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Review Article

A review of long-term deficits in memory systems following radiotherapy for pediatric posterior fossa tumor

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ABSTRACT

Introduction: In recent years, progress in pediatric posterior fossa tumor (PFT) treatments has improved survival rates. However, the majority of survivors present neurocognitive sequelae that impact academic achievement.

Methods: This review examines the literature from 2000 to 2020 on long-term outcomes in different memory systems for survivors of pediatric PFT, considering the impact of radiotherapy which is a well-known prognostic factor for global neurocognitive function.

Results: Of the 43 articles selected, 31 explored working memory, 19 episodic memory, 9 semantic memory and 2 procedural memory. Irradiated survivors had scores of <−2 standard deviation (SD) (n = 4 studies/25) or between −2SD and −1SD (n = 7 studies/25) for working memory; <−1SD for anterograde memory (n = 11/13), with a progressive decline in these two memory systems; <−1SD (n = 4/7) in semantic memory, and a deficit in perceptual-motor procedural learning (n = 1/1). Reducing craniospinal irradiation dose, limiting tumor bed boosts, and using proton therapy seem to have had a beneficial effect with better preservation of the memory score and a reduction in the decline over time. Non-irradiated survivors had memory systems that were less affected, with preservation of anterograde memory and maintenance of long-term stability.

Conclusion: Memory deficits are a core feature in survivors of pediatric PFT, especially when treatment requires radiotherapy. To limit these effects, dose constraints for specific brain areas involved in memory should be defined. During long-term follow-up, specific attention is essential to identify these deficits in order to limit their impact on the quality of life.

Two-thirds of the central nervous system tumors, the most common solid neoplasm in children, occur in the posterior fossa. With improvements in surgical technologies, chemotherapy and radiotherapy protocols over the past decades, the 5-year survival rate for children with a posterior fossa tumor (PFT) have increased for the main histological types of tumors diagnosed during childhood. The survival rate is 90% for astrocytoma (30% of PFT), 60% for ependymoma (10% of PFT), and 80% for medulloblastoma (40% of PFT). Treatments differ from one histological form to another, currently including only surgery for astrocytomas, surgery and focal radiotherapy for ependymomas and a combination of surgery, craniospinal radiotherapy and chemotherapy depending on the risk factors and age for medulloblastomas.

Medical follow-up of patients with pediatric PFT showed a frequent occurrence of global and specific neurocognitive disorders that impact academic achievement and professional integration. Many studies have focused on changes in intellectual quotient (IQ), an age-adjusted composite index of several neuropsychological processes, showing lower mean scores and a progressive decline in IQ over time for patients with medulloblastoma [1]. Among the factors that cause late effects (tumor itself, hydrocephalus, surgery, chemotherapy), the most significant for these neuropsychological sequalae is probably the whole brain irradiation dose. Recently, authors have identified more specific neurocognitive disorders in PFT patients that affect learning, memory, processing speed, attention, and executive function [2].

Abbreviation: CSI, craniospinal irradiation; IQ, intellectual quotient; PFB, posteiror fossa boost; PFT, posterior fossa tumor; SD, standard deviation; SRT, serial reaction time; TBB, Tumor bed boost.

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Palmer et al. showed that this impairment is not the consequence of a loss of anterior learning but rather slowness in learning new skills [3].

Memory is a highly complex cognitive process that develops through childhood. Multiple systems are involved, which concern short-term memory (working memory) or long-term memory (episodic, semantic and procedural memory). These systems, which are often studied in isolation, constantly interact, based on the neuropsychology of memory in the Memory Neo-Structural Inter-Systemic model (MNESIS) [4], and involve distinct and common brain areas and neural circuits that can be affected in PFT (Table 1). While the involvement of the hippocampus and parahippocampal regions in long-term episodic memory is well known [5], brain structures and networks involved in memory systems are larger. The cerebellum and cortico-cerebellar circuits in particular, are both involved in working memory (cerebellar posterior lobe (lobules VII and VIII), prefrontal and parietal cortices) [6,7] and procedural memory (left lobules V & VI, dentate nuclei) [8]. Moreover, the cerebellum may also participate in episodic memory, both in encoding [9] and retrieval [10]. Knowledge of the role of the cerebellum in memory is currently limited [11], but some authors suggest that the internal predictive model initially developed for motor skills could be applied to cognitive and memory skills [12,13]. Based on this idea, it can be hypothesized that the localization of a tumor in the posterior fossa and the impact of surgery on the cerebellum and on afferent and efferent tracts alters memory, especially working memory and procedural memory. Moreover, the consequences of a tumor (such as hydrocephaly) and its treatment (chemotherapy, radiotherapy) on the supratentorial brain parenchyma of PFT survivors could alter the different memory systems.

Except for infants, patients with malignant tumors receive multimodal treatment including radiotherapy. At present, ependymoma radiotherapy is limited to the tumor bed with high doses ranging between 54 and 59.4 Gy. Due to the high risk of craniospinal dissemination, medulloblastoma is treated by craniospinal irradiation (18–36 Gy depending on the tumor risk group) followed by a localized boost of up to a total of 54 Gy. The craniospinal irradiation dose is an important factor in the pathogenesis of global neurocognitive sequelae, including specific cognitive functions such as memory. One current challenge is to find the optimal balance between sufficient irradiation to cure the patient while limiting the impact of irradiation by reducing the cranio-spinal dose of radiotherapy and/or avoiding or limiting the dose to the normal brain.

In the past two decades, radiotherapy techniques used to manage the two main, malignant PFTs (medulloblastoma and ependymoma) have improved. The changes in these techniques and their impact on therapeutic protocols are indicated in Fig. 1. The common aim of these improvements is to limit the irradiation dose to the normal brain. Knowledge of threshold doses with deleterious effects on the different brain structures helps to guide these

Table 1
Memory systems. A short definition is given for the four main memory systems and memory processes of interest and specific tests commonly used to asses them, brain areas involved and changes during the 2 first decades of life are summarized. Yo: years old.

			Definition	Process	Neuropsychological tests	Brain areas	Development
Short-term memory		Working memory	Allows maintenance, control and processing of information for immediate use	*Load:* quantity of information that can be kept in mind *Updating:* ability to replace the information stored a moment ago to update it	Verbal and visual span tasks N-back tasks	**Prefrontal cortex,** anterior cingulate gyrus, parietal lobe, Broca's, occipital lobe, cerebellar posterior lobe	Forward span: progressively improves from 2 to 9 yo. Backward span: improve from 6 yo to adolescence [5]
Long term memory	Declarative memory	Episodic memory	Information about personally experienced events, associated with their spatiotemporal context of acquisition and their emotional content.	*Retrograde:* ability to remember information encoded before the diagnosis of brain tumor *Anterograde:* ability to encode new information after the diagnosis of brain tumor	Questionnaires on episodes specific to an individual's life since birth Word lists or picture lists: learning, free recall, an indexed recall and/or a task of recognition after a predefined time period	**Medial temporal lobe**, especially hippocampus, fornix, cingulum bundle, prefrontal and parietal cortices.	Moderately improves from 3 to 9 yo, with a quick increasement from 9 to 10 yo [6]
		Semantic memory	General knowledge information (facts, ideas, meaning and concepts) regardless of the spatiotemporal context of acquisition.	Language-based semantic information retrieval tasks	Word generation, image naming	**Prefrontal cortex**, especially frontal inferior gyrus (semantic representation access) and **temporal cortex** (storing information).	Progressively improves from birth to adolescence [7]
	Non-declarative memory	Procedural memory	Knowledge that is acquired during perceptual-motor and cognitive activities whose learning requires repetition, and of which expression is automatic.	*Cognitive:* ability to learn a cognitive procedure *Perceptual-verbal:* linked to reading *Perceptual-motor:* ability to learn a perceptual-motor procedure	Probabilistic classification task, Tour of Hanoï Mirror writing test Sequence learning or motor adaptation tasks	**Cerebellum** and cerebello-cortical circuit (motor-adaptation), **striatum** and cortico-striatal circuit (motor sequence learning), frontal associative regions, medial temporal lobe (hippocampus) and temporal cortex	First memory system to mature. Progressively improves during the two first decades or stable over time [8]

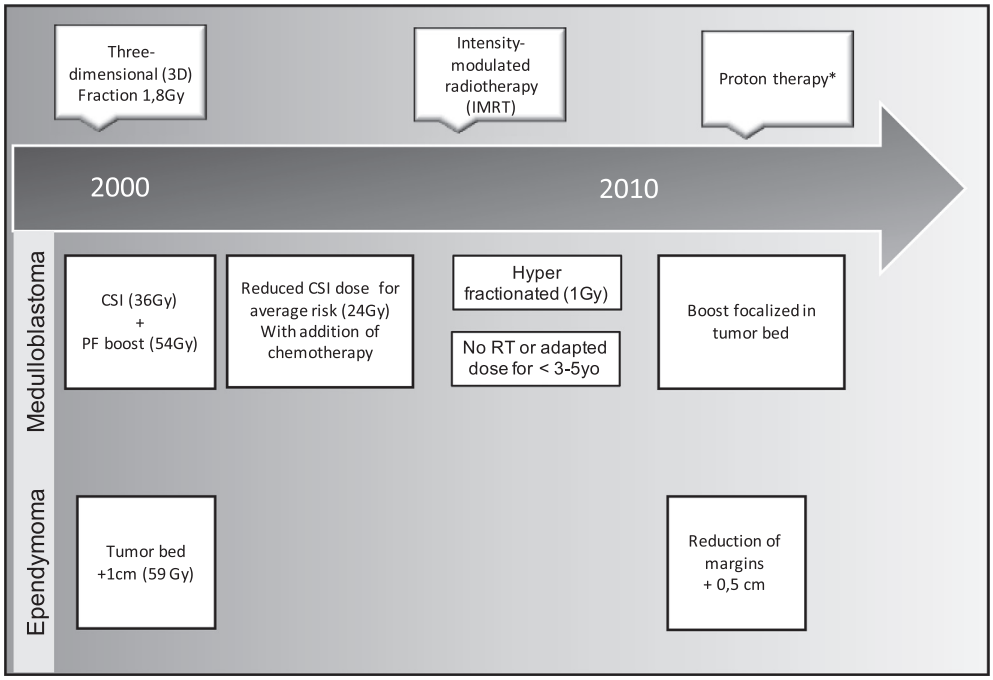

Fig. 1. Changes in radiotherapy techniques in the management of malignant posterior fossa brain tumors since 2000: Increased survival and decreased long-term side effects. CSI: craniospinal irradiation; Gy: gray; PF: posterior fossa; RT: radiotherapy; yo: years old * Inequality of access between countries and centers.

advances. However, these threshold doses are not known for the structures involved in memory development in children and their determination is vital.

The physiopathology of radiotherapy-induced brain lesions is better understood as a result of MRI studies. Brain damage occurs early after radiotherapy (<1 month), especially in white matter, with an alteration in diffusion tensor imaging MRI that has been linked to cognitive deficit [11]. Damage to neuronal dendritic spines, neuronal metabolic changes, oligodendrocyte injury and loss, neuroinflammation and vascular endothelial damage are early damages that persist and change the signaling microenvironment in neuronal tissue, leading to a loss of cognitive function and memory. The hippocampus, which is involved in episodic memory, seems to be particularly vulnerable to irradiation with a specific impact on the proliferation of hippocampal subgranular zone progenitor cells and their differentiation into neurons [11]. These damages largely depend on the irradiation dose. Radiotherapy has been implicated in learning and memory impairments observed in brain tumor patients with an impact of radiotherapy dose on the hippocampus [12,13]. The irradiation dose to the left hippocampus is linked with difficulties in verbal learning and memory in adults [14] and children with infra- and supratentorial brain tumors [15,16]. Some authors have built hippocampal dose volume histograms to predict verbal learning scores after brain irradiation in adults [17]. These data are sparse and not widely replicated.

The aim of this work is to review the literature that reports on actual knowledge of long-term performances in the different memory systems after PFT treated during childhood, detailing the impact of radiotherapy on the posterior fossa and the entire developing brain.

Methods

Eligibility criteria

To be eligible for this literature review, studies had to meet the following criteria: (1) patients had to be treated for a PFT, or if supra- and infratentorial tumors were included, specific data had to be available for the infratentorial group, (2) treatment had to be administered before the age of 18 years, (3) there had to be at least one neuropsychological task used to assess memory, (4) the mean period between tumor treatment and neuropsychological assessment had to be at least 3 years, (5) patients treated with radiotherapy were analyzed separately from patients treated without, and (6) the study had to be published in English between 2000 and 2020.

Search strategy

A literature search was performed using the PubMed search engine. Combinations of the terms "Infratentorial Neoplasms", "Cerebellar Brain Tumors" and "Episodic Memory", "Working Memory", "Procedural Memory", and "Semantic Memory" were used. We then completed with a wider search including the terms "neuropsych*" and "cognition" and we selected articles in which neuropsychological tests that assess memory were used. References cited in relevant articles were also searched as an additional resource for articles. Case reports and case series were excluded from the search.

Data extraction

From each study, the following data were extracted for the groups: number of participants, tumor type, age (mean, standard deviation, range) and the period between tumor treatment and neuropsychological assessment. The number of participants included in the control group, if any, was also reported.

The neuropsychological tests were numerous. Therefore, in order to clarify the results, we classified them: (1) according to the different memory systems (working, episodic, semantic and procedural memory) and (2) for each memory system, according to the memory processes involved. Table 2 summarizes memory tasks used in this literature review according to the memory system and memory function assessed.

Table 2
Memory tasks used in the literature review.

Memory system	Process		Memory Task
Working memory	Load	Verbal	Digit span forward (WISC/WAIS)
			Digit span backward (WISC/WAIS)
			Letter-Number sequencing (WIE/HAWIK)
			Digit span total (WISC/WAIS)
			Working Memory Index (WISC/WAIS)
			Working memory (WJ-IV)
		Visual and visuo-spatial	Corsi or Wechsler blocs forward
			Corsi or Wechsler blocs backward
			Block board test
			Feature identification (Amsterdam Neuropsychological task)
			Working Memory Test Battery for Children
	Updating		Paced Auditory Serial Addition Test
			N-back task
			Working memory reaction times (Test-battery for Attentional Performance)
			Working memory omissions (Test-battery for Attentional Performance)
Episodic & Anterograde Memory	Episodic		Recall of a personal life event, one that occurred before and one after radiotherapy
	Verbal Anterograde	Learning	California Verbal Learning Test
			Rey Auditory Verbal Learning Test
			Verbal Learning and Memory Test
			Signoret BEM 144 module
			Children's Auditory Verbal Learning Test
			Children's memory scale
			Korean version of the auditory verbal learning test
		Long delay Free recall	California Verbal Learning Test
			Rey Auditory Verbal Learning Test
			Verbal Learning and Memory Test
			Signoret BEM 144 module
			Children's Auditory Verbal Learning Test
			Verbal delayed index (Children's memory scale)
			Korean version of the auditory verbal learning test
		Recognition	Verbal Learning and Memory Test
			Korean version of the auditory verbal learning test
		Global	California Verbal Learning Test
			Children's memory scale
			Wide Range Assessment of Memory and Learning
			Verbal Learning and Memory Test
	Visual Anterograde	Learning	Rey visual design learning test
			Brief Visuospatial Memory Test – revised learning
			Continuous Visual Memory Test total learning
			Korean complex figure test immediate recall
			Children's memory scale visual immediate index
		Long delay Free recall	Rey Complex Figure Test and Recognition Trial
			Brief Visuospatial Memory Test - revised delayed recall
			Continuous Visual Memory Test delayed recognition
			Korean complex figure test delayed recall
		Recognition	Rey Complex Figure Test and Recognition Trial
			Visual recognition test
		Global	Children's memory scale visual composite score
	Global Anterograde		Wechsler Memory Scale - Revised
			Children's memory scale general index
			Recognition Memory Test
			Wide Range Assessment of Memory and Learning.
Semantic Memory			Subtest Information (WISC/WAIS)
			Subtest Information (HIE/HAWIK)
			Known people and places
Procedural Memory	Perceptual-Motor		Serial reaction time task

BEM: Batterie d'Efficience Mnésique; HAWIK: Hamburg-Wechsler-Intelligenztest für Kinder und Jugendliche; HIE: Hamburg-Wechsler-Intelligenztest für Erwachsene; WAIS: Wechsler Adult Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WJ: Woodcock-Johnson Tests of Cognitive Abilities.

Depending on the article, the results of the neuropsychological tests is presented heterogeneously as raw, standardized or z-score data. Moreover, the term "impaired" is sometimes used for scores <−1SD, <−1.65SD or <−2SD. For simplicity, we associated each score with: a normal range (between −1SD and +1SD) which does not reflect a deficit in memory performance; a low range (between −1 and −2SD) which represents poor memory performance that can lead to repercussions on academic learning and everyday life; or an impaired range (<−2SD) which reflects a deficit in memory performance with a memory disorder in everyday life.

Considering that the techniques and recommendations concerning radiotherapy have developed over the last 20 years, the data concerning these techniques, craniospinal irradiation dose and boost dose were specified when they were available in the original articles.

Others prognostic factors for memory were also extracted based on neurocognitive prognostic factors reported in the literature: age at treatment, length of time since treatment, hydrocephalus or the need for a shunt, tumor characteristics (volume and localization), surgical complications and medical events, posterior fossa syndromes and socioeconomic status.

Finally, we extracted neuroimaging data when available, for a better understanding of neural substrates of memory functions in PFT survivors.

Results

Forty-three studies met the eligibility criteria: 31 assessed working memory, 19 episodic memory, 9 semantic memory and 2 procedural memory. See Fig. 2 for a flow diagram of the study selection process. Details of studies included are summarized in Table 3.

Nineteen studies reported memory data on ***PFT survivors treated without radiotherapy*** (pilocytic astrocytomas or low-grade tumors). Most of the studies presented a relatively preserved verbal [18,19,28,20–27] and visual [18,19,22,29,30] **working memory** load, regardless of the period between diagnosis and assessment in non-irradiated patients. Concerning updating, studies showed a non-significant difference compared to the norm [28] and/or the control group [21,28,31]. Studies reported results for preserved memory on the verbal and visual or global score for **anterograde memory** in learning, long-delay free recall and recognition [20–22,25,28,32–35]. Aarsen et al. showed that in comparison to patients with supratentorial astrocytomas, patients with infratentorial astrocytomas had lower scores for verbal memory and visuo-spatial memory. Studies that explored **semantic memory** reported scores within the normal [21,22,25] or low range [26] in non-irradiated patients. Finally, only two studies focused on **procedural memory** using a serial reaction time (SRT) task [33,36]. The authors showed preserved learning scores with results similar to the control in Berger's study. However, Quintero et al. found an alteration in motor sequence learning with only a trend for statistical significance in a small sample of eleven non-irradiated participants.

In summary, non-irradiated patients treated at least 3 years before for PFT, mainly showed results in the different memory tasks that were between −1SD and the norm, stable over time and lower than the results of the control subjects but not significantly. Although the results of the evaluation of semantic and procedural memory systems should be viewed with caution due to the small number of studies and patients per study, it would appear that the performance of non-irradiated patients is lower in cerebellum-dependent working and procedural memory and in semantic memory, than in hippocampal-dependent anterograde memory.

Thirty-three studies included ***patients treated for high-grade PFT with radiotherapy***. Radiotherapy characteristics are indicated in supplementary data 1.

Studies exploring verbal **working memory** load in patients treated for medulloblastoma with PFB and CSI (standard and reduced dose), reported scores in the normal [18,23,24,26,37–41], low [42–45] or deficit range [25,28,37,46]. Studies showing a deficit score concerned children who were younger at the time of treatment [25] or who had a higher mean time since treatment [28,46]. Differences were also linked to tests used. Impairment was more significant with the backward than the forward digit span [37,46]. The two main findings of these studies were that (1) irradiated patients performed significantly worse compared to non-irradiated patients [24,25,28] and (2) in irradiated patients, the change in the working memory index showed a decline of approximately 2 points per year [38,39,41,44]. Among patients treated for medulloblastoma with posterior fossa boost and CSI, patients treated with a reduced dose of CSI had better results

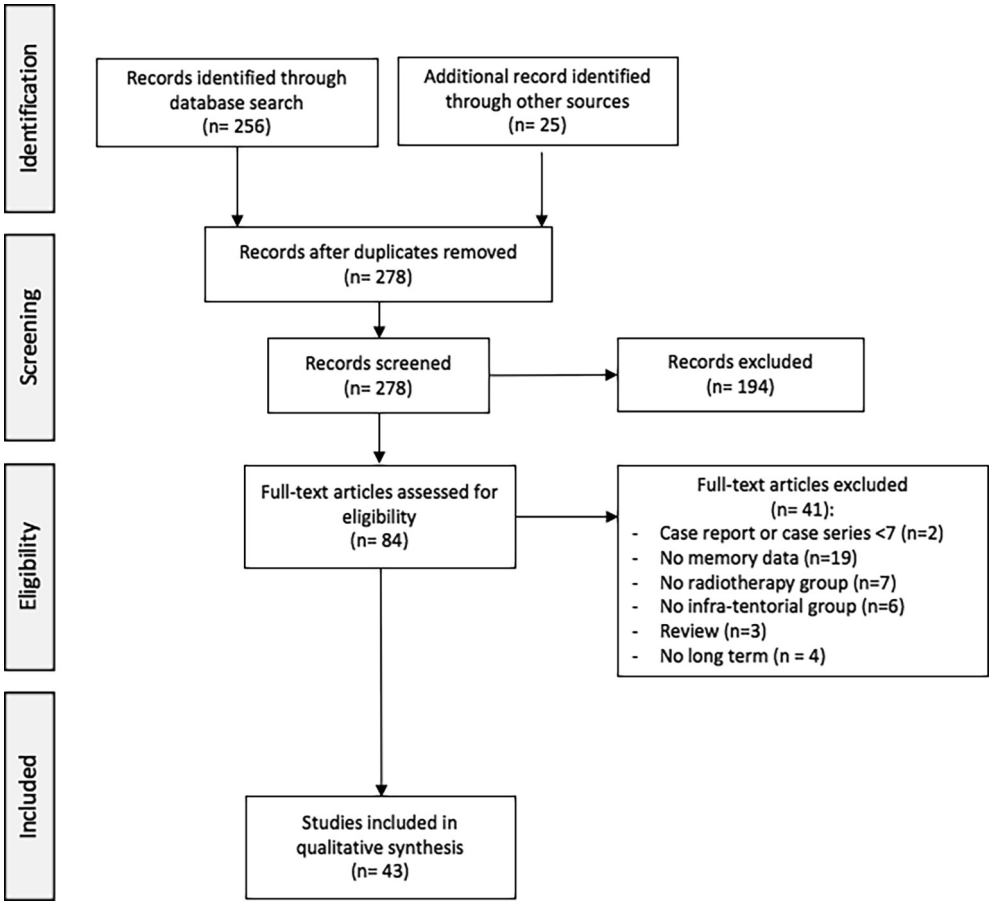

Fig. 2. PRISMA Flow diagram.

Table 3
Characteristics of the study population and the memory system assessed.

STUDIES	POPULATION									MEMORY SYSTEM EXAMINED			
	Non-irradiated Group				Irradiated Group				Control Group				
	N	Tumor type	Age at diagnosis (year)	Follow-up time (year)	N	Tumor type	Age at diagnosis (year)	Follow-up time (year)		WM	EM	SM	PM
Aarsen et al. 2004	**23**	AS	9.3 (SD = 3.7; R: 3.9–16.6)	3,4 (SD = 2.2; R: 1.0–8.1)					**No**		+		
Aarsen et al. 2009	**35**	AS	7.7 (R: 3.2–11.4)	3,5 (R: 2.0–5.0)					**No**		+		
Ait Khelifa et al. 2015	**17**	AS	5 (SD = 2.1; R: 2–10)	6 (SD = 4; R: 1–15)					**61**	+			
Benavides et al. 2019	**11**	AS	11.2 (SD = 1.8; R: 6.2–12.5)	2.45 (R: 0.6–5.5)					**11**	+			
Berger et al. 2004	**8**	AS/NMC	7.2 (R: 1–11)	5.9 (SD = 2.76)					**8**				+
Brinkman et al. 2012					**20**	MB	29 (R: 2–17)	18	**No**	+	+		
Callu et al. 2009	**19**	AS	6.1 (SD = 1.8; R: 1.8–8.5)	2.9 (SD = 2.0)	**20**	HGT	4.7 (SD = 1.9; R: 0.5–8.9)	2.9 (SD = 2.0)	**No**	+	+	+	
Camara et al. 2015					**137**	MB	7.1 (SD = 4.1)	12.9 (SD = 4.3; R: 5–22)	**No**	+			
Edelstein et al. 2011					**20**	MB	7.2 (SD = 3.8; R: 1.1–13.8)		**No**	+			
Glass et al. 2017					**92**	MB	8.7 (R: 3.2–21.6)	3	**72**	+			
Hardy et al. 2008					**25**	MB	8.2 (SD = 2.8; R: 4–14)	2.2 (SD = 1.83; R: 1–7)	**No**		+		
Hazin et al. 2011	**13**	AS	9.2 (R: 4–13)	9 <= 3 yo	**7**	MB	6,0.5 (R: 2–12)	4 <= 3 yo	**No**	+		+	
Hoang et al. 2019					**11**	MB	NA	3.6 (SD = 1.2; R: 2.25–6.1)	**23**	+			
Kahalley 2020					**79**	MB	8.9 (SD = 2.9; R: 3.5–14.4) *	4	**No**	+			
Khajura et al. 2015	**17**	AS	6.7 (R: 0.9–12.2)	6.3 (SD = 2.6)	**17**	MB	7.6 (R: 2.2–16.6)	5.6 (SD = 3.2)	**No**		+		
Khalil et al. 2019					**16**	MB	6.8 (SD = 2.3; R: 4–11)	4	**No**	+			
Kieffer-Renaux et al. 2000					**36**	MB	13.1 (SD = 4.1)	4.3 (SD = 4.7)	**No**	+	+	+	
Knight et al. 2014					**167**	MB	9.2 (SD = 3.9)	5	**No**	+			
Konczak et al. 2005	**14**	LGT	8.79 (SD = 4.69; R: 1–17)	8.36 (SD = 4.31; R: 3–17)	**6**	HGT	9.66 (SD = 2.66; R:7–13)	7.5 (SD = 3.02; R: 4–13)	**14**	+			
Koustenis et al. 2015	**17**	AS	9.21 (SD = 5.2)	2.52 (SD = 2.10)	**25**	MB/EP	9.7 (SD = 4.5)	4.3 (SD = 3.01)	**No**	+			
Law et al. 2017					**25**	MB	13.3 (SD = 3.5; R: 8.0–19.0)	6.3 (SD = 4.1; R: 1.2–13.6)	**20**	+			
Mabbott et al. 2008	**32**	LGT	5.2 (SD = 3.6)	6.3 (SD = 2.6)	**32**	HGT	6.85 (SD = 2.66)	4.6 (SD = 2.5)	**10**	+			
Maddrey et al. 2005					**16**	MB	7.3 (SD = 4.5; R: 1–15)	14.6 (SD = 3.5)	**No**		+		
Moberget et al. 2015	**20**	AS	7.1 (SD = 4.1)	12.9 (SD = 4.3; R: 5–22)					**26**	+	+		
Moxon et al. 2014					**115**	MB	7.5 (SD = 3.4, R: 1.1–15.0)	6,1 (SD = 3.4, R: 1.5–14.2)	**No**	+			
Mulhern et al. 2001					**42**	MB	8.2 (SD = 3.8)	4.9 (SD = 2.5)	**No**		+	+	
Palmer et al. 2001					**44**	MB	4.6 (SD = 3.3; R: 1,1–12,5)	5.2 (SD = 2.4; R: 1.9–12.6)	**No**			+	
Palmer et al. 2013					**126**	MB	9.8 (SD = 4.4)	5	**No**	+			
Pletschko et al. 2018	**14**	AS	13.3 (R: 3–21)	8.1 (SD = 2.8; R:3.7–13.7)					**14**	+	+	+	
Quintero-Gallego et al. 2006	**11**	AS	8.0 (SD = 3.2; R: 1.9–10.8) **	4.8 (SD = 3.6; R: 0.4–12.6) **	**7**	MB	8.0 (SD = 3.2; R: 1.9–10.8) **	4.8 (SD = 3.6; R: 0.4–12.6) **	**12**		+		+
Reitchert et al. 2017	**11**	LGT	6.6 (SD = 3.3)	16 (SD = 3.9; R:7.8–20.5)					**17**	+			
Riggs et al. 2014					**20**	HGT	12.4 (R: 7.2–17.2)	5.1 (R: 1.1–11.6)	**13**		+		
Roncadin et al. 2008	**29**	AS	6.4 (SD = 3.8; R: 1.2–15.9)	11.1 (SD = 6.1; R: 4.8–22.2)					**No**		+		
Ronning et al. 2004	**12**	AS	8.6 (SD = 3.9; R: 3–14.9)	14.9 (SD = 3.1; R: 10.0–21.1)	**11**	MB	6.1 (SD = 3.4; R: 1.8–12.1)	17.0 (SD = 4.9; R: 10.7–27.0)	**No**	+	+		
Schreiber et al. 2018					**36**	MB	8.4 (SD = 2.7)	5	**36**	+			
Sekeres et al. 2018					**13**	MB/EP	6.59 (SD = 2.7; R: 2.8–11.8)	7.42 (SD = 4.1; R: 1.6–13.8)	**28**		+		
Spiegler et al. 2004					**34**	MB/EP	6.1 (SD = 2.7)	4.7 (R: 1.3–15.3)	**No**	+	+		
Steinlin et al. 2003	**23**	LGT	8.3 (R: 3.6–15.5)	7,5 (R: 2.1–18.3)					**No**	+	+	+	
Szentes et al. 2019					**34**	MB	7.53 (SD = 3.3)	2.71 (SD = 1.8)	**46**	+			
Vaquero et al. 2008	**13**	AS	8.2 (SD = 4.0)	3.3 (SD = 2.7)	**7**	MB	7.1 (SD = 2.1)	6.5 (SD = 2.8)	**12**	+			

Table 3 (*continued*)

STUDIES	POPULATION									MEMORY SYSTEM EXAMINED		
	Non-irradiated Group				Irradiated Group				Control Group			
	N	Tumor type	Age at diagnosis (year)	Follow-up time (year)	N	Tumor type	Age at diagnosis (year)	Follow-up time (year)		WM	EM	SM	PM
von Hoff et al. 2008					**23**	EP	7.2 (R: 0.3–14.2)	4.5 (R: 1–15.5)	**No**	+		+	
Yoo et al. 2016					**58**	MB	8 (R: 1–22)	5.7	**No**	+	+	+	
Zapotocky et al. 2019					**24**	EP	4.94 (R: 0.43–17.68)	5.54	**No**	+			

AS: astrocytoma; EM: episodic memory; EP: ependymoma; HGT: high-grade tumor; LGT: low-grade tumor; MB: medulloblastoma, NMC: non-malignant cyst, PM; procedural memory; SM: semantic memory; WM: working memory.

* mean only for 37 patients treated with proton therapy. For 42 patients treated with photon therapy: mean age at diagnosis 8.4 yo (SD: 3.1; R: 3.6–15.3).

** mean for both groups AS and MB.

(lower range) compared to those treated with a standard dose [42]. Studies that explored verbal working memory load in patients treated for medulloblastoma with a tumor bed boost and adapted-risk CSI, reported scores in the normal [47–50] or low range for the posterior fossa syndrome group [49] and in the standard dose CSI group [50]. Changes in the working memory index showed a decline of approximately 2.2 points per year for standard CSI, while the reduced CSI dose improved relative stability with a decrease of −0.2 points per year [50]. Knight et al. found a decline in the working memory index of −0.93 points per year for standard and reduced dose CSI. In medulloblastoma treated with hyperfractionated radiation therapy, Camara et al. found no significant difference in the working memory index (WISC/WAIS) compared to standard radiation therapy, with results within the normal range for both groups. In medulloblastoma treated with risk-adapted CSI with photon therapy and tumor bed boost (TBB) with proton therapy, Kahalley et al. found a working memory index within the normal range with score stability over time (+0.1 point per year), while a decline of 2.2 points was reported in the photon therapy group. In ependymoma treated with TBB or posterior fossa boost (PFB), von Hoff et al. and Zapotocky et al. found a working memory index within the normal range with relative stability over time (-0.56 points per year in Zapotocky's study). Only one study on ependymoma treated with TBB reported mean scores within the normal range but the population was heterogeneous as 3 participants out of 19 had deficit scores <−2SD. Studies that explored visual working memory in irradiated patients reported scores in the low [29,30] or deficit range [18] using either forward or backward Wechsler block tasks in patients treated with risk-adapted CSI. Irradiated patients were both slower and more inaccurate than non-irradiated patients and differences between groups increased when working memory load was higher [30]. In medulloblastoma, Rønning et al. found updating scores in the deficit range using PASAT, with a significant difference in non-irradiated patients. Hoang et al. showed a greater difference between the medulloblastoma and the control group in the 2-back than the 1-back tasks, both in accuracy and speed, and found an association between left posterior cerebellar lobe lesions and working memory impairment.

Only one neuroimaging and behavioral study was published on **episodic memory** and its neural substrates in posterior fossa medulloblastomas. Sekeres et al. evaluated autobiographical memory using the Children's Autobiographical Interview and assessed episodic and non-episodic details for events that either preceded (i.e., remote) or followed (i.e., recent) treatment [51]. The authors highlighted episodic memory preservation before treatment, with equivalent episodic details in the PFT group compared to control subjects. However, they showed an alteration in episodic memory after treatment, with fewer episodic details of post-treatment events in the PFT group compared to the control subjects, which is consistent with a lower score on the Children's Memory scale (CMS). This suggests an alteration in anterograde memory and preservation of retrograde memory. Neuroimaging results are discussed in the neuroimaging section of this review.

Studies that explored verbal **anterograde memory** in patients treated for medulloblastoma with posterior fossa boost and CSI (standard and reduced dose), reported scores in the normal [35,38,52] or low range [28,37,46,53–55]. Lower scores were found in studies that included children who were younger at the time of treatment, with a higher mean time since treatment (respectively 14, 17 and 18 years old [28,46,54]) and a lower proportion of reduced CSI doses or boosts limited to the tumor bed. Two findings were of interest in these studies: (1) irradiated patients performed significantly worse than non-irradiated patients [28,35] and (2) in the irradiated patients, changes in the scaled score showed relative stability in learning, long-delay free recall and the global verbal score [38]. Among patients treated for medulloblastoma with a

posterior fossa boost and CSI, those treated with a reduced dose of CSI had lower learning scores and deficit scores in long-delay free recall, while patients treated with a standard dose had scores in the deficit range [42]. Only one study was conducted on ependymoma treated with a TBB and reported mean scores within the normal range but the population was heterogeneous as 3 participants out of 19 had deficit scores <−2SD.

Few studies explored visual anterograde memory in patients treated for medulloblastoma with PFB and CSI (standard and reduced dose), and they reported scores within the normal [38], low [25,28,37,52,55] or deficit range [54]. Two findings were of interest in these studies: (1) irradiated patients performed significantly worse than non-irradiated patients [25,28] and (2) in irradiated patients, changes in the visual composite score on the Children's Auditory Verbal Learning Test showed a progressive decline in visual scores of −1.54 points per year [38]. This is consistent with the fact that studies that assessed memory at a longer time after radiotherapy found more impaired scores [11,35]. In several visual memory assessment tests, Rønning et al. found lower results in the delayed copy of the Rey figure than in the total recognition and learning of the Continuous Visual Memory Test. Among patients treated for medulloblastoma with PFB and CSI, those treated with a reduced dose of CSI had non-significantly higher scores than patients treated with a standard dose [42]. Global anterograde memory (including both verbal and visual subtests) was in the lower range for patients irradiated by CSI with PFB or TBB [46,52,55,56].

Results of studies were contradictory concerning memory process impairment in PFT survivors. Maddrey et al. (2005) showed better performance in short and long delay recall, compared to immediate recall, suggesting an encoding defect. Therefore, memory problems may be the result of information learning or encoding difficulties, rather than information storage or retrieval difficulties. Quintero-Gallego et al. (2006) qualitatively highlighted that in a medulloblastoma group, learning remained within the limits for a normal population. Khajuria et al. (2015) found a tendency for medulloblastoma patients to learn less in the same period than astrocytoma patients. However, Kieffer-Renaux et al. (2000) found that delayed recall was slightly more deficient than immediate recall in medulloblastomas suggesting a storage or retrieval deficit.

Studies that explored **semantic memory** in patients treated for medulloblastoma with PFB and CSI (standard and reduced dose), reported scores in the normal [37,53] or low range [3,25]. Differences in scores between these studies may be explained by an older mean age at the time of treatment (8 and 8.5 yo *vs.* 4.6 and 4 yo) in both studies with scores in the normal range. Two findings were of interest in these studies: (1) irradiated patients performed significantly worse than non-irradiated patients [25] and (2) in irradiated patients, the change in information scaled score significantly declined by 0.41 points per year, and was more pronounced in patient who were younger at the time of treatment (<8.02 yo) than in those who were older (−0.53 *vs.* −0.17, respectively) [3]. Among patients treated for medulloblastoma with PFB and CSI, patients treated with a reduced dose of CSI showed better results (normal or lower range scores depending on the tests used) vs. the standard dose group (lower or deficit range) [42]. Moreover, in a study of only patients who received a standard CSI dose, Hazin et al. found that results were more altered than in other studies with scores in the deficit range. Only one study focused on ependymoma treated with a TBB and reported mean scores in the normal range but the population was heterogeneous as 2 participants out of 23 had deficit scores <−2SD.

Only one study explored **procedural memory** using SRT Task in a medulloblastoma group of 7 patients treated with radiotherapy for which we do not have details of the type and doses of radiotherapy. They had a significantly lower number of correct responses than the control group and motor sequence learning was absent.

In summary, irradiated patients showed worse results, with an impact on all the memory systems. However, these results differ according to the type of irradiation received. Patients treated with standard-risk CSI and PFB had scores in the lower range in the different memory systems, and a decline over time especially in working memory and in visual anterograde memory. Reducing CSI dose, limiting TBB, and using proton therapy seem to have had a beneficial effect with better preservation of the memory score and a reduction in decline over time. Neuropsychological scores in different memory systems are summarized in Fig. 3 and are detailed in Supplementary data 2.

Studies reported few prognostic factors of memory impairment. Radiotherapy is undoubtedly the main prognostic factor for secondary memory impairment as shown in the previous section [18,23–26,28,30,33,35].

A younger age at the time of treatment was linked with a poor memory prognosis in the medulloblastoma group, as shown by a comparison between children treated before 8 years old and those treated after in most of the studies [37,53]. However, in non-irradiated patients, the impact of age at the time of treatment is controversial. Roncadin et al. found poorer memory in younger patients [56] while Rønning et al. showed better results, which they linked to more plasticity in the early stage of development [28]. In an astrocytoma population, Steilin et al. compared preschool children (3.5–6.5 yo), elementary school children (7–9.5 yo) and middle school children (10–15.5 yo) and found that elementary school children were most affected in terms of verbal anterograde memory and semantic memory [22] than the other categories.

Concerning hydrocephalus, Rønning et al. negatively correlated neuropsychological effects with shunts in an astrocytoma group but not in a medulloblastoma group [28]. In a medulloblastoma population, Hardy et al. also found that the presence of hydrocephalus requiring the placement of a ventriculoperitoneal shunt was associated with more severe intellectual and academic deficits but not with lower scores in working or anterograde memory [55].

Whether tumor size is a risk factor is controversial. Khajuria et al. found that astrocytoma patients with a larger cerebellar lesion had significantly decreased verbal memory performances in learning but not medulloblastoma patients [35]. However, Steinlin et al. showed that tumor size had no influence on outcome in astrocytoma [22]. In an astrocytoma population, Aarsen et al. found a correlation between maximum tumor diameter and long-term verbal memory, but this is probably related to hydrocephalus since a correlation was also found between maximum tumor diameter and ventricular dilatation [32].

Undoubtedly, surgical complications impact memory outcomes. In an astrocytoma population, Roncadin et al. found that poorer memory was predicted by a higher number of medical events in the first 5 years after surgery [56]. Posterior fossa syndrome (PFS) was a factor in poorer neuropsychological outcomes with working memory performances approximately 1SD below the performances of children without PFS [47,49]. Studies differed in terms of the long-term changes, with some showing an increase in the decline in working memory compared to non PFS medulloblastomas [49], or parallel changes [47].

Lastly, Khalil et al. linked socioeconomic status in a low-income Moroccan medulloblastoma population, with global neurocognitive performance below −2SD and a low range for working memory [45].

In summary, radiotherapy is the most important prognostic factor for memory. In non-irradiated patients, more refined

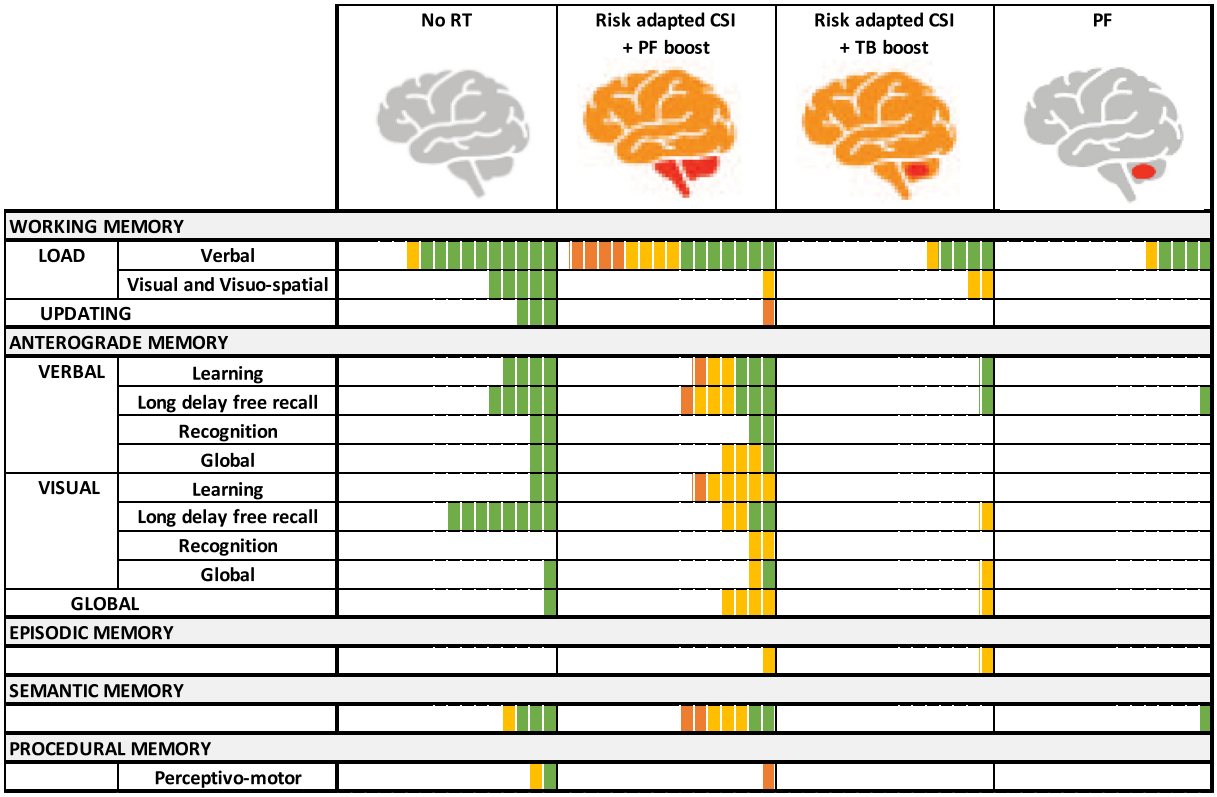

Fig. 3. Summary of the neuropsychological scores in different memory systems according to the memory process assessed and the radiotherapy treatment. Each colored squared corresponds to the results of one article. The color green represents scores within the normal range (−1SD to 0SD), orange the low range (−2SD to −1SD) and red the deficit range (<−2SD). In this table, standard and reduced CSI doses were not differentiated. CSI: craniospinal irradiation; PF: posterior fossa; RT: radiotherapy; TB: tumor bed.

prognostic factors could modulate the results, but reproducibility between studies is not always achieved.

Finally, concerning memory neuroimaging in PFT survivors, only six of the studies included used MRI to explore the neural substrates of memory after radiotherapy, but none included an analysis of the radiotherapy doses delivered to brain structures.

Sekeres et al. explored hippocampal volumes, white matter tracts involved in episodic memory (fornix) and five cortical regions of recollection networks [51]. A significant difference was found, with smaller hippocampal, fornix, precuneus and lateral temporal cortex volumes in the radiotherapy group compared to the control group. Probably because of the small sample, no correlation was found between hippocampal volume and episodic memory scores. Based on rodent models, the authors hypothesized that radiotherapy acted by suppressing hippocampal neurogenesis and thereby produced dissociable anterograde versus retrograde effects on memory. No studies were found on cerebellar macrostructural correlates of memory.

Diffusion Tensor Imaging (DTI) is a magnetic resonance neuroimaging technique based on the detection of the diffusion of water molecules along the main direction of axons and myelin sheaths. This enables the estimation of microstructural connectivity based on location, orientation, and anisotropy of the white matter tracts of the brain. Two parameters are commonly used: mean diffusivity (MD) which reflects microstructural integrity and fractional anisotropy (FA) which reflects microstructural orientation. Using DTI in adult survivors of pediatric medulloblastoma, Brinkman et al. showed that FA in the parietal lobe was positively correlated with working memory scores and in the right hemisphere and bilateral temporal lobes with visual memory scores [46]. In a medulloblastoma group, Law et al. showed higher indices of diffusivity (FA, MD, and axial and radial diffusivity), especially in the left cerebello-thalamo-cortical pathway related to variances in working memory outcome [29]. Riggs et al. explored the uncinate fasciculus using DTI and the size of the hippocampus in medulloblastomas [52]. They showed that the PFT group had a significantly lower FA on the bilateral uncinate fasciculus and significantly smaller right hippocampal volumes compared to healthy controls. Medulloblastoma survivors had significantly lower performances on the general Children's Memory Scale index that are correlated with the FA of the left uncinate fasciculus and the right hippocampal volume.

fMRI is a magnetic resonance neuroimaging technique based on the detection of fluctuations in blood oxygenation level-dependent (BOLD) signals during a task that indirectly reflects neuronal activation. Using a N-back task in eleven surgically treated low-grade PFTs compared to control, Reitchert et al. (2017) found that most group differences in functional connectivity were observed in the least cognitively demanding tasks. Hoang et al. (2019) used an experimental fMRI N-back task in children treated for PFT medulloblastoma and failed to find any cerebellar activation in this group. The explanatory hypothesis put forward by the authors for the difficulties in demonstrating cerebellar activation in PFT survivors, was a small sample size (low statistical power), fMRI limitations to investigating the postoperative brain harboring magnetic susceptibility artifacts, anatomical deformities of the posterior fossa uncompensated by the anatomical normalization and inter-individual spatially significant activation variability.

Discussion

The majority of studies show an alteration of all the memory systems in children who have received CSI, whereas non-irradiated children have a lesser impairment, placing them below the performance of typically developing children, but remaining

mostly within the norm, except for working and procedural memory, whose neural substrates depend in part on the cerebellum.

In non-irradiated children, despite a relative preservation of memory systems at the group level, individual impairment could be seen especially when risk factors were present. This impairment could be underestimated for procedural memory due to the fact that a repeated sequence learning task, which mainly involves the cortico-striatal circuit, was used in the studies examined. We hypothesize that tests to explore motor adaptation such as mirror writing would indicate more impaired results since they explore cerebello-cortical circuits. Interestingly, scores for semantic and episodic memory were also lower, although treatment did not include chemotherapy or radiotherapy which affect infratentorial areas. Few hypotheses could be formulated to explain these results. Firstly, PFT and PFT surgery could alter cerebello-cortical networks involving brain areas concerned with episodic memory. Secondly, preoperative hydrocephalus or postoperative complications such as meningitis could have an impact on infratentorial area white matter microstructure [20]. Lastly, the different memory systems are interconnected (MNESIS model), which could explain why some memory systems that do not directly depend on cerebellar areas could be impaired by a PFT tumor. Neuroimaging studies suggest that the tumor has an impact on left posterior localization and damages dentate nuclei in visual working memory [57]. But most studies failed to highlight the relationship between specific memory impairment and tumor localization.

Radiotherapy has a major impact on all memory system outcomes in PFT survivors. In the past two decades, progress in the global management of FPT tumor and especially the improvement in radiotherapy techniques has allowed partial preservation of the memory process, limiting posterior fossa irradiation to the tumor bed and using intensity-modulated radiation therapy or proton therapy. The addition of chemotherapy for chemosensitive tumors (medulloblastoma) enabled the reduction of the CSI dose in patients with an average risk (non-metastatic disease and no histological high-risk factors) at diagnosis with a clear beneficial impact on all neuropsychological outcomes. At present, treatment protocols for children with medulloblastoma tend to become more and more complex according to age, risk and the molecular biology of the tumor, and the dual aim is to improve survival and limit the long-term sequelae of these treatments. Another way to limit these effects is to set dose constraints for the specific brain areas involved in memory, such as the medial temporal lobe for episodic memory, and to adapt conformational radiotherapy to avoid these areas as is already done for the pituitary to avoid endocrinal sequelae or the optic chiasma to limit visual function impairment. Less is known about the impact of concomitant treatment for medulloblastoma on the entire brain, with a potentially negative effect of chemotherapy, or a synergic neurotoxic effect of concomitant administration of radiotherapy and chemotherapy [58,59], and medications such as steroids [60].

In contrast to non-irradiated patients, longitudinal studies of patients treated with CSI show a progressive decline in intellectual and memory functions over time [38,39,41,44] with a rapid decline in performance in the first 5 years and slower decline thereafter [38]. Depending on the patient's initial level of performance, this may place them in a deficit or low performance zone and have an impact on their general life and school functioning.

In terms of neuroimaging, MRI helps to investigate the damage caused by radiotherapy on normal-appearing brain *in vivo*, especially in infratentorial structures. CSI patients have both lower cerebral volumes and an alteration in the microstructure of the brain area involved in memory.

It is actually well-established that a young age at the time of radiotherapy is a poor prognosis for IQ scores and memory, with evolutive damage to brain structures causing progressive neuropsychological decline. Impairments in memory acquired after radiotherapy treatment but not in memories acquired before [51] confirm that PFT survivors have difficulties learning new skills, but no alteration in abilities acquired before tumor treatment [3].

Concerning non-irradiated patients, brain lesions caused by a tumor and tumor surgery can be considered as fixed, with the possibility to improve over time thanks to neuroplasticity stimulated by rehabilitation. The impact of age at the time of treatment and surgery is not so clear, with studies showing a worse prognosis for a young age at the time of treatment [56] and other studies highlighting a worse prognosis when tumor surgery occurred at school age (probably because it is a critical time to acquire general knowledge). This suggests that there should be specific care for younger and school-age patients.

Results concerning the long term-memory process that is impacted in the pediatric population varies, and includes deficits in learning [33,35,54] or storage and retrieval [42]. In adult patients, retrieval is the process that is most affected [58]. Indeed, Durand et al. (2018) showed predominant impairment in retrieval (92%) compared to storage (41%) or encoding (23%). These studies indicate the need to use tests to assess the different forms of antegrade memory in order to gain a broader perspective of the processes that are affected.

Because of the high frequency of memory impairment, particular attention and systematic assessment of children with risk factors are needed during long-term follow-up of PFT survivors. The main risks factors are radiation therapy, neurologic complications, hydrocephalus, PFS and an age below 8 years at the time of treatment.

However, disease and treatment are not the only neurocognitive risk factors and patient characteristics and the environmental context are also important to consider [61]. Assessment of prior neurocognitive and academic skills and of the socio-familial context is important for neurocognitive management of these patients [62]. In fact, cognitive decline in a child with good initial skills, good school integration and a supportive environment will have less impact than in a child who was previously limited, poorly integrated or poorly supported [63]. The results of neuropsychological tests carried out early during the first months of medical care are often difficult to interpret because of the child's fatigue and the psychological context of a serious illness that may be life-threatening. An alternative could be to identify elements of psychomotor, school and socio-familial development when interviewing the child and their family and to systematically include a psychologist and a social worker in the care in order to detect children at risk and to support their families.

Lastly, various tests have been used in the literature which may partially explain variations in memory results. Moreover, in some memory systems such as procedural memory, few tests are available. An effort should be made to establish a panel of tests that are not too time-consuming, in several languages, and that can be easily carried out in current practice and in world-wide research protocols to make results comparable.

This review has some limits. Firstly, memory is a broad and complex field and, to our knowledge, no study has reported on assessments of all memory systems in the same population and which provides an overview of memory deficit. Moreover, the multiplicity of tests used sometimes makes the interpretation and comparison of studies difficult. As raw data, normalized data or z-scores used to present the results in articles are not directly comparable, we transformed data into z-scores. However, this transformation does not make the data totally equivalent. In fact, the normalized data include age correction which is not present in the raw data, and the z-transformation of raw-data could have changed the magnitude of impairment. In addition to this heterogeneity, there is also the

multiplicity of protocols used over the past two decades, with different surgical and radiotherapy techniques and various chemotherapies, as well as the heterogeneity of the population (i.e. Including PFS who have a more impaired neuropsychological profile. Finally, to date most studies have a small sample size due to the low number of cases and difficulties in the long-term follow-up of patients, or do not include a control group.

Conclusion

All the studies are consistently show that PFT survivors have lower performances in all memory systems. Although these scores are slightly lower than in the control and stay within the normal or low ranges in non-irradiated patients, they are often in the low or deficit range for irradiated patients. Irradiation techniques that reduce doses and avoid normal brain show better preservation of memory performances. There is a need to set dose constraints on the specific brain areas involved in memory to further reduce the impact of radiotherapy on learning and memory. We are currently conducting a prospective study to develop methods to define theses dose constraints [64]. However, radiotherapy is not the only prognostic factor. Age at the time of treatment, hydrocephalus, surgical complications, posterior fossa syndrome or socio-economic status can also affect the cognitive prognosis. During the long-term follow-up of children treated for a PFT, specific attention is essential to identify learning and memory deficits, and to address them at an early stage and adapt schooling in order to assist children individually to achieve autonomy in their future adult life.

Declarations

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Competing interests

No competing interests.

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Authors' contributions

EB conceived the methodology, selected articles, wrote the first draft of this manuscript and prepared the figures and tables. LP selected and classified neuropsychological tests. LP, SI, AIB and YC reviewed the draft with specific attention to the neuropsychological part. LP and SI are neuropsychologists and EB and YC are pediatric neurologists who specialize in learning disorders in children. FT reviewed the draft with specific attention to the neuroimagery part. AL reviewed the draft with specific attention to the radiotherapy part. All the authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.05.022.

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