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TOPIC REVIEW

A systematic review of cognitive performance in patients with childhood craniopharyngioma

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Abstract Craniopharyngiomas are rare brain tumors of the sellar/suprasellar region, often adversely affecting patients' physical and psychosocial functioning. Until a few years ago, knowledge on cognitive deficits in craniopharyngioma patients was based on little valid evidence, with considerable inconsistencies across studies. Findings from recent research, with partly larger sample sizes, add to existing evidence to provide a more clear and reliable picture. The current review aims to summarize and systemize current findings on cognitive deficits in childhood craniopharyngioma, taking account of patient- and treatment-related variables where possible. Those studies were included that reported results of childhood craniopharyngioma patients tested with formalized neuropsychological tests (irrespective of their age at study, group size ≥10). A systematic assignment of test results to subcomponents of broader cognitive domains (e.g. to specific memory systems and processes) allows for a first comprehensive overview of patterns of spared and impaired cognitive functions. We show that episodic memory recall in particular is impaired, largely sparing other memory components. In accordance with recent knowledge on mammillary function, patients with hypothalamic involvement appear to be at particular risk. Deficits in higher cognitive processes, relying on the integrity of the prefrontal cortex and its subcortical pathways, may also occur, but results are still inconsistent. To gain deeper insight into the pattern of deficits and their association with patient- and treatment-related variables, further multi-site research with larger cohorts is needed.

Keywords Brain tumors · Cognitive · Hypothalamus · Craniopharyngioma · Dysexecutive · Memory

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Introduction

Craniopharyngiomas are rare primary brain tumors of low-grade malignancy (WHO, grade I), most commonly found within the sellar/and or parasellar region. The tumor may occur at any age, but approximately 30–50 % of all cases are diagnosed during childhood and adolescence [1]. Due to their close anatomical proximity to the hypothalamus, the pituitary, and the optic nerves, craniopharyngiomas are frequently associated with visual, endocrine and neurobehavioral deficits which may seriously limit functional capacity and quality of life. Within the past three decades, advances in treatment strategies and techniques have led to decreasing mortality and less severe morbidity. Improved outcomes have encouraged researchers to increasingly focus attention on issues related to neurobehavioral, social, and emotional dysfunctions [2, 3], and quality of life, including cognitive functions [4–8].

Up until a few years ago, the great majority of studies which claimed to account for cognitive performance either used (i) standardized intelligence testing to assess global cognitive functioning [7, 9–13], or (ii) educational achievement, subsequent employment or IQ scores, as well as a combination of these to indicate outcome [14–20]. Characterization of deficits in different cognitive domains had received little attention and the few studies, which used formal neuropsychological testing, yielded heterogeneous results. Some studies found deficits in memory [21, 22], executive functions [22], attention [23] or processing speed [24, 25], while others did not (see for memory [25, 26], executive functions [26], attention [24, 26]). Interestingly, IQ was shown to be within normal limits in the great majority of studies, e.g. [21, 24, 25].

Research conducted in the last few years [27–29], with partly larger sample sizes and higher methodological quality, add to existing evidence and may provide a clearer and more unified picture regarding patterns of spared and impaired functions. Patient and treatment related variables that may additionally affect physical status and cognitive outcomes, like lesion site, radiation therapy, and age at treatment are now being increasingly taken into account and are especially promising in studies with larger sample sizes [23, 28, 29].

With respect to lesion site, it has been known for a long time that hypothalamic damage, caused by the tumor and/or its treatment, is associated with particular adverse endocrine and autonomic outcomes [30]. More recent evidence revealed that hypothalamic involvement may also adversely affect quality of life and cognitive status [3, 6, 8, 27, 28, 31]. Moreover, as the mammillary bodies at the posterior margin of the hypothalamus are known to be crucial for learning and memory, it is likely that the site of the lesion within the hypothalamus is of additional relevance [27].

To our knowledge, this is the first systematic analysis of cognitive outcome in craniopharyngioma patients. The objective of the review was to systemize the findings of studies that used formalized neuropsychological testing to investigate subcomponents of cognition. Analyzing subcomponents of cognition rather than overall cognitive outcome may help to understand the specific difficulties of the patients and to provide appropriate support measures. Due to the paucity of studies available, we included both, comparisons based on control groups and those based on age appropriate norms.

Methods

Note that a systematic review generally provides information on a higher number of patients than available for the current review. However, to ensure a high quality in reporting, the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [32].

Search strategy

We systematically searched the whole databases of Medline (via the PubMed interface), Web of Science, and PsycINFO (psychology and psychiatry literature) up to April 2014. A final additional search was performed in January 2015, shortly before submission. The full electronic search strategy was conducted in all fields as follows:

> craniopharyngioma AND (child* OR pediatric OR adolescen*) AND (cognit* OR neuropsycholog* OR psycholog* OR memory OR attention OR executive OR neurobehavioral OR intelligence OR IQ OR processing speed).

In addition, reference lists of all included articles and of reviews were hand-searched to identify additional studies relevant to the topic of the current article.

Study selection

Study inclusion and exclusion criteria were developed prior to the study selection process. The following inclusion criteria were used: (a) peer reviewed articles published in English or German, (b) childhood-onset craniopharyngioma patients, irrespective of their age at testing (c) studies with both, adulthood and childhood onset craniopharyngioma patients only, if results of the latter were reported separately, (d) group size for cognitive assessments of at least 10 patients, (e) use of formalized neuropsychological testing to assess cognitive functioning beyond mere overall cognitive assessment (IQ testing), (f) proper characterization/referencing of the tests used, (g) results of each distinct neuropsychological test specified separately, (h) outcome measures that allowed for an assessment of statistical significance. For study selection, full-text articles of all studies were obtained, except for those in which lack of eligibility was obvious from the title or abstract. In a first step, each article was assessed for the first four inclusion criteria by one reviewer (J.Ö). As a second step, all articles reporting cognitive outcomes for childhood craniopharyngioma groups of eligible study size were assessed for the last four eligibility criteria by two reviewers independently (J.Ö. and C.M.T; N = 40). Disagreements between the reviewers were discussed to reach consensus. Where uncertainties remained, a further reviewer (H.L.M.) was asked for clarification.

Data extraction

For the articles included in the review, data were extracted independently by two investigators (J.Ö and C.M.T), using a specifically designed form that included author and year of publication, study location, time of first treatment, primary objective, study design, eligibility criteria, study and comparison groups, treatment/interventions, hypothalamic involvement (pre-operative tumor involvement and/or post-operative hypothalamic lesion), complications, neuropsychological tests used, and cognitive outcome. Where relevant information was found to be missing in the studies or inconsistencies were detected, the study authors were contacted by email and asked for clarification. In some studies that used age appropriate norms, only the number of patients with performance in the clinical range was reported [24, 25]. In these cases, we performed binominal distribution analyses to assess (for a given clinical cut-off value) whether the proportion of individuals exhibiting impaired performance significantly exceeded a specific proportion that would be expected for the general population. Formal meta-analyses could not be performed due to a paucity of studies that investigated distinct cognitive domains with commonly-employed outcome measures.

Results

Included studies

The flow of papers for review and the study selection process are depicted in Fig. 1. The database searches identified 229 non-duplicate and potentially relevant references. 21 additional articles were identified by hand searching. Thus, a total of 250 articles were screened and in a first step, 83 were excluded based on title and abstract. In a second step, full-texts of the remaining 167 articles were retrieved and reviewed. The review process resulted in the exclusion of 158 articles not meeting eligibility criteria and the inclusion of nine articles eligible for further qualitative synthesis.

Description of included studies

Details of the nine studies are depicted in Table 1. All of these studies were published within the last 17 years, five of them even within the past 6 years [26–29, 33]. Most of them aimed at assessing the cognitive status after surgical treatment for childhood craniopharyngioma, providing results based on data from one assessment, with a median period from diagnosis/first treatment to assessment ranging from <3 month to 20 years. [21, 24–28, 33]. Two studies reported results from one and the same prospective longitudinal intervention trial, explicitly focusing on the effects of radiotherapy on memory [29] and attentional performance [23]. These studies had a partly overlapping sample and provided results which were obtained prior to conformal radiation therapy (CRT) (baseline), at different times after initial therapy, up to 5 years after radiation therapy. Sample sizes of participants attending the neuropsychological tests ranged from n = 10 [24] to n = 44 [29], with a median cohort size of n = 16 and were higher in two of the most recent studies [28, 29], compared to older studies. Overall, studies covered results on patients who were first diagnosed and treated between 1958 and 2010. One of the most recent studies covered patients where the operation took place up to 40 years ago [28]. Within studies that provided data from one assessment, the use of a control group, besides merely reporting norm-based outcomes, is common to the more recent ones [26–28]. Unfortunately, detailed neuroradiological assessment of tumor or lesion site with respect to the hypothalamus was only performed in few of the studies that aimed to test cognitive functioning [21, 27, 28]. The two most recent studies, however, explicitly investigated the effect of hypothalamic involvement on cognitive performance [27, 28]. In addition to whole group comparisons (all patients vs. controls), Fjalldal et al. [28] conducted analyses where patients with and without hypothalamic involvement were separated to compare each of the groups to their matched controls.

Information relevant for the interpretation of the results was found to be missing in some studies [24–26, 33]. In these cases, the corresponding author or senior author was contacted with a request for clarification and as far as additional information was provided, this was included in Table 1 and Supplement 1 (Table S1) and identified as such.

Neuropsychological tests

All tests, which were used to examine individual cognitive domains, are shortly outlined in Table S1 (Supplement 1). In addition, the table provides information regarding the key measures of the tests that were used in each individual study. For further information on neuropsychological tests see Strauss et al. [34].

General cognitive functioning

With the exception of one study [26], which observed significantly lower scores for patients' performance IQ compared to a healthy control group, IQ was reported to be in the normal range or not different from healthy controls [21, 24, 25, 27, 33]

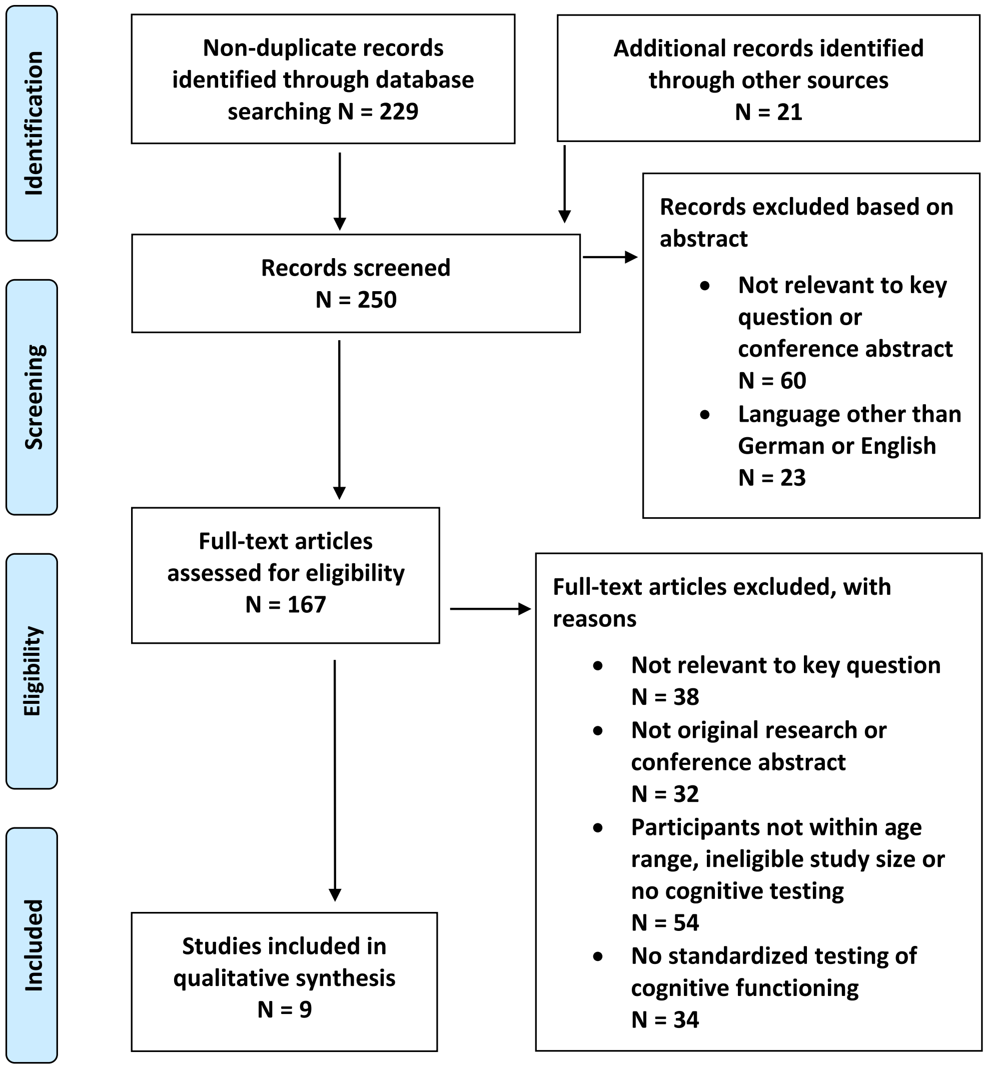

Fig. 1 Flow diagram according to PRISMA standards

Memory performance

Results for different memory domains are depicted in Table 2. Five of the seven studies which tested episodic memory reported deficits in immediate and/or delayed memory retrieval [21, 24, 27, 28, 33]. Interestingly, in studies which tested both, impairments in delayed recall were found together with preserved delayed recognition capabilities [21, 27]. Short-term and working memory [21, 24, 25, 27 and semantic memory [28] were intact in all patient samples tested as a whole. However, in the study by Fjalldal et al. [28], subgroup analyses revealed the particular significance of hypothalamic involvement: Compared to their matched controls, patients with hypothalamic involvement were significantly impaired in episodic recall and semantic memory, whereas patients without hypothalamic involvement were not impaired.

Language and visual abilities

Word retrieval was found to be impaired in one study [21] whereas both, word retrieval and passage comprehension, were preserved in another study [24] (Table 2). With the exception of one study [29], all studies that tested visuo-spatial long-term memory also assessed performance in visuo-spatial or visuo-perceptual abilities and none of them could find impairments in the patient group (see Table 2).

Processing speed, attention, and executive functioning

All three studies that tested processing speed found significantly impaired performance in patients compared either to healthy controls [28] or to age appropriate norms

Table 1 Details of included studies

Study Location Treatment time	Aim Study design	(a) Eligibility criteria (b) Groups[a]/N[b]	(a) Treatment (b) Hypothalamic involvement	Age (years) at (a) Diagnosis (b) Study follow-up time	(a) Analyses (b) Confounds (significant results are in bold)	Neuropsychological tests/outcomes (test/domains with significant results in bold)
Riva et al. [25] Milan, Italy 1986-n.a. All treated at the author's institution	To evaluate neurological, behavioral and neurocognitive outcome of children and adolescents surgically treated for CP Cross-sectional study	(a) Regular neurological examination MRI and CT scans every 6–12 months (b) CP N = 12	(a) Radiotherapy N = 0 Multiple surgeries N = 4 (b) Hypothalamic involvement N = n.a	(a) Mean 7.5 Range 2.7–14.9 (b) Mean 10.5 Range: 6.0–15.5 Follow-up: mean 2.9 Range 0.3–9.3	Age appropriate norms *Confounds* accounted for in analyses: multiple surgeries, surgical approach, visual deficits, frontal signs, fits of anger, academic performance	*Intelligence*: WISC-R, Raven Test *Learning and Memory*: Digit Span (WISC-R) and Benton visual retention test *Attention and psychomotor speed*: cancellation test; **Trail making test (form A)** *Executive*: wisconsin card sorting test
Carpentieri et al. [21] Boston, USA 1992–1999 All treated at the author's institution	To assess cognitive functioning after surgical treatment of CPs Cross-sectional study evaluation was part of a protocol	(a) Age: 6–16 years. Complete resection or postoperative mass of ≤5 cm diameter (b) CP N = 16	(a) Radiotherapy N = 0 Multiple surgeries N = 5 (b) Hypothalamic involvement N = 13	(a) and (b) Median: 9 Range: 6–15 Follow up: max 3 month	Age appropriate norms Binomial distribution analyses *Confounds* accounted for in analyses: age at diagnoses, multiple surgeries	*Intelligence*: WISC-III (subtests) **Learning and memory: WRAML** (**story memory**; Sentence memory) **Rey Osterrieth complex figure test** *Visuospatial abilities*: developmental test of visual motor integration, Rey Osterrieth complex figure test (copy) **Language: Boston naming test**
Waber et al. [24] Boston, USA 1990–2002 All treated at the author's institution	Assess the relationship between everyday cognitive complaints and formal neuropsychological test performance in children with pediatric CP Cross-sectional study	(a) Age 12–24 years. No medical condition that precluded participation (b) CP N = 10	(a) Radiotherapy N = 7 Multiple surgeries N = n.a. (b) Hypothalamic involvement N = n.a.	(a) Median : 8.5 Range : 3–15 (b) Median : 17 Range : 13–24 Follow-up: n.a.	Age appropriate norms *Confounds* accounted for in analyses: None for the neuropsychological tests used	*Intelligence*: WASI **Learning and memory**: **RBMT-II**; CVLT-2/CVLT-C; Rey Osterrieth complex figure, spatial working memory (CANTAB) *Tests of Academic Achievement*: WJ-III (passage comprehension, calculation) **Processing speed**: **coding/digit symbol** (WISC-III/WAIS-III) *Attention* connors continuous performance test *Visuospatial abilities*: Rey Osterrieth complex figure test (Copy) *Language:* Boston naming test

Table 1 continued

Study Location Treatment time	Aim Study design	(a) Eligibility criteria (b) Groups[a]/N[b]	(a) Treatment (b) Hypothalamic involvement	Age (years) at (a) Diagnosis (b) Study follow-up time	(a) Analyses (b) Confounds (significant results are in bold)	Neuropsychological tests/outcomes (test/domains with significant results in bold)
Kiehna et al. [23][d] Memphis/TN, USA 1997–2003 All treated at the author's institution	To prospectively assess the impact of conformal radiation therapy (CRT) and demographic and clinical variables on attentional functioning in pediatric and young adult patients with localized primary brain tumors Prospective longitudinal testing	(a) Localized primary brain tumors with no history of previous RT No significant visual or motor deficits For neuropsychological testing: age >= 6 years (b) All brain tumors N = 120 CP N = 20	(a) Radiotherapy: all treated with CRT Surgical interventions incl. biopsy: 95 % of all brain tumor patients (b) Hypothalamic involvement N = n.a.	(b) Median age at the start of CRT: 9.2 Range 2.0–24.4 Testing before the start of CRT, weekly during CRT, and 6, 12, 24, 36, 48, up to 60 months after CRT was completed	Linear mixed effects model Age appropriate norms *Confounds* accounted for in analyses (for the who brain tumor group): sex, tumor type and site, multiple surgeries, hydrocephalus, age at CRT, shunt, type of surgery, ommaya reservoir, seizure history, pre-CRT tumor progression, steroids during CRT	**Attention**: **Connors continuous performance test** Significant worsening over the first five yrs. after conformal radiation therapy
Bawden et al. [26] Nova Scotia, Canada n.a.	Neuropsychological functioning of CP patients after surgical removal was compared to that of an endocrine control group, an obese control group and a normal control group Cross-sectional study	(a) n.a. (b) CP: N = 12 Endocrine group: N = 14 Obese control: N = 10 Normal control: N = 13	(a)Radiotherapy: none of the CP Multiple surgeries:None of the CP (b) Hypothalamic involvement N = n.a.	(a) n.a. (children and adolescents)[c](b) mean 20.8; SD 115.2 month Follow up: n.a.	Between-Group Analyses: ANOVA Corrections for multiple comparisons *Confounds* accounted for in analyses: none	**Intelligence**: WISC-III/WAIS-R: Full scale IQ, Verbal IQ, **Performance IQ** *Learning* and *memory*: CVLT / CVLT-C Rey Osterrieth complex figure test *Attention* and *impulsivity*: Connors continuous performance test *Executive:* Wisconsin Card sorting test, category test, trail making test (part B), ruff figural fluency test, word fluency test *Visuospatial abilities*: Rey Osterrieth complex figure test (copy)
Ondruch et al. 33] Poland, Warsaw 2001–2006 All treated at the author's institution	To assess cognitive, emotional and social functioning in children and adolescents after CP removal Cross-sectional study	(a) Age at study < 19 (b) CP N = 18[3]	(a) Radiotherapy N = 4 Multiple surgeries N = n.a. (b) Hypothalamic involvement N = n.a.	(a) Median 7.5[c] Range 2.8–15.1 (b) Median 13.7[c] Range 8.6–16.9 Follow up: Median 4.5[c] Range 1.8–14.0	Significance test for comparing two proportions[c] Age appropriate norms *Confounds* accounted for in analyses: none	*Intelligence*: WISC-R/WAIS-R (subtests) **Learning** and **memory: Rey Osterrieth complex figure test** *Visuospatial abilities*: Rey Osterrieth complex figure test (copy)

Table 1 continued

Study Location Treatment time	Aim Study design	(a) Eligibility criteria (b) Groups[a]/N[b]	(a) Treatment (b) Hypothalamic involvement	Age (years) at (a) Diagnosis (b) Study follow-up time	(a) Analyses (b) Confounds (significant results are in bold)	Neuropsychological tests/ outcomes (test/domains with significant results in bold)
Di Pinto et al. [29][d] Memphis/TN, USA 1997–2007 All treated at the author's institution	To assess whether children with low-grade glioma or CP had a decline in verbal and visual-auditory learning several years after completion of conformal radiation therapy (CRT) Prospective longitudinal testing	(a) Ages 1–21 at irradiation, no prior irradiation or ongoing chemotherapy predefined performance status (b) CP N = 44	(a) All treated with CRT or intensity modulated radiation therapy Pre-CRT multiple surgeries N = 13 (b) Hypothalamic involvement N = n.a.	(b) Median age at the start of CRT: 8.2 Testing before the start of CRT, weekly during CRT, and 6, 12, 24, 36, 48, up to 60 months after CRT was completed	Multiple regression analyses Age appropriate norms *Confounds* accounted for in analyses: **Hydrocephalus, shunt insertion, age at CRT, sex,** tumor volume	*Learning* and *memory*: CVLT-C visual-auditory learning test (from Woodcock-Johnson test of cognitive ability-revised)
Fjalldal et al. [28] Sweden 1958–2000 Recruited from the south medical region of Sweden	To assess whether quality of life, psychosocial health, and cognitive performance in adults with childhood onset CP on hormone substitution, differed to matched healthy controls Cross-sectional study	(a) No adverse medical conditions (b) CP N = 42 (with HI N = 25; without HI N = 17) HC N = 42	(a) Radiotherapy N = 20 Multiple surgeries N = 11 (b) Hypothalamic involvement N = 25	*CP* (a) Median 12 Range 3–22 (b) Median 28 (female/male) Range: 17–57 Follow up: median 20 range 1–40 *HC*: one to one similar in age	Between-group analyses CP versus.HC CP with HI versus HC CP without HI versus HC Nonparametric tests but no corrections for multiple comparisons *Confounds* accounted for in analyses: **years since operation,** age at treatment, **hypothalamic involvement**	**Learning and memory**: Semantic memory (SRB1), Information (WAIS-R); **Cronholm-Molander verbal memory test**; **Austin Maze test** **Attention and processing speed**: **Digit symbol** (WAIS-R); **automated psychological test system** (APT-Two-way reaction time, APT Inhibition, APT k-test for sustained attention) *Visuo-spatial ability*: Block design (WAIS-R)
Özyurt et al. [27] Germany 2001–2010 Recruited from a multicenter multinational trial (Germany, Austria, Switzerland)	To test memory performance and executive functions in patients with childhood CP and hypothalamic Involvement Cross-sectional study	(a) Hypothalamic involvement No visual impairment Age ≥12 years at study (b) CP N = 15 HC N = 24	(a) Radiotherapy N = 5 Multiple surgeries N = 3 (b) Hypothalamic involvement N = 15	*CP* (a) Median 11.4 Range 7.5–17.6 b) Median 17.3 Range 14.6–27.2 Follow-up: median 7.7; range 1.9–18.9 *HC* (b)Median 17.6 Range 15-26	Between-group analyses and age appropriate norms CP versus HC CP with low versus high HI Nonparametric analysis, corrections for multiple comparisons *Confounds* accounted for in analyses: age at diagnosis/treatment, age at study, depression, IQ, **HI**, intracranial pressure, irradiation	*Intelligence*: culture fair intelligence test II (CFT-II), short version **Learning** and **memory: Auditory verbal learning test** Spatial working memory, spatial span (CANTAB) **Attention and executive functioning**: **intra/extra-dimensional shift**; **rapid visual processing** (CANTAB)

Table 1 continued

Study Location Treatment time	Aim Study design	(a) Eligibility criteria (b) Groups[a]/N[b]	(a) Treatment (b) Hypothalamic involvement	Age (years) at (a) Diagnosis (b) Study follow-up time	(a) Analyses (b) Confounds (significant results are in bold)	Neuropsychological tests/outcomes (test/domains with significant results in bold)

CP craniopharyngioma, *HC* healthy controls; *HI* hypothalamic involvement, *n.a.* not available, *CANTAB* Cambridge neuropsychological test automated battery, *CVLT-2* California verbal learning test, 2nd edition/(CVLT-C: child version), *RBMT-II* rivermead behavioural memory test, 2nd edition, *WAIS-III* Wechsler adult intelligence scale, 3rd edition, *WASI* Wechsler abbreviated scale of intelligence, *WISC-R* Wechsler intelligence scale for children-revised, *WISC-III* Wechsler intelligence scale for children; 3rd edition, *WJ-III* Woodcock-Johnson, 3rd edition, *WRAML* Wide range assessment of memory and learning

[a] Disclosure was restricted to patient groups that were compared with craniopharyngioma patients

[b] Disclosure was restricted to the number of craniopharyngioma patients that participated in the neuropsychological part of the study

[c] Information provided by authors on request

[d] Results reported from the same trial with an overlapping patient sample

[24, 25]. Mixed findings were observed with other tests assessing attention and executive performance (Table 3).

Patient- and treatment-related variables

Very few of the studies could find a significant effect of patient- and treatment-related variables on cognitive performance (Table 1). In the study by Özyurt et al. [27], multiple linear regression analyses revealed that a higher degree of postoperative hypothalamic involvement predicted worse sustained attentional performance. In the study by Fjalldal et al. [28], a negative correlation was found between years since surgical treatment and the mean z-score of all cognitive tests. Additional analyses revealed that reduced cognitive performance mainly in patients with hypothalamic involvement were responsible for this finding. In the study by Di Pinto et al. [29], hydrocephalus, shunt insertion, and female gender were found to be predictive of worse episodic learning performance 5 years after conformal radiation therapy.

Discussion

In accordance with several other reports [35–37] (but also see [11, 38]), all reviewed studies that included intelligence testing obtained a full-scale IQ in the normal range for the patient group [21, 24–27, 33]. Despite preserved overall cognitive abilities, patients revealed deficits in specific neuropsychological test assessing memory, attention, processing speed, and executive functioning. This implies that the full scale IQ either masks deficits in individual subtests or that the IQ (sub-) tests largely do not cover assessment of cognitive subprocesses that may be affected in craniopharyngioma patients.

Memory performance

Based on anatomical considerations and frequently reported complaints of the patients and/or their caregivers, learning and memory was the domain most investigated in patients with childhood craniopharyngioma. A systemized assignment of test results to subcomponents of memory, as shown in Table 2, demonstrates a clear pattern of spared and impaired memory functions. In the literature reviewed, verbal and visuo-spatial memory span and working memory were found to be in the normal range [21, 24, 25] and not different from controls [27]. A different picture emerged when information to be retained exceeded immediate memory span and had to be recalled either immediately or after a delay. In several studies, verbal and/or visual episodic memory were significantly impaired [21,

Table 2 Pattern of spared and impaired functions in childhood craniopharyngioma: Memory, language (word retrieval), and visual/visuo-spatial performance

	Working memory		Long-term memory				
	Memory span	Working memory	Episodic			Semantic	
			Recall immediate/ learning	Recall delayed	Recognition delayed		
Verbal memory							Word retrieval
Özyurt et al. [27][a,b]			Impaired	Impaired	Normal		
Fjalldal et al. [28][a]			Impaired	Impaired		Normal	
Di Pinto et al. [29][c]			Normal				
Bawden et al.[26][a]			Normal	Normal			
Waber et al. [24][b]			*	*			Normal
Carpentieri et al. [21][b]	Normal		Normal	Impaired	Normal		Impaired
Riva et al. [25][b]	Normal	Normal					
Visual and visuo-dpatial memory							Visuospatial
Özyurt et al. [27][a]	Normal	Normal					
Fjalldal et al. [28][a]			Impaired				Normal
Di Pinto et al. [29][c]			Normal				
Ondruch et al. [33][b]				Impaired			Normal
Bawden et al. [26][a]				Normal			Normal
Waber et al. [24][b]		Normal	Normal				Normal
Carpentieri et al. [21][b]			Impaired	Impaired			Normal
Riva et al. [25][b]	Normal						

For further details on the definition of impaired performance in studies using age-appropriate norms only, see 'Data Extraction' in the Methods section

* Waber et al. tested verbal episodic memory with a word list task (California Verbal Learning Test; CVLT) and a narrative task (Story Memory). Patients performed in the normal range when required to immediately recall word lists but were severely impaired in the story memory task. Unfortunately, it is not known if it was immediate or delayed recall for narrative information which was found to be impaired. Information could not been obtained upon request

[a] Compared to controls

[b] Age-appropriate norms

[c] Repeated measures model

24, 27, 28, 33], despite normal language [24] and visuo-spatial abilities [21, 28, 33]. However, some inconsistencies remain regarding the question, whether deficits in delayed recall are indicative of a true retrieval deficit [21, 27], or solely due to impairments already obvious at the immediate recall stage [28] (which could be due to an encoding deficit).

In the study by Fjalldal et al. [28], additional subgroup analyses indicated that patients with hypothalamic involvement were mainly responsible for the memory deficits reported for the whole patient group. The finding of episodic memory deficits, with hypothalamic involvement in particular, is in line with the importance of the mammillary part of the hypothalamus for the extended hippocampal system, which is known to be vital for episodic memory [39–41]. Noteworthy, two studies that tested both, episodic recall and recognition performance, suggested impaired delayed recall together with relatively preserved delayed recognition [21, 27]. A similar dissociation has been reported in previous studies in patients with damage to the mammillary bodies or its connections [40, 41].

Attention, processing speed and executive functioning

Hypothalamic involvement is frequently associated with neurobehavioral problems which may be indicative of frontal dysfunctions, such as emotional lability, rage attacks, deficits in memory and higher cognitive abilities [16, 42, 43]. Regarding patients treated in the pre-microsurgical era, those deficits have been ascribed to frontal damage induced by surgery [22, 25]. However, it is conceivable that hypothalamic damage itself may result in a loss of input to prefrontal regions, leading to deficits in

Table 3 Pattern of spared and impaired functions in childhood craniopharyngioma: attention, processing speed, and executive performance

	Attention and processing speed			Executive performance		
	Selective attention	Sustained attention	Processing speed	Cognitive flexibility	Verbal and figural fluency	Concept formation
Özyurt et al. [27][a, b]		Impaired		Impaired		
Fjalldal et al. [28][a]		Impaired	Impaired			
Bawden et al. [26][a]		Normal		Normal	Normal	Normal
Kiehna et al. [23][c]		Impaired*				
Waber et al. [24][b]		Normal	Impaired			
Riva et al. [25][b]	Normal		Impaired	Normal		

For further details on the definition of impaired performance in studies using age-appropriate norms only, see 'Data Extraction' in the Methods section

* Significant worsening over the first five years after conformal radiation therapy

[a] Compared to controls

[b] Age-appropriate norms

[c] Repeated measures model

executive and attentional control [44, 45]. Currently, the evidence base for functioning in these cognitive domains is still rather limited.

Within the articles reviewed, cognitive flexibility is the only executive function that was tested in more than one study. This cognitive component, which is of vital importance for the ability to adapt to changing situations and goals, was shown to be significantly impaired in one study [27], but unimpaired in two others [25, 26]. Outside the set of publications considered for this review, additional evidence for executive dysfunctions comes from a study that observed impaired cognitive flexibility in a childhood craniopharyngioma group treated with radical surgery [22] and another study that used a standardized questionnaire to assess everyday problems with executive functions [3].

Sustained attention, with its requirement for top-down monitoring and control, is a further cognitive component, which is in part mediated by the frontal lobes. Two of the included studies found impairments in sustained attention [27, 28]. On the other hand, two other studies found patient's performance in the normal range [24] or not different from the control group [26].

Processing speed has been frequently observed to be impaired in survivors of childhood brain tumors [46] and was shown to be critically dependent on the structural integrity of white matter pathways to frontal, parietal and temporal cortices [47]. Fronto-thalamic pathways, which may be affected by a tumor or its treatment, are assumed to play an important role in modulating the efficiency of information processing [48]. Processing speed was tested in three of the studies included and all reported a significant proportion of patients in the clinical range or a significantly slower performance compared to controls [24, 25, 28].

Effects of radiotherapy on memory performance and attention

Radiation therapy of brain tumors has often been found to significantly heighten the risk of neurocognitive deficits [49]. Within the last decade, more refined irradiation methods have been established, being further developed on a continuous basis. With its potential to better target the tumor and to spare healthy brain tissue, CRT in particular is assumed to result in less cognitive sequelae compared to previous methods [49]. Two studies, reporting results from a longitudinal trial and with partly overlapping samples, investigated the impact of CRT on cognition up to 5 years after irradiation. Di Pinto et al. [29] reported episodic learning performance in the normal range at baseline, with no performance decline in the further course of the study. On the other hand, Kiehna et al. [23] found sustained attentional performance in the borderline normal range at baseline assessment and a significant decline during radiation, up to five years after completion of the therapy. It was, however, pointed out that this performance decline was likely not caused by CRT alone, as comparable courses of outcome have been reported after surgery alone [23].

Other patient- and treatment-related variables

Besides hypothalamic involvement and radiation therapy, numerous other factors can influence cognitive outcomes, and their identification may be crucial for informed treatment decisions. Presumably due to the mostly small sample sizes and an associated lack of statistical power, few significant findings were available from the studies included. Two more recent studies, comprising larger cohort sizes, identified a small number of relevant patient- and treatment related variables. The negative correlation between years since surgical treatment and global performance, reported for patients with hypothalamic involvement in the study by Fjalldal et al. [28], was possibly due to late effects associated with irradiation of normal brain tissue. This interpretation is supported by the fact that the large majority of the patients had received radiation therapy, with the first patients' treatment dating back to the late fifties. The finding of younger age at radiation therapy as predictor for worse cognitive performance in the study by Di Pinto et al. [29] is also well in line with other studies [13, 22, 50] and clearly supports approaches to delay radiation in very young patients [51]. In the same study, hydrocephalus and shunt insertion also predicted worse cognitive performance, illustrating the relevance of an early identification and treatment of hydrocephalus [23].

Limitations

The interpretation of the findings is limited by the paucity of studies that tested specific cognitive functions. In addition, the limited number of studies eligible for the review and the small sample sizes in most of these studies clearly restrict the conclusions on the influence of patient and treatment variables on cognitive outcomes (e.g. hypothalamic involvement, presence of hydrocephalus, type and extent of surgery, irradiation). Finally it should be noted that some of the studies were of poor to limited quality.

Conclusions and future directions

Research published within the last years, added new evidence providing a clearer and more reliable picture of cognitive sequelae associated with childhood craniopharyngioma. The current summary of available findings indicates dysfunctions in cognitive processes mediated by extended hippocampal and fronto-hypothalamic pathways [52]. Episodic long-term memory in particular is shown to be affected in patients, and hypothalamic involvement was shown to be an essential risk factor for adverse outcomes. We believe that this review will provide a starting point for more targeted cognitive testing. There is an urgent need for studies with larger sample sizes, ideally conducted as part of follow-up protocols that are used by multiple centers in parallel, to enable more in-depth insights into cognitive deficits and their relation to patient- and treatment-related variables. As results of cognitive testing cover only part of psychological outcomes and may in some cases significantly differ from patients' subjective evaluation or overall functional outcome, these objective neuropsychological measures should be combined with measures of quality of life and of neurobehavioral, social and emotional/affective outcomes. In Supplement 2, we provide recommendations for a set of domain-specific neuropsychological tests that may be used for research or clinical practice, and a list of further key clinical variables to include in future reports that focus on psychological outcomes.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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