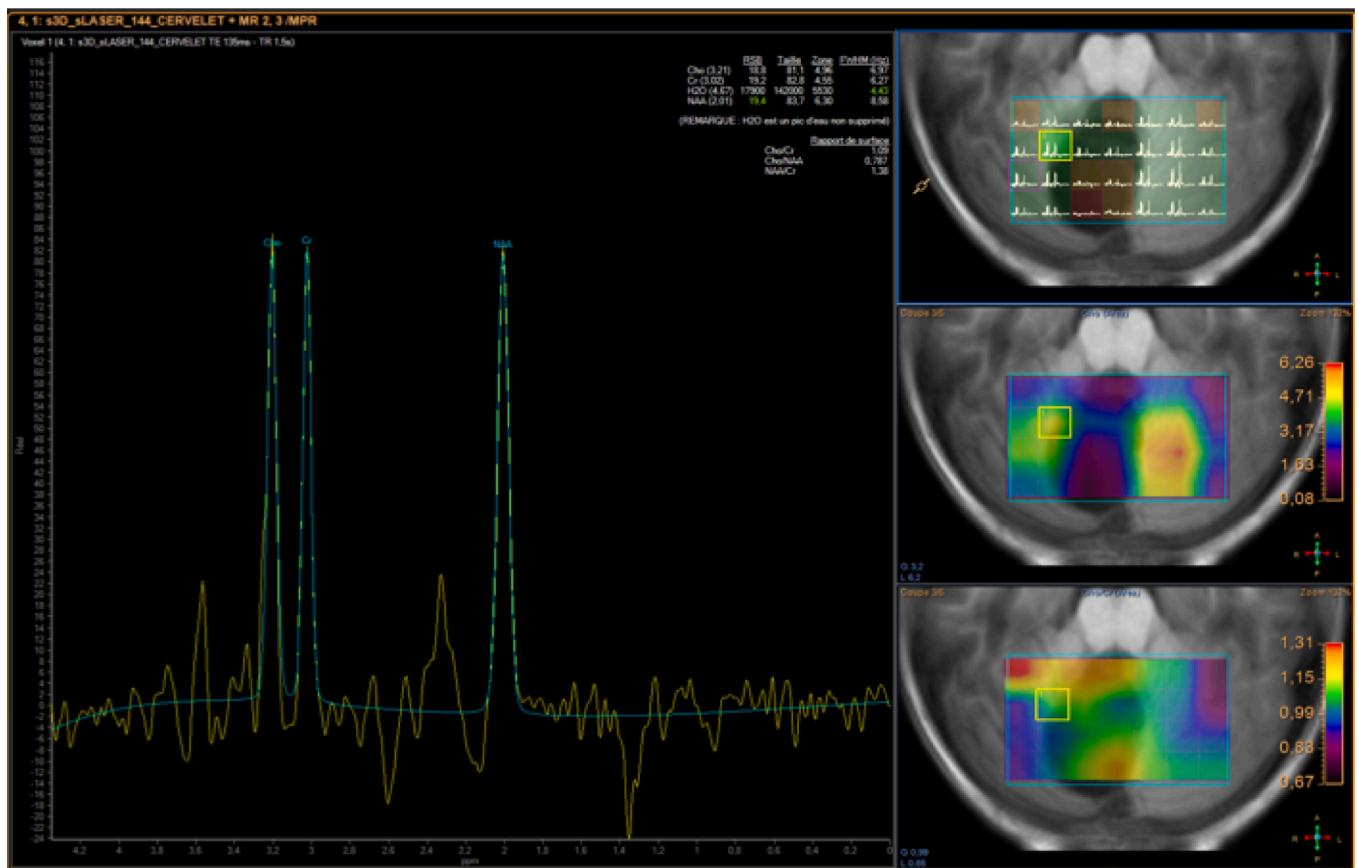


Fig. 3. Example of MR spectroscopic imaging of cerebellum for a PFT survivor showing normal spectra. Post-processing of spectral acquisition, quantification, and creation of metabolic maps are carried out with SpectroView Analysis package.

### Participants

90 participants will be enrolled in three groups, as follows:

- Group 1: patients with radiotherapy (irradiated);
- Group 2: patients without radiotherapy (nonirradiated);
- Group 3: healthy volunteers (control).

#### Preselection:

Forty patients from the city of Toulouse and surrounding regions who have been cured of a PFT and who received radiotherapy in childhood between 2005 and 2015 at the Claudius Regaud Institute of the Toulouse University Cancer Institute (IUCT-Oncopole) have been identified from clinical databases. Similarly, 40 patients from the city of Toulouse and surrounding regions who have been cured of a PFT and who were treated by surgery with or without chemotherapy, but not radiotherapy, in childhood between 2005 and 2015 at Toulouse Children's Hospital have been identified from clinical databases. Healthy volunteers matched for age, sex and handedness with the irradiated group, will be recruited via a call for volunteers on the Toulouse Neuroimaging Center (ToNIC) website, INSERM, and in the press.

#### Patient selection: Inclusion criteria

For all participants:

- French mother tongue;
- Sufficient visual, auditory, speaking and writing skills to perform neuropsychological tests;
- Written informed consent for adults, and parental (or legal guardian) consent for minors;

for irradiated patients:

- Treated before age 18 years;
- Considered cured after irradiation of a PFT (complete clinical and imaging response 5 years after completion of radiotherapy);
- Underwent localized brain irradiation or craniospinal irradiation for a brain tumor whose treatment includes first-line radiotherapy (ependymoma or medulloblastoma);

for patients treated by surgery with or without chemotherapy:

- Underwent resection of a PFT without radiotherapy (i.e., brain tumor whose treatment does not include first-line radiotherapy: low-grade glioma such as pilocytic astrocytoma);
- Treated before age 18 years;
- Considered cured 5 years after end of treatment.

#### Patient selection: Exclusion criteria

for all participants:

- Under legal guardianship (adult);
- Severe ataxia;
- Participation in a research study involving treatment within the previous 3 years;
- Contraindication for MRI;

for healthy volunteers:

- Known neurological or psychiatric history;
- History of learning disability or neurodevelopmental disorder;
- Receiving psychotropic treatment (methylphenidate, antidepressants, etc.).



## Procedure

The protocol will be implemented by the DEVIN team at ToNIC in two 1-day sessions 3 weeks apart. In the morning of Day 1, participants will undergo a medical visit with a neuropediatrician (the same for all participants) who is experienced in the care and multidisciplinary follow-up of children with brain tumors. They will then perform the procedural learning tasks on a tablet and undergo an MRI. In the afternoon, they will perform memory tests during a 2-hour session with a qualified neuropsychologist (LP). On Day 2, the neuropsychological assessment will continue, with an episodic memory recall test and a full assessment of IQ in a morning session lasting 2½ hours, and other cognitive tests in an afternoon session lasting approximately 1¼ hours.

## Medical and sociofamilial data

Sociofamilial data will be carefully reported, as they are important to neuropsychological outcomes [20] (parents' occupations, highest degree obtained, and number of years of study). Data concerning the disease, initial symptomatology, initial hydrocephalus and tumor location, details of surgical management, radiotherapy and chemotherapy will be collected. The clinical exam will include a cerebellar syndrome rating using the ICARS score [21], and the Edinburgh Handedness Test (short form) [22]. Details of each child's school career before and after treatment for the tumor will be collected, including school adaptations and arrangements, as well as the length and nature of rehabilitation. For older patients, the impact on employability and autonomy will also be evaluated, according to highest qualification, number of years of study, occupation, driver's license and housing status. Neurological, endocrine (hormonal balance), ophthalmological and auditory complications will be collected, as they can impact results in neuropsychological assessments.

The dose values received by the brain structures involved in memory systems will be extracted from the dose volume histogram, along with the dose distribution map from the dosimetry data calculated prior to radiotherapy treatment using Eclipse™ treatment planning software (Varian Medical Systems).

## Neuropsychological assessment

The neuropsychological assessment will be carried out by the same qualified neuropsychologist (LP) in the same order for all participants. It will take place in the same office, over three half-days. The tests used (see Fig. 1) will include the Wechsler Intelligence Scale for Children-5th edition [23], Wechsler Adult Intelligence Scale 4th edition [24], Wechsler Nonverbal scale of ability [25], naming (EVOLEX software) [26], EPIREAL [27,28], autobiographic questionnaire [29], Wechsler Memory Scale 3rd edition [30], Children's Memory Scale [31], serial reaction time task (SRTT [32]), Trail Making Test [33,34], Stroop test [35], D2 [36], Test Battery for Attentional Performance [37], PPVT: Peabody Picture Vocabulary Test [38], and Purdue Pegboard Test [39]. We will use the scores of normative tests when they will be available. To better assess declarative memory, these classic tests will be supplemented by an ecological episodic memory test developed at Toulouse University Hospital for adults (EPIREAL), which we have adapted for younger participants. This test takes the form of controlled mini-events (e.g., ringing telephone, offer of a glass of water or fruit juice), and will take place during the neuropsychological assessment in the afternoon of Day 1. Participants will not be informed of the experimental nature of these mini-events. Free recall, cued recall, and recognition of these events and their spatiotemporal context will be tested on Day 2, and this process will be tested 3 weeks later. To explore procedural memory, we have selected a SRTT, which is the most widely used paradigm for probing sequence learning in humans (for a meta-analysis, see Janacsek et al. 2020 [40]), and a motor adaptation task. The latter consists in writing three cursive (attached) letters in both the usual direction of

writing (from left to right in a French population) and the opposite direction (from right to left).

## MRI data acquisition

MRI will be acquired at the INSERM/UPS ToNIC technical platform using a Philips Achieva dStream 3.0 T MRI scanner equipped with a 32-channel head coil. This multimodal MRI session will include T1 without injection of a contrast agent, fluid attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), pseudocontinuous artery spin labeling (pCASL), and 3D MR spectroscopic imaging of the cerebellum and hippocampi. The whole session will last 60 min. Details are set out in Table 1.

During the 10-minute resting-state acquisition, participants will be asked to keep their eyes open, look at a cross on a screen, and think of nothing.

For the spectroscopic images, the placement of the 3D-CSI box will be adjusted for each participant, taking the individual anatomy into account, in order to involve most of the cerebellum and posterior hippocampi, carefully avoiding bones and vascular structures that could corrupt the spectra (occipital and temporal bones for posterior fossa, sella turcica and circle of Willis for hippocampi). Post-processing of spectral acquisition, quantification, and creation of metabolic maps will be carried out with the SpectroView Analysis package.

Before inclusion began, MRI was performed on three volunteer participants to evaluate the quality of the images and spectra acquired. A team including the coordinating radiation oncologist, imaging-radiotherapy engineer, a physicist and the platform's technical MRI team met to perform any necessary modifications or improvements before the trial began.

A systematic reading of the MRI examinations (FLAIR, 3DT1, T2) of participants who have been treated for a PFT will be performed by a neuroradiologist experienced in the pediatric neuroradiological monitoring of tumors, and compared with previous explorations, in order to detect possible radiological recurrence or relapse.

## Imaging analysis

The structural integrity of brain structures will be assessed using a multimodal approach.

T1 analysis and diffusion imaging will allow us to extract the volume, shape, cortical thickness and microstructural integrity parameters for each participant. Brain's substructures of interest (left and right anterior and posterior cerebellum, left and right hippocampus) will be segmented manually using the European Particle Therapy Network guidelines on neuro-oncology [41]. These parameters will be used to carry out tests between groups.

Functional data will be determined for the hippocampus and cerebellum. Individual maps of functional connectivity between the cerebellum and the whole brain and between the hippocampus and the whole brain will be calculated. These maps will then be used to perform a multiple comparison-corrected *t* test with the maps for each of the three groups.

Cerebral blood volume maps will be obtained from the ASL perfusion imaging.

Magnetic resonance spectrometric imaging will be used to measure post-therapy hypoxia (lactate as a surrogate) and neuronal density (N-acetylaspartate). The spectroscopic processing protocol consists of water subtraction, low-pass filtering, frequency shift correction, baseline correction, phase correction, and curve-fitting in the frequency domain allowing different ratio analysis.

## Time schedule of enrolment

First inclusion was performed on February 2020 and inclusions are planned until September 2021.

**Table 1**  
Acquisition parameters and outcome measures.

	3D-T1	Rs-fMRI	FLAIR	DTI	pCASL	3D semi-laser sequence MRS of cerebellum and hippocampi registered on T2-weighted images.
<b>TR/TE (ms)</b>	TR/TE = 7.4/3.4	TR/TE = 1300/30	TR/TE = 8000/135	TR/TE = 4920/80	TR/TE = 4066 / 12	TR/TE = 1500/135
<b>FA</b>	8	90	100	90	90	90
<b>FOV</b>	240	240	230 × 186	200 × 200	240 × 240	120 × 90
<b>matrix</b>	240 × 240	80 × 78	356 × 167	148 × 146	80 × 80	12 × 9
<b>Voxel size (mm)</b>	1 × 1 × 1	3.0 × 3.0 × 3.0	0,65x1,12x4,00	1.35 × 1.35 × 2	3x3x4	10 × 10 × 15
<b>Number of slices</b>	180 sagittal	44 axial	28	70	24	5
<b>Slice thickness (mm)</b>	1	3	4	2	4	5
<b>Other parameters of interest</b>		Each scan session will last 642 s and include 500 volumes	In-plane resolution = 1 × 0.1 mm	34 non-collinear directions b = 0/1,000	Label duration: 1650 ms Post-label delay: 1600 ms	VOI selection method = sLASER Water suppression = VAPOR
<b>Duration (min)</b>	6:21	10:55	2:40	10:00	4:12	5:58 (x 2)
<b>Outcome measures</b>	Volume and shape of brain structures involved in memory	Functional connectivity of memory networks	(only to eliminate a relapse)	Fractional anisotropy, mean diffusivity, radial diffusivity and axial diffusivity of brain structures involved in memory	Cerebral blood volumes of brain structures involved in memory	Lactates, choline, N-acetylaspartate, creatine, and choline/ N-acetylaspartate, choline/creatine and N-acetylaspartate/creatine ratios

3D-T1: T1-weighted imaging; DTI: diffusion tensor imaging; FFE: fast field echo; EPI: echoplanar imaging; FA: flip angle; FLAIR: fluid attenuated inversion recovery; FOV: field of view; MRS: magnetic resonance spectroscopy; pCASL: pseudocontinuous arterial spin labeling; rs-fMRI: resting-state functional magnetic resonance imaging; TR: time repetition; TE: time echo.

#### Adverse events and other unintended effects of trial interventions or trial conduct

This events are collected by the research technicians and reported.

#### Statistical analysis

##### Main analysis: Evaluation of the neuronal substrate of declarative memory.

The impact of radiotherapy on declarative memory will be investigated using a two-factor analysis of variance (ANOVA): Group (participants with irradiated brain tumor vs. participants with nonirradiated brain tumor vs. controls) × Modality (verbal vs. visual episodic declarative memory). This ANOVA will be performed on the different subscores exploring episodic declarative memory in each modality. An adjustment to the mean IQ level will be made to take into account a possible difference in the distribution of IQ between the three groups. These analyses will be supplemented by a multivariate analysis of the multiple linear regression type, to take into account potential confounding factors such as the histological type of the tumor or the participant's social environment. The mean values of each neuro-imaging marker will also be entered into logistic regression models, to explore possible links between the imaging data and the neuropsychological and behavioral data.

##### Secondary endpoint analysis

The exploratory analysis of data yielded by the neuropsychological assessment, aimed at objectifying the variables and individuals with a similar variance, will be carried out as follows:

- Principal component analysis. This unsupervised exploratory analysis will allow us to (i) visualize the relatively abundant data, and (ii) observe whether a natural grouping of participants corresponding to the three groups occurs in the first main planes. If this is the case, we can then perform targeted analyses of the variables that contribute most to the components involved, thus making it possible to reduce the multiplicity of tests (mixed linear models with variables of interest and group as fixed effects, and participant as random effect).

Post hoc analyses ( $p = .05$  considered statistically significant [42]) and effect sizes will be calculated.

- Discriminating factor analysis. This supervised method will allow us to construct a representation space that best separates the participants in the irradiated group from the other two groups, and then to identify the quantitative variables on the relevant axes that most clearly discriminate between the groups.

##### Comparison of study MRI data with dosimetry data for treatment received during childhood:

Correlating the doses received with current MRI results, taking account of brain growth (which also differs according to the region) will require considerable methodological work, and will involve the elastic registration of MRI and radiotherapy computed tomography scans performed in childhood with the images acquired in the present study.

Lastly, the use of supervised learning will allow us to build a regression model that is capable of predicting neuropsychological scores (i.e. intellectual abilities, memory, etc.) and/or MRI imaging markers (i.e., volume of hippocampi, cortical thickness). This will be a dynamic model, including time since treatment in childhood, as well as age, dose, and type of disease. Several algorithms will be calculated (LASSO, ridge and gradient boosting with decision trees). A robust cross-validation will allow us to measure the efficiency of our model (k-fold cross-validation, leave-one-out cross-validation).

##### Statistical power

The exploratory nature of this study makes it impossible to calculate the sample size needed to achieve statistical power. In the absence of sufficient data in the literature to make reliable assumptions for calculating enrollment, recommendations for pilot studies suggest including at least 30 participants per group [43]. We therefore plan to include 30 participants per group for this exploratory study (i.e., 90 participants in total).

#### Discussion

The IMPALA study will involve calculating innovative dose-neurocognition-imaging correlations using multimodal brain imaging.

This will allow us to better understand the long-term structural, microstructural, vascular and metabolic impact of radiotherapy, as well as its behavioral impact on learning and memory.

In contrast to previous studies investigating long-term memory outcomes, IMPALA will study the different memory systems (working, episodic, semantic and procedural) in the same population, using an extensive battery of normative memory tests. Moreover, IMPALA will use new and interesting tools, such as an ecological episodic memory test that is easy to perform in a routine clinical setting, as it does not require complex equipment. This may provide a better reflection of real-life deficits in episodic memory than commonly used learning tests that do not consider the spatiotemporal context (learning lists of words or faces) or else rely on previously experienced episodes that cannot be controlled (autobiographical questionnaire). In addition, we will carry out an evaluation of procedural motor learning, including both a motor sequence learning task eliciting striatal-cortical networks, and a motor adaptation task eliciting cerebellar-cortical networks. To the best of our knowledge, no such adaptive motor task has yet been used in PFT, even though we can assume that tumor location and treatment can have an impact on this skill.

A further aim of the IMPALA study is to validate a procedure that can be used in a national multicenter study allowing a larger sample to be included.

#### Declarations

#### Ethical approval and consent to participate

The IMPALA study is sponsored by INSERM.

It was granted approval by a local ethics committee (Comité de Protection des Personnes) on 14/10/2019 and registered in a public trials registry (NCT04324450). All study participants (or legal representatives for participants under 18) gave their written informed consent to participation, in line with French legal guidelines.

#### Consent for publication

Not applicable.

#### Availability of data and materials

Data sharing is not applicable to this article.

#### Declaration of Competing Interests

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.

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#### Authors' contributions

AL is the main investigator and coordinates the study. EB wrote the first draft of this manuscript and prepared the figures and tables. AL, PP, JP and YC elaborated the trial design. AL, FT, GA, PP and HG participated in the development of the MRI protocol. FT, LP, AL, MC, HG, JD

and JT revised the manuscript. JP and YC devised the neuropsychological program and LP and EB finalized and set it up. JT, JD, JP and BL participated in the elaboration of the experimental procedural task and ecological memory test. AB, MG, DLC and AD participated in the patient selection. EB and LP are participating in the patient inclusion and the testing. AS and MR will perform the neuroradiological review of MRI scans acquired with the research MRI scanner. All the authors read and approved the final manuscript.

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