Routledge
Taylor & Francis Group

Child Neuropsychology

A Journal on Normal and Abnormal Development in Childhood and Adolescence

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ncny20

Neurocognitive development after pediatric brain tumor - a longitudinal, retrospective cohort study

Ingrid Tonning Olsson, Johan Lundgren, Lars Hjorth, Per Munck Af Rosenschöld, Åsa Hammar & Sean Perrin

To cite this article: Ingrid Tonning Olsson, Johan Lundgren, Lars Hjorth, Per Munck Af Rosenschöld, Åsa Hammar & Sean Perrin (2023): Neurocognitive development after pediatric brain tumor - a longitudinal, retrospective cohort study, Child Neuropsychology, DOI: 10.1080/09297049.2023.2172149

To link to this article: https://doi.org/10.1080/09297049.2023.2172149

CHILD NEUROPSYCHOLOGY
https://doi.org/10.1080/09297049.2023.2172149

Routledge
Taylor & Francis Group

Neurocognitive development after pediatric brain tumor - a longitudinal, retrospective cohort study

Ingrid Tonning Olsson [a,b,c], Johan Lundgren [b,c], Lars Hjorth [b,c], Per Munck Af Rosenschöld [d,e], Åsa Hammar [a,f] and Sean Perrin [a]

[a]Department of Psychology, Lund University, Lund, Sweden; [b]Department of Paediatrics, Skåne University Hospital, Lund, Sweden; [c]Department of Clinical Sciences, Paediatrics, Lund University, Lund, Sweden; [d]Medical Radiation Physics, Lund University, Lund, Sweden; [e]Radiation Physics, Dept of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden; [f]Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

ABSTRACT

Survivors of Pediatric Brain Tumors (PBTs) treated with cranial radiation therapy (CRT) often experience a decline in neurocognitive test scores. Less is known about the neurocognitive development of non-irradiated survivors of PBTs. The aim of this study was to statistically model neurocognitive development after PBT in both irradiated and non-irradiated survivors and to find clinical variables associated with the rate of decline in neurocognitive scores. A total of 151 survivors were included in the study. Inclusion criteria: Diagnosis of PBT between 2001 and 2013 or earlier diagnosis of PBT and turning 18 years of age between 2006 and 2013. Exclusion criteria: Death within a year from diagnosis, neurocutaneous syndromes, severe intellectual disability. Clinical neurocognitive data were collected retrospectively from medical records. Multilevel linear modeling was used to evaluate the rate of decline in neurocognitive measures and factors associated with the same. A decline was found in most measures for both irradiated and non-irradiated survivors. Ventriculo-peritoneal (VP) shunting and treatment with whole-brain radiation therapy (WBRT) were associated with a faster decline in neurocognitive scores. Male sex and supratentorial lateral tumor were associated with lower scores. Verbal learning measures were either stable or improving. Survivors of PBTs show a pattern of decline in neurocognitive scores irrespective of treatment received, which suggests the need for routine screening for neurocognitive rehabilitation. However, survivors treated with WBRT and/or a VP shunt declined at a faster rate and appear to be at the highest risk of negative neurocognitive outcomes and to have the greatest need for neurocognitive rehabilitation.

ARTICLE HISTORY
Received 18 March 2022
Accepted 18 January 2023

KEYWORDS
Pediatric brain tumor; neurocognition; survivorship; late complications; longitudinal

Children treated for Pediatric Brain Tumors (PBTs) are at increased risk for impairment in neurocognitive functioning (de Ruiter et al., 2013; Stavinoha et al., 2018) e.g., sequelae in cognitive processing speed, attention, working memory, and executive functions (Kahalley et al., 2013). The vast majority of studies examining neurocognitive function

CONTACT Ingrid Tonning Olsson ingrid.tonning_olsson@med.lu.se Department of Paediatrics, Skåne University Hospital, Lund SE-22185, Sweden

Supplemental data for this article can be accessed at https://doi.org/10.1080/09297049.2023.2172149

in survivors of brain tumors are cross-sectional and have shown several factors to be associated with a less favorable neurocognitive outcome: demographic factors (low socio-economic status (Oprandi et al., 2022; Patel et al., 2015) young age at diagnosis (de Ruiter et al., 2013; Schreiber et al., 2014), clinical factors (type, grade, size, and location of tumor (Fraley et al., 2019; Tonning Olsson et al., 2014), and treatment factors (cranial radiation therapy (CRT) (de Ruiter et al., 2013; Robinson et al., 2013), chemotherapy (Riva et al., 2002), surgical complications (Ater et al., 1996). Also, post-treatment factors have been associated with worse neurocognitive outcomes, e.g., chronic health conditions (Williams et al., 2021), health behaviors (Tonorezos et al., 2019), and pain (Krull et al., 2018; Tonning Olsson et al., 2021). Longer time since diagnosis have been associated with worse neurocognitive outcomes in cross-sectional studies (de Ruiter et al., 2013), which might indicate exacerbation of neurocognitive sequelae over time. Longitudinal studies are few, almost exclusively North American, and focus on survivors treated with CRT and/or chemotherapy (de Ruiter et al., 2013). Less is known about the longitudinal development of survivors treated with surgery only and survivors treated outside North America.

The existing longitudinal studies of survivors of PBTs find different neurocognitive trajectories depending on treatment modality: *1) whole-brain radiation therapy (WBRT), 2) focal radiation therapy (RT), or 3) surgery only*.

(1) Studies examining *survivors treated with WBRT* (the majority of longitudinal studies) suggest a significant decline over time with Full Scale IQ (FSIQ) scores drops ranging from 1 to 4.3 standard scores (SS; $m = 100$, $sd = 15$) per year (Kieffer-Renaux et al., 2005; Knight et al., 2014; Moxon-Emre et al., 2014; Mulhern et al., 2005; Palmer et al., 2013; Ris et al., 2001, 2013). Data from a longitudinal study (Palmer et al., 2001), examining both raw data and standardized IQ scores in 44 survivors of medulloblastoma, suggest that the decline may reflect slower development rather than deterioration of intellectual capacity. It is not known for how long this decline in neurocognitive scores continues. A few studies, fitting quadratic statistical models to their data, as compared to linear ones, have found a steep decline in IQ immediately following treatment, then plateauing over several years (Mabbott et al., 2005; Palmer et al., 2003; Spiegler et al., 2004). Factors associated with a faster decline in neurocognitive scores in survivors treated with WBRT are higher radiation dose (Merchant et al., 2014; Moxon-Emre et al., 2014) younger age at diagnosis (Merchant et al., 2014; Mulhern et al., 2005; Palmer et al., 2003; Ris et al., 2001, 2013), treatment with ventriculo-peritoneal (VP) shunting (Moxon-Emre et al., 2014), higher baseline IQ (Palmer et al., 2013; Ris et al., 2001, 2013), and posterior fossa syndrome (Moxon-Emre et al., 2014). Some studies have shown females to have a steeper decline in neurocognitive scores (Ris et al., 2001), while others have found no sex differences (Mulhern et al., 2005).

(2) Few longitudinal studies have examined neurocognitive development after *focal cranial radiation therapy (CRT)* and the results are mixed. In an early longitudinal study of 43 survivors, Ellenberg et al. found WBRT, but no other type of treatment, to be related to a decline in neurocognitive scores (Ellenberg et al., 1987). Netson et al. (2012) found no decline in IQ scores in a study including 123

survivors of childhood ependymoma, and similar results in another study including 139 survivors of craniopharyngiomas and low-grade gliomas (Netson et al., 2013). However, in a re-analysis of these data, also including survivors of high-grade gliomas and using person-oriented statistical methods, the authors found 38% of the 350 survivors to improve slightly over the first years post-diagnosis, followed by a decline in neurocognitive scores from 4 years post-diagnosis (Willard et al., 2019). Survivors showing this pattern were more likely to be younger at diagnosis, to have been treated with more surgeries before CRT and to have hydrocephalus requiring ventriculo-peritoneal shunting (Willard et al., 2019). Few longitudinal studies have found, or even explored, sex differences in survivors treated with focal RT. One study examining processing speed in a mixed group of survivors of PBT found females to outperform males after stratifying survivors on age, but found no differences in rate of decline in scores (Jacobson et al., 2019). Even if tumor location might be thought of as an important factor when examining neurocognition in survivors treated with focal radiation, quite few studies have explored this and findings are inconclusive. In a large study including 194 survivors of brain tumors treated with and without WBRT and/or focal RT, hemispheric location of tumor (as compared to midline location) was associated with a faster decline in IQ scores (Fouladi et al., 2005). In contrast, another study found infratentorial location to be associated with worse neurocognitive performance (Weusthof et al., 2021) and yet another study found no significant associations (Jacobson et al., 2019).

(3) Several cross-sectional studies have found significant neurocognitive impairment in survivors treated with *surgery only* (Aarsen et al., 2004; Beebe et al., 2005; Ris et al., 2008). Longitudinal studies on this group of survivors are few. Existing studies are typically small, including survivors treated with surgery only as a control group. Results from these studies are inconclusive, most of them showing no decline in neurocognitive scores over time (Fraley et al., 2019; Heitzer et al., 2019; Kahalley et al., 2019; Packer et al., 1989; Stargatt et al., 2007). Fouladi et al. (2004) even found improved neurocognitive performance in a subsample of survivors of PBTs, treated with surgery only (n = 37). However, in this study 20% of the subsample treated with surgery only had "severe mental retardation" (a much higher rate than expected in the general population). A more recent study (Weusthof et al., 2021), including 47 survivors treated with surgery only, found declining scores from baseline to 42 months post-diagnosis, for measures of non-verbal reasoning and processing speed. In sum, previous studies, longitudinal and cross-sectional, suggest that survivors treated with surgery only are at risk for negative neurocognitive sequelae, albeit to a lesser extent than survivors treated with chemotherapy and CRT (Brinkman et al., 2016; Ris & Beebe, 2008) but more research is needed on long-term neurocognitive development.

The aim of this retrospective longitudinal cohort study was twofold: (1) to analyze the rate of decline in neurocognitive scores in a large European population-based, heterogeneous sample of survivors of PBTs and (2) to examine the influence of clinical variables on the rate of decline in neurocognitive scores.

Materials and methods

Participants

Skåne University Hospital supplies cancer treatment to all patients diagnosed with PBTs and living in the southern part of Sweden. In 2006, a neuropsychological follow-up screening program for all survivors of PBTs was started at our institution with a neuropsychological assessment scheduled at baseline (i.e., before surgery if possible, or directly after surgery when the child had recovered), one, three, and five years after diagnosis, and at 18 years of age before transfer to adult healthcare. The goal of the program was to identify and offer rehabilitation to survivors with neurocognitive sequelae and to learn more about risk factors and neurocognitive trajectories. The study period was 2006–2013, and all survivors included in the neuropsychological follow-up program during these years were included in the study, i.e., all survivors diagnosed with a PBT between year 2001 and 2013 ($n = 199$), together with survivors diagnosed 1993–2001, turning 18 years of age between year 2006 and 2013 ($n = 25$), see Figure 1. Exclusion criteria were death within a year of diagnosis ($n = 20$), presence of a neurocutaneous syndrome affecting cognitive performance ($n = 30$), (De Winter et al., 1999; Winterkorn et al., 2007) or severe intellectual disability, i.e., at a neurocognitive level where neuropsychological assessment was not feasible ($n = 3$).

Of the 171 survivors eligible for the study, 20 did not undergo neuropsychological screening and were excluded from the study. The main reasons for these survivors not entering the neuropsychological follow-up program were as follows: unclear diagnosis, older age (soon to be transferred to adult healthcare), and caregivers opting out of the program because the survivor did not report any cognitive difficulties. This left 151 survivors in the study (88.3% participation rate).

Measures

All data were collected retrospectively from medical and neuropsychological records. All neurocognitive assessments were recorded, including those done outside the fixed intervals of the neuropsychological assessment program. The neuropsychological assessment program included a test battery designed to measure cognitive abilities commonly affected in survivors of PBTs (J. A. Limond et al., 2015; J. Limond et al., 2020) i.e., measures of general intelligence, verbal and non-verbal reasoning, cognitive processing speed, working memory (auditory and visual), verbal learning, sustained attention, and executive function. Unfortunately, measures of visual working memory, sustained attention, and executive function were collected for a minority of survivors and were therefore excluded from further analyses. Measures of general intelligence (full scale IQ) were excluded in the final analyses as many participants' neurocognitive profiles were uneven and their ability considered to be better represented by sub-scales. During the course of the study, different neuropsychological measures (or versions) were used, and data from similar tests were collapsed. Data were collected within five different domains:

(1) Verbal reasoning: a full Verbal Comprehension Index from an age-appropriate Wechsler test (Wechsler, 2003) or an estimation from administered subtests (Information, Similarities, Vocabulary, and Comprehension; for children younger

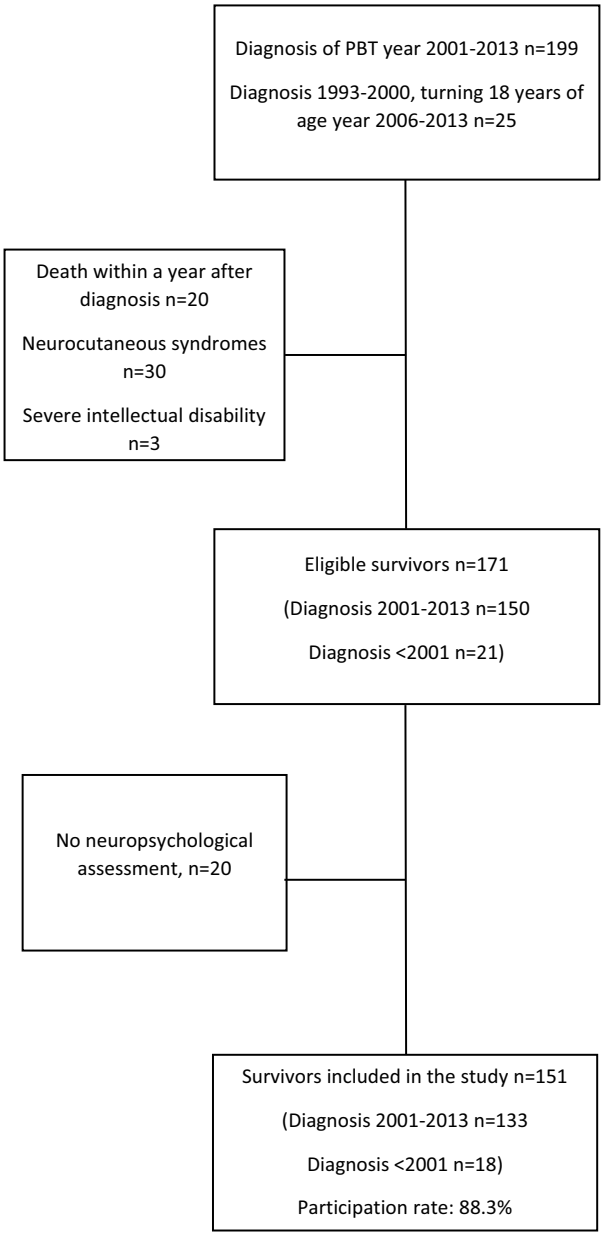

Figure 1. Flowchart participants, PBT=pediatric brain tumor.

than 4 years of age also Receptive Vocabulary and Picture Naming). For children younger than 2.5 years of age: Bayley Scales of Infant and Toddler Development III (Bayley, 2006) language subscale.

(2) Non-verbal reasoning: a full Wechsler Perceptual Organization Index, an estimation from administered subtests (Picture Completion, Picture Arrangement, Block Design, Object Assembly), or Raven's Standard or Colored Matrices (Raven et al., 2000) (in a few cases when a Wechsler test was not administered).

(3) Auditory working memory: A full Wechsler Freedom from Distractibility Index (subtests Digit Span and Arithmetic) or a single result on Wechsler Digit Span.
(4) Cognitive processing speed: a full Wechsler Processing Speed Index (subtests Coding and Symbol Search) or a single result on Wechsler Coding.
(5) Verbal learning: Nepsy Wordlist Memory (Korkman, 2000) or Rey Auditory Verbal Learning Test (total score for 5 presentations), (Schmidt, 1996) or, for children younger than 8 years of age, Nepsy Narrative Memory (Korkman, 2000).

Most neuropsychological evaluations were carried out by neuropsychologists working in the Pediatric Neuropsychology Service at Skåne University Hospital, with an order of subtests and administration routines optimized to reduce fatigue and increase rapport. All raw scores were converted to standard scores (SS) with an average of 100 and a standard deviation of 15, using age- and culture-appropriate norms; higher scores reflecting better performance. Norms given in percentile intervals were converted to standard scores using the exact location within the interval.

The following clinical variables were extracted from medical records retrospectively, i.e., after year 2013, and included in the multivariate analyses: sex, age at first diagnosis, localization of tumor, size of tumor (largest diameter in cm at any timepoint before the end of year 2013), cancer treatment, increased intracranial pressure (IICP) at diagnosis, placement of ventriculo-peritoneal (VP) shunt (including ventriculostomy), and relapse at any point before the end of year 2013. Tumor localization was coded at first diagnosis as infratentorial, supratentorial lateral, or supratentorial midline. Treatments were categorized into five mutually exclusive groups: 1) no treatment or surgery only, 2) chemotherapy with or without surgery, 3) focal RT with or without surgery, 4) Focal RT, chemotherapy, and surgery, 5) Focal RT, WBRT, chemotherapy, and surgery. Treatment was coded as yes if administered at any time before the end of year 2013. Over time, radio- and chemotherapy protocols for this patient cohort were altered. All survivors were treated with photon RT. The study period encompasses several major technological radiotherapy advances including CT- (during the 1990's) and MR-simulation (routine from 2012-), introduction of intensity modulated radiotherapy (from about 2006-), as well as image-guided radiotherapy (gradual improvements from 2005-). Technological advances have allowed for gradual improvements in the precision and consequently the conformality of the radiation-dose distribution around the target.

Statistical methods

Overall neurocognitive performance was compared to national norms using one-sample T-tests with assessments grouped according to time since diagnosis (pre-surgery assessment within 1 year from diagnosis, post-surgery assessment within a year from diagnosis, assessments one to six years post-diagnosis, and assessments more than six years post-diagnosis). For descriptive purposes, the frequency of impaired test results was calculated with impairment defined as results below the 10^{th} percentile compared to national normative data. Drop-out analyses were done in four steps using Chi^2-tests for categorical variables and independent sample T-tests for continuous variables (Table S1). At each step survivors undergoing less than n assessments were compared to survivors undergoing n or more assessments. Drop-out analyses were performed for all clinical

variables (sex, age at diagnosis, tumor localization and size, IICP at diagnosis, VP shunt, relapse, and treatment). Drop-out analyses were also performed for neurocognitive outcome variables using Student's T-tests (Table S2), comparing results on test n with results on test n + 1, i.e., if results at a specific timepoint predicted receiving or not receiving further assessments.

Multilevel Linear Models (MLM) were used to evaluate changes over time. Only linear trends were explored. Each of the eight clinical variables was added one at a time in separate models, as well as an interaction variable (e.g., time since diagnosis, VP shunt placement, and time since diagnosis*VP shunt placement). An unstructured covariance matrix was chosen to evaluate both random slopes and random intercepts. Following the multivariate analyses, three different explorative analyses were performed on 1) sex differences, 2) the association between IICP and cognitive processing speed, and 3) a possible bias in verbal learning scores. The explorative analyses were performed using Chi^2-tests, student's T-tests, and Pearson correlations, and by rerunning the MLM for cognitive processing speed excluding survivors with IICP at diagnosis treated with VP shunting.

A significance level of $p = .05$ was used with no correction for multiple analyses since the focus of this study was to explore the overarching tendencies in the data. All analyses were carried out using SPSS Version 27.0 (IBM C, 2020).

Results

Descriptives

One hundred and fifty-one survivors with a total of 387 neuropsychological examinations were analyzed. Descriptive statistics for the 151 survivors are shown in Table 1. More than half of the sample (55.6%) received surgery only ($n = 82$) or no treatment ($n = 2$). Nineteen survivors (11%) were treated between 1992 and 1999 and the remainder during years 2000–2014. Participants were followed for an average of 4.2 years (range = 0.8 to 13.6 years). Seventy-one of the survivors (47%) underwent their first assessment at diagnosis before surgery, and 36 (24%) underwent their first assessment post-surgery within a year after diagnosis. Fifteen survivors (10%) underwent their first assessment one to two years post-diagnosis, and the remaining 29 (19%) underwent their first assessment three to 13 years post-diagnosis.

Neurocognitive performance assessed less than three years post-diagnosis did not differ from a normative mean of 100 SS on measures of verbal and non-verbal reasoning or verbal learning (Table 2). Measures of cognitive processing speed and working memory were significantly lower compared to the normative mean at all timepoints, both pre- and post-surgery (Table 2). At neurocognitive follow-ups more than 6 years post-diagnosis, 28% and 38% of the survivors, respectively, scored in the impaired range (<10%tile compared to national norms) on measures of verbal and non-verbal reasoning, and 40% and 55%, respectively, fell in the impaired range on measures of cognitive processing speed and working memory.

Forty-six survivors (26%) underwent one assessment, 43 (24%) underwent two assessments, 50 (28%) three assessments, 27 (15%) four assessments, and 11 (6%) underwent five or six assessments. Drop-out analyses showed few significant differences between

Table 1. Study group, demographics and clinical characteristics, total group, and per sex.

	Total, n = 151	*Female, n = 63*	*Male, n = 88*	*p*
	N(% of total group)/ M (SD)	*N(% of females)/ M (SD)*	*N(% of males)/ M (SD)*	
Average age at first diagnosis (years)	*8.4 (4.9)*	*9.1 (4.7)*	*8.0 (4.9)*	*.14*
Type of tumor, WHO ICCC-III *				.58
III a, Ependymomas and choroid plexus tumors	13 (8.6)	4 (6.3)	9 (10.2)	
III b, Astrocytomas	64 (42.4)	29 (46.0)	35 (39.8)	
III c, Intracranial and intraspinal embryonal tumors	21 (13.9)	6 (9.5)	15 (17.0)	
III d, Other gliomas	13 (8.6)	5 (7.9)	8 (9.1)	
III e, Other specified intracranial neoplasms	35 (23.2)	16 (25.4)	19 (21.6)	
IIIf, Unspecified neoplasms	3 (2.0)	1 (1.6)	2 (2.3)	
Xa, Germ cell tumors	1 (0.7)	1 (1.6)	0 (0.0)	
VIIId, Other specified malignant bone tumors	1 (0.7)	1 (1.6)	0 (0.0)	
Treatment given				.80
Surgery only or no treatment	84 (55.6)	36 (57.1)	48 (54.5)	
Chemotherapy with or without surgery	10 (6.6)	4 (6.3)	6 (6.8)	
Focal RT with or without surgery	18 (11.9)	7 (11.1)	11 (12.5)	
Focal RT, chemotherapy, and surgery	15 (9.9)	8 (12.7)	7 (8.0)	
Focal and WBRT with chemotherapy and surgery	24 (15.9)	8 (12.7)	16 (18.2)	
Average size of tumor at diagnosis (widest diameter)	4.1 cm (1.8)	3.9 cm (1.7)	4.2 cm (1.9)	.41
Increased intracranial pressure at diagnosis	83 (55)	32 (50.8)	51 (58.0)	.41
One or more relapses	43 (28.5)	21 (33.3)	22 (25.0)	.28
Ventriculo-peritoneal shunt or ventriculostomy	29 (19.2)	11 (17.5)	18 (20.5)	.68
Localization				.78
Infratentorial	72 (47.7)	28 (44.4)	44 (50.0)	
Supratentorial lateral	44 (29.1)	20 (31.7)	24 (27.3)	
Supratentorial midline	35 (23.2)	15 (23.8)	20 (22.7)	

Abbreviations: ***WHO ICCC-III:*** World Health organization: International Classification of Childhood Cancer, third edition, (**WB) RT**: (whole brain) radiation therapy, **ICP**: intracranial pressure. P-values indicate difference between males and females, Chi^2-tests for categorical variables and Student's T-tests for continuous variables.

survivors undergoing fewer assessments as compared to survivors undergoing more assessments (Supplemental Table S1). Compared to those with two or fewer assessments, survivors undergoing three or more assessments were younger at diagnosis (7.3 years vs 9.6 years, $p = 0.004$) and were more likely to have experienced a relapse (36.4% vs 20.3%, $p = 0.03$). A borderline significant trend was found for verbal learning scores, with survivors undergoing two or fewer assessments achieving higher scores compared to survivors undergoing three or more assessments ($p = 103.8$ vs 98.0, $p = 0.057$, Supplemental Table S2). No statistically significant differences were found for neurocognitive scores for survivors receiving vs not receiving a follow-up assessment at any timepoint (Supplemental Table S2).

Multilevel linear models

Most models showed a significant negative one-way association between neurocognitive outcomes and time since diagnosis (Table 3), with scores declining 0.8 to 1.8 SS per year. No decline in neurocognitive scores was shown for verbal learning, and two models, controlling for treatment with VP shunt and relapse, respectively, showed a positive development (VP shunt: $\beta = 0.8$SS/year, $p = .01$, relapse: $\beta = 0.9$SS/year, $p = .03$). Since different measures were used for children younger vs older than 8 years of age Nepsy

Table 2. Cognitive measures at different time intervals since diagnosis.

Assessment time point	Pre-surgery ≤1 year post-diagnosis				Post-surgery ≤1 year post-diagnosis				>1 year ≤2 years post-diagnosis				>2 years ≤3 years post-diagnosis			
	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)
Verbal reasoning	100.1 (16.1)	61	.97	8 (13.1)	96.0 (16.3)	42	.12	8 (19.0)	100.2 (16.3)	65	.92	9 (13.8)	97.5 (18.5)	35	.42	7 (20.0)
Non-verbal reasoning	101.7 (15.1)	64	.37	8 (12.5)	100.8 (16.7)	43	.76	4 (9.3)	98.1 (16.7)	63	.38	9 (14.3)	99.1 (15.2)	34	.72	4 (11.8)
Cognitive processing speed	**91.9 (12.4)**	**60**	**<.01**	**12 (20.0)**	**93.5 (19.1)**	**40**	**.04**	**10 (25.0)**	**91.7 (16.2)**	**61**	**<.01**	**16 (26.2)**	**93.9 (16.4)**	**32**	**.04**	**8 (25.0)**
Working memory	**93.2 (13.2)**	**57**	**<.01**	**10 (17.5)**	**95.0 (14.6)**	**40**	**.04**	**5 (12.5)**	**91.6 (15.6)**	**61**	**<.01**	**14 (23.0)**	**94.8 (10.9)**	**32**	**.01**	**4 (12.5)**
Verbal learning	99.2 (12.4)	57	.65	6 (10.5)	99.2 (12.8)	32	.73	2 (6.3)	100.8 (13.1)	56	.66	3 (5.4)	100.0 (13.8)	30	.99	2 (6.7)
	>3 years ≤4 years post-diagnosis				>4 years ≤5 years post-diagnosis				>5 years ≤6 years post-diagnosis				>6 years post-diagnosis			
	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)	Mean(*SD*)	*n*	*p*	Impaired *n* (%)
Verbal reasoning	**94.5 (16.2)**	**41**	**.04**	**9 (22.0)**	**92.7 (14.7)**	**27**	**.02**	**5 (18.5)**	**92.5 (17.2%)**	**31**	**.02**	**7 (22.6)**	**89,1 (16.0)**	**51**	**<.01**	**14 (27.5%)**
Non-verbal reasoning	**93.6 (15.5)**	**41**	**.01**	8 (19.5)	92.7 (20.6)	28	.07	10 (35.7)	**92.2 (16.9)**	**30**	**.02**	**5 (16.7)**	**88,0 (18.8)**	**56**	**<.01**	**21 (37.5)**
Cognitive processing speed	**88.4 (19.6)**	**39**	**<.01**	**16 (41.0)**	**88.4 (18.9)**	**26**	**<.01**	**8 (30.8)**	**84.9 (18.4)**	**30**	**<.01**	**11 (36.7)**	**79,7 (16.0)**	**52**	**<.01**	**21 (40.4)**
Working memory	**89.0 (16.3)**	**40**	**<.01**	**14 (35.0)**	**90.8 (16.6)**	**25**	**.01**	**7 (28.0)**	**86.9 (16.3)**	**29**	**<.01**	**10 (34.5)**	**78,3 (15.0)**	**56**	**<.01**	**31 (55.4)**
Verbal learning	101.1 (14.4)	37	.66	4 (10.8)	102.0 (14.5)	19	.55	2 (10.5)	97.6 (16.0)	29	.42	3 (10.3)	102,1 (15.0)	47	.35	5 (10.6)

Measures in standard scores (m=100, sd=15). p indicates statistical significance from anormative mean of 100 (one-sample T-test). **Note**: n here indicates number of data-points, i.e., each individual has several assessments. A total of 387 assessments of 151 survivors were recorded. **Bold text** indicates p<0.05. Impairment=results <10th percentile of national norms. Percentages represent % impaired of survivors tested at this specific timepoint.

Table 3. Clinical variables related to cognitive outcomes.

	Verbal reasoning			Non-verbal reasoning			Cognitive processing speed			Working memory			Verbal learning		
	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI
Model 1. time since diagnosis															
Intercept	99.4	<.01	96.5–102.3	98.6	<.01	95.8–101.4	91.1	<.01	88.3–93.9	93.8	<.01	91.3–96.2	98.6	<.01	96.3–100.8
Time dx	−1.4	<.01	−1.9–0.8	−0.7	.02	−1.3–0.1	−0.6	.05	−1.2–0.01	−1.1	<.01	−1.6–0.6	0.5	.09	−0.1–1.1
Model 2. Sex female (as compared to male)															
Intercept	97.0	<.01	93.3–100.7	97.7	<.01	94.0–101.4	85.7	<.01	82.2–89.1	90.6	<.01	87.4–93.7	96.4	<.01	93.4–99.4
Time dx	−1.1	.01	−1.8–0.3	−1.0	.01	−1.8–0.2	−0.3	.40	−1.0–0.4	−0.8	.03	−1.4–0.1	0.4	.27	−0.3–1.2
Female	5.8	.049	0.03–11.6	2.3	.43	−3.4–7.9	12.6	<.01	7.4–17.8	7.2	<.01	2.4–11.9	4.9	.03	0.4–9.4
Female* Time dx	−0.8	.16	−1.90.3	0.6	.28	−0.5–1.8	−0.5	.40	−1.6–0.7	−0.7	.17	−1.7–0.3	0.2	.73	−1.0–1.4
Model 3. Age at diagnosis															
Intercept	**101.3**	**<.01**	**95.3–107.3**	**95.3**	**<.01**	**89.1–101.5**	**91.3**	**<.01**	**85.0–97.7**	**98.7**	**<.01**	**93.1–104.3**	**94.1**	**<.01**	**88.6–99.6**
Time dx	−0.8	.13	−1.90.2	**−1.3**	**.03**	**−2.45–0.1**	**−1.6**	**.01**	**2.8–0.4**	**−1.7**	**.00**	**−2.8–0.7**	−0.01	.99	−1.2–1.2
Age at diagnosis	−0.2	.53	−0.8–0.4	0.3	.29	−0.3–1.0	−0.1	.87	−0.7–0.6	−0.5	.05	−1.1–0.01	0.4	.11	−0.1–0.9
Time dx * Age at diagnosis	−0.1	.18	−0.2–0.04	0.1	.15	−0.04–0.3	**0.2**	**.03**	**0.02–0.3**	0.1	.22	−0.1–0.22	0.1	.14	−0.04–0.3
Model 4. Tumor size															
Intercept	**102.1**	**<.01**	**95.3–108.9**	**99.4**	**<.01**	**92.4–106.5**	**95.6**	**<.01**	**88.7–102.4**	**90.4**	**<.01**	**84.3–96.5**	**99.7**	**<.01**	**94.2–105.2**
Time dx	**−1.8**	**.01**	**−3.2–0.4**	−0.9	.27	−2.4–0.7	0.4	.66	−1.3–2.0	−0.2	.72	−1.5–1.1	0.5	.50	−1.0–2.0
Tumor size (cm)	−0.8	.32	−2.3–0.8	−0.2	.76	−1.8–1.4	−1.2	.12	−2.8–0.4	0.8	.26	−0.6–2.2	−0.4	.56	−1.6–0.9
Time dx * Tumor size (cm)	0.1	.47	−0.2–0.4	0.03	.85	−0.3–0.4	−0.2	.25	−0.6–0.2	−0.2	.14	−0.5–0.1	0.01	.97	−0.3–0.4
Model 5. Localization (as compared to infratentorial tumor)															
Intercept	99.2	**<.01**	94.8–103.5	**98.0**	**<.01**	**93.9–102.1**	**89.6**	**<.01**	**85.4–93.8**	**95.8**	**<.01**	**92.1–99.5**	**96.4**	**<.01**	**92.9–100.0**
Time dx	−0.6	.11	−1.4–0.2	−0.3	.46	−1.1–0.5	**−0.9**	**.04**	**−1.8–0.04**	**−1.3**	**<.01**	**−2.1–0.6**	0.8	.06	−0.1–1.7
Supratentorial lateral	−2.6	.44	−9.3–4.1	−0.1	.97	−6.6–6.4	2.4	.47	−4.1–8.8	**−5.9**	**.04**	**−11.5–0.3**	4.1	.12	−1.1–9.3
Supratentorial midline	3.2	.39	−4.0–10.3	2.9	.43	−4.2–9.9	3.2	.38	−4.0–10.3	0.1	.99	−6.2–6.3	2.8	.34	−3.1–8.7
Supratentorial lateral * Time dx	−1.1	.07	−2.3–0.1	−1.0	.15	−2.3–0.4	1.0	.18	−0.5–2.4	0.2	.70	−1.0–1.4	−0.5	.42	−1.9–0.8
Supratentorial midline * Time dx	**−1.4**	**.03**	**−2.6–0.1**	−0.6	.36	−2.0–0.7	0.5	.47	−1.0–2.1	0.5	.47	−0.8–1.7	−0.6	.45	−2.0–0.9
Model 6. Increased intracranial pressure (IICP) at diagnosis (as compared to no IICP at diagnosis)															
Intercept	**99.3**	**<.01**	**95.0–103.6**	**100.3**	**<.01**	**96.2–104.4**	**92.8**	**<.01**	**88.7–96.9**	**92.1**	**<.01**	**88.5–95.8**	**99.0**	**<.01**	**95.7–102.3**
Time dx	**−1.2**	**.01**	**−2.1–0.3**	−0.7	.13	−1.6–0.2	0.2	.65	−0.7–1.1	**−0.9**	**.02**	**−1.7–0.1**	0.8	.06	−0.04–1.7
IICP at diagnosis	0.2	.94	−5.6–6.0	−3.1	.28	−8.7–2.5	−3.2	.26	−8.9–2.4	3.0	.23	−1.9–8.0	−0.8	.72	−5.4–3.7
IICP at dx* Time dx	−0.3	.57	−1.4–0.8	−0.02	.97	−1.2–1.2	**−1.3**	**.03**	**−2.4–0.1**	−0.3	.54	−1.3–0.7	−0.5	.35	−1.7–0.6

(*Continued*)

Table 3. (Continued).

	Verbal reasoning			Non-verbal reasoning			Cognitive processing speed			Working memory			Verbal learning		
	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI	β	*p*	95%CI
Model 7. VP shunt or ventriculostomy (as compared to no VP shunt placement or ventriculostomy)															
Intercept	**99.3**	**<.01**	**96.1102.5**	**98.5**	**<.01**	**95.5–101.6**	**92.1**	**<.01**	**89.1–95.2**	**93.5**	**<.01**	**90.8–96.2**	**98.5**	**<.01**	**96.1–101.0**
Time dx	**−1.1**	**<.01**	**−1.7–0.5**	−0.4	.15	−1.0–0.2	−0.5	.11	−1.1–0.1	**−1.1**	**<.01**	**−1.7–0.6**	**0.8**	**.01**	**0.2–1.4**
VP shunt or ventriculostomy	0.4	.91	−7.0–7.9	0.6	.88	−6.9–8.1	−5.4	.16	−13.0–2.2	1.6	.64	−4.9–8.1	1.0	.76	−5.3–7.3
Time dx*VP shunt or ventriculostomy	**−1.5**	**.04**	**−2.8–0.1**	**−1.5**	**.04**	**−3.0–0.1**	−0.8	.26	−2.3–0.7	0.2	.74	−1.1–1.6	**−1.9**	**.01**	**−3.3–0.4**
Model 8. Relapse at any point before end of study period															
Intercept	**97.9**	**<.01**	**94.3101.4**	**97.5**	**<.01**	**94.1–100.9**	**89.7**	**<.01**	**86.3–93.2**	**92.7**	**<.01**	**89.6–95.7**	**97.4**	**<.01**	**94.5–100.4**
Time dx	**−1.3**	**<.01**	**−2.0–0.6**	**−0.7**	**.046**	**−1.4–0.01**	−0.7	.06	−1.40.04	**−1.0**	**<.01**	**−1.7–0.4**	**0.9**	**.03**	**0.1–1.6**
Relapse	4.5	.14	−1.5–10.5	3.3	.26	−2.4–9.0	4.2	.16	−1.7–10.0	3.2	.22	−2.0–8.4	2.7	.29	−2.2–7.6
Relapse* Time dx	−0.3	.56	−1.5–0.8	0.1	.86	−1.11.3	0.3	.59	−0.9–1.5	−0.2	.74	−1.2–0.9	−0.9	.16	−2.1–0.4
Model 9. treatment (as compared to no treatment or surgery only)															
Intercept	**98.5**	**<.01**	**94.6–102.4**	**100.0**	**<.01**	**96.2–103.8**	**92.9**	**<.01**	**89.1–96.6**	**95.0**	**<.01**	**91.8–98.3**	Convergence not achieved		
Time dx	**−1.1**	**.01**	**−1.8–0.3**	−0.5	.22	−1.4–0.3	−0.3	.52	−1.1–0.6	**−1.2**	**<.01**	**−1.9–0.5**			
Chemotherapy	4.3	.50	−8.3–17.0	−0.3	.97	−14.3–13.7	−1.5	.86	−18.4–15.5	9.4	.14	−3.2–22.1			
Focal RT	3.2	.51	−6.3–12.7	−2.4	.59	−11.3–6.4	−5.6	.21	−14.2–3.1	−0.2	.95	−7.8–7.3			
Focal RT + chemotherapy	3.5	.49	−6.5–13.6	−1.0	.84	−10.6–8.6	−2.8	.56	−12.4–6.8	−3.8	.37	−12.2–4.5			
Focal RT+WBRT +chemotherapy	−0.03	.99	−8.3–8.3	−4.4	.27	−12.2–3.5	−3.9	.33	−11.8–4.0	−5.8	.10	−12.7–1.1			
Time dx* chemotherapy	−0.9	.45	−3.3–1.5	−1.7	.21	−4.4–1.0	0.1	.96	−3.2–3.3	−0.5	.68	−2.7–1.8			
Time dx* Focal RT	−0.4	.55	−1.8–1.0	0.2	.77	−1.2–1.6	−0.1	.93	−1.5–1.3	0.6	.31	−0.6–1.8			
Time dx* focal RT+ chemotherapy	0.1	.92	−1.7–1.9	−0.4	.69	−2.4–1.6	−0.7	.44	−2.7–1.2	−0.6	.51	−2.2–1.1			
Time dx*focal RT +WBRT+ chemotherapy	**−2.0**	**.03**	**−3.8–0.1**	−1.7	.10	−3.7–0.3	**−2.3**	**.02**	**−4.2–0.4**	−0.7	.42	−2.5–1.1			

Multilevel linear models. Separate models for each cognitive outcome and for each clinical variable. Independent variables in the models are listed in the left column and cognitive outcome variables in the top row. β=non-standardized estimates in standard scores ($m = 100$ sd = 15). Time dx=time since diagnosis in years. IICP=increased intracranial pressure at diagnosis. VP shunt=ventriculo-peritoneal shunt. RT=radiotherapy. WBRT: whole brain radiotherapy. Radiotherapy with photons. **Bold** text indicates $p < 0.05$. Non-dichotomous categorical variables (tumor location and treatment) were dummy-coded with "infratentorial location" and "no treatment/surgery only" as reference categories.

Narrative Memory (Korkman, 2000) vs Nepsy Wordlist memory (Korkman, 2000)/Rey Auditory Verbal Learning Test (Schmidt, 1996), an explorative analysis was done comparing Nepsy Narrative Memory results with word list results. Seventy-one of 307 (23%) assessments of verbal learning were performed with children <8 years of age, i.e., with Nepsy Narrative Memory. Results were slightly higher on list learning measures as compared to Narrative Memory (M(sd) 101.1SS(14.2) vs 97.6SS (11.8), $p = 0.04$). Removing those assessments from the analysis impeded further multivariate analyses due to low N. However, a correlation analysis, not controlling for repeated measures, showed no correlation between time since diagnosis and results on measures of verbal learning (Pearson $p = 0.07$, $p = .29$). That is, a change of assessment method at 8 years of age might have inflated the positive association, but has probably not shadowed a negative association.

Female sex was associated with significantly higher scores on most neurocognitive measures (verbal reasoning $\beta = 5.8$SS, $p = .049$; cognitive processing speed $\beta = 12.6$SS, $p < .01$; working memory $\beta = 7.2$SS, $p < .01$; verbal learning $\beta = 4.90$SS, $p = .03$) but was not associated with rate of decline. There were no significant sex differences in clinical or demographic variables (Table 1). However, there were non-significant trends, such that males compared to females tended to be younger at diagnosis ($p = 8.0$ years vs 9.1 years, $p = .14$), to have a higher prevalence of embryonal tumors (17.0% vs 9.5%, $p = .58$), and to have received WBRT (18.2% vs 12.7%, $p = .80$). Supratentorial lateral localization of tumor (as compared to infratentorial localization) was associated with significantly lower scores on measures of working memory (β = -5.9SS, $p = .04$).

Treatment with VP shunt placement (or ventriculostomy) was associated with a faster decline over time (i.e., a statistically significant interaction effect) in measures of verbal (β = -1.5SS/year, $p = .04$) and non-verbal reasoning (β = -1.5SS/year, $p = .04$) and verbal learning (β = -1.9SS/year, $p = .01$), see Table 3. For verbal learning, the same model showed a positive one-way association ($\beta = 0.8$SS/year; $p = .01$), resulting in a total decline of −1.1 SS/year for survivors treated with VP shunt placement.

Older age at diagnosis was associated with a slower rate of decline in measures of cognitive processing speed (β = -0.2SS/year of age at diagnosis, $p = .03$). Increased intracranial pressure (IICP) at diagnosis was associated with a faster rate of decline in measures of cognitive processing speed (β = -1.3SS/year, $p = .03$). Since the majority of survivors receiving a VP shunt also had IICP at diagnosis (exceptions being three survivors receiving VP shunt years after first diagnosis) an explorative analysis was done removing survivors receiving a VP shunt. In doing so, the association was still present, however statistically non-significant (β = -0.9SS/year; $p = .13$).

Treatment with WBRT together with focal RT, chemotherapy, and surgery (as compared to no treatment/surgery only) was associated with a faster decline in measures of verbal reasoning (β = -2.0SS/year; $p = .03$) and cognitive processing speed (β = -2.3SS/year; $p = .02$), i.e., scores for those survivors declined 2.3 standard scores more per year, adding to a total decline of 3.3 standard scores per year for measures of verbal reasoning.

Discussion

This is one of the first larger European studies examining longitudinal outcome in survivors of PBT. In a heterogeneous sample of survivors, longitudinal

neuropsychological assessments revealed a pattern of general decline in age-related neurocognitive test scores, following diagnosis and treatment of PBT. This pattern was present regardless of treatment received and clinical variables, which is a new finding since most previous studies have shown neurocognitive development after treatment with surgery only to be either stable or improving (Fouladi et al., 2004; Fraley et al., 2019; Heitzer et al., 2019; Kahalley et al., 2019; Packer et al., 1989; Stargatt et al., 2007). Scores for survivors treated with WBRT together with focal RT and chemotherapy declined at a faster rate, as did scores for survivors treated with ventriculo-peritoneal shunting. On measures of cognitive processing speed, the rate of decline was faster for younger survivors and for survivors with IICP at diagnosis. Demographic and clinical variables associated with lower neurocognitive scores but not affecting rate of decline were male sex and having a supratentorial lateral tumor. Verbal learning scores did not decline over time, except for survivors treated with VP shunting or ventriculostomy. Factors not associated with neurocognitive outcomes were relapse and tumor size.

The observed decline in neurocognitive scores after treatment with WBRT is in line with previous research reporting a decline of 2–3 standard scores per year in survivors receiving WBRT (Knight et al., 2014; Moxon-Emre et al., 2014; Mulhern et al., 2005; Palmer et al., 2013; Ris et al., 2013). Importantly, the survivors in this study were treated with photon WBRT. A 2015 study reported promising results regarding neurocognitive outcomes following proton radiation therapy for PBT (Pulsifer et al., 2015). However, a more recent study, comparing focal versus whole-brain proton RT, found WBRT to be associated with declining neurocognitive scores, but at a slower pace (Kahalley et al., 2019). Thus, survivors treated with WBRT continue to be at high risk for a less favorable neurocognitive outcome and should be offered continuous neuropsychological rehabilitation.

We found declining neurocognitive scores also for survivors not receiving WBRT, irrespective of other treatments received (focal irradiation, chemotherapy, and surgery). In fact, we found the percentage of survivors scoring within the impaired range on all measures except verbal learning, to be very high (28–55% impaired as compared to 10% in national norms) at assessments performed more than 6 years post-diagnosis. Results from previous studies regarding survivors treated with focal irradiation are inconclusive, with some reporting a decline in neurocognitive scores (Willard et al., 2019), while others do not (Ellenberg et al., 1987; Netson et al., 2012, 2013). Previous longitudinal studies on survivors treated with surgery alone are very few and small, and typically report neurocognitive deficits, but no further decline in cognitive scores (Fouladi et al., 2005; Fraley et al., 2019; Kahalley et al., 2019; Packer et al., 1989; Stargatt et al., 2007). However, our results are in line with one previous study, showing declines in measures of non-verbal reasoning and cognitive processing speed in survivors of PBTs treated with surgery alone (Weusthof et al., 2021). In this study, we included pre-surgical evaluations for 42% of the survivors, which might contribute to the findings regarding an overall decline, since some survivors suffer quite extensive sequelae as a result of surgery, e.g., following posterior fossa syndrome (Armstrong et al., 2011; Schmahmann, 2020). Still, scores for verbal and non-verbal reasoning were in the normal range during the first three years post-diagnosis (Table 2), indicating a stagnation/decline in this aspect of neurocognitive functioning several years after diagnosis.

It could be argued that declining neurocognitive scores should be evident in all survivors treated for brain tumors, especially in children younger at diagnosis, since tumor and surgery may produce memory and attention deficits, which in turn may impede further acquisition of skills and knowledge (Dennis et al., 1998; J. Limond & Leeke, 2005). In addition, deficits in certain skills, such as those associated with executive functioning and working memory, may be present at a younger age, but become more evident as the child ages, i.e., the child "grows into the injury." Clearly, more research is needed to understand longitudinal development in survivors not treated with WBRT. These survivors need personalized neuropsychological follow-up, since some survivors require extensive rehabilitation, and others do not experience any neurocognitive late complications. Cost-efficient health-care strategies are needed to allocate neuropsychological resources to those survivors who need it the most.

Consistent with previous studies, examining survivors treated with WBRT (Ellenberg et al., 1987) or focal CRT (Willard et al., 2019) we found placement of a VP shunt to be associated with a faster decline in neurocognitive scores. As noted above, longitudinal studies of survivors of PBTs treated with surgery are only scarce and, to our knowledge, no previous study has been able to identify any risk factors for decline in neurocognitive scores or, in most studies, any decline in cognitive scores at all (Fraley et al., 2019; Kahalley et al., 2019; Packer et al., 1989; Stargatt et al., 2007). Nevertheless, cross-sectional studies have found placement of a VP shunt to be associated with worse neurocognitive outcome (Reimers et al., 2003). Ventriculo-peritoneal shunt placement could be regarded as a proxy for the level of brain damage, as it is most often needed when circulation of cerebrospinal fluid (CSF) cannot be restored even after the tumor is removed. In the present study, 55% of the study group ($n = 83$) had IICP at diagnosis, but only 19% ($n = 29$) of the total group needed VP shunting or a ventriculostomy, i.e., CSF circulation was restored in most cases. For measures of cognitive processing speed, IICP at diagnosis (but not placement of VP shunt) was associated with a faster rate of decline, while further explorative analysis showed this association to be non-significant ($n = .12$) when removing survivors treated with VP shunt from the analysis. It is therefore not clear if this association between IICP at diagnosis and a faster decline in scores of cognitive processing speed is a "true" association or a statistical artifact caused by collinearity between IICP and treatment with VP shunting. However, measures of cognitive processing speed were already lowered at pre-surgery assessments, which might be interpreted as IICP before and at diagnosis having a negative impact on processing speed. If so, early detection and treatment of brain tumors involving IICP might be associated with less negative neurocognitive outcomes in survivors. Further studies are needed to explore these hypotheses.

Male sex was associated with lower neurocognitive scores, but sex was not related to the rate of decline in neurocognitive scores. There were no statistically significant sex differences regarding clinical or demographic variables, however, there was a tendency toward males receiving more treatment and being younger at diagnosis, which might account for the lower scores in males. We could not replicate the findings of earlier longitudinal studies showing female survivors to experience a steeper decline in neurocognitive measures after treatment with WBRT (Netson et al., 2013; Ris et al., 2001). Since this study includes survivors treated with surgery only, another

hypothesis might be that females are more vulnerable to neurocognitive sequelae after PBT treatment with chemotherapy and/or radiation, while males are more vulnerable to sequelae related to the PBT itself, e.g., surgery and hydrocephalus. This hypothesis is further supported by previous research showing female sex to be a risk factor for neurocognitive impairment in survivors of acute lymphoblastic leukemia (ALL) treated with WBRT, while the same findings have not been consistently reported in survivors of brain tumors (Armstrong et al., 2007). Clearly, more studies on sex differences in survivors of PBTs are needed in both irradiated and non-irradiated survivors, and variables like hydrocephalus, tumor size, and incidence and survival rates need to be taken into account, since both incidence and survival rates show sex differences (Lannering et al., 2009; Weil et al., 1998).

The present study revealed that some aspects of neurocognitive functioning remained largely intact in the years after treatment for PBT. Verbal learning showed a positive or stable trajectory. The positive trajectory might be due to utilization of different measures for younger and older children, but the subsequent exploratory analysis did not indicate declining scores but rather a stable development. This is consistent with two previous longitudinal studies (DiPinto et al., 2012; Spiegler et al., 2004) finding stable performance on word list learning, while several cross-sectional studies (Kieffer-Renaux et al., 2000; Robinson et al., 2013) have found this aspect of functioning to be suppressed along with other neurocognitive abilities (Carey et al., 2001). However, we found declining verbal learning scores for survivors having received a VP shunt (or a ventriculostomy). A cross-sectional study, examining 26 survivors of intracranial pediatric germ cell tumors, found a high prevalence of memory deficits, more so in survivors diagnosed at an older age (Wilkening et al., 2011). These deficits were not associated with general neurocognitive ability or with IICP at diagnosis. The authors argued that these memory deficits may be due to damage, caused by the tumor or treatment, to central structures associated with memory performance (hippocampus, amygdala, fornix, thalamus, and, tentatively, also the habenular nuclei) (Wilkening et al., 2011). The decline in verbal learning measures for survivors with VP shunt in the present study might be associated with damage to these structures in a subgroup of survivors. However, the absence of repeated structural assessments, small sample size, and heterogeneity of this sample limit the inferences that can be drawn about damage to brain structures and specific neurocognitive impairments in survivors of PBTs. Further studies are needed.

The above findings must be viewed within the context of certain limitations. While the sample was relatively large and drawn from a specialist center serving the entire region of southern Sweden, these findings might not apply to other cohorts of survivors of PBTs. While the participation rate was high with 88.3% of survivors diagnosed undergoing at least one neurocognitive assessment, approximately half of the survivors only had one or two assessments. Drop-out analyses showed very few differences in clinical characteristics between survivors undergoing 1–2 versus 3 or more assessments, except that the latter group were younger at diagnosis and had a higher rate of relapses (Supplemental Table S1). Patients who entered the PBT clinic (and this study) closer to their 18th birthday had fewer follow-up assessments as they were transferred to adult health care at 18 years of age, thus the younger age at diagnosis in survivors undergoing more assessments. Since younger age at diagnosis is associated with a higher rate of neurocognitive sequelae (Oyefiade et al., 2021) and a decline in

cognitive scores (Willard et al., 2019) this might inflate the rate of survivors showing declining neurocognitive scores. There is also a risk that survivors experiencing more severe neurocognitive sequelae might have been undergoing more assessments, since clinical assessments outside the timepoints scheduled for the neuropsychological follow-up program, were included in the study. This assumption was not confirmed in the drop-out analyses, with no differences on neurocognitive test scores at any assessment point, between survivors who did or did not undergo a subsequent assessment (Supplemental Table S2). It is still possible though that survivors who experienced a decline in neurocognitive scores were more likely to be offered and complete further neurocognitive assessments, thereby inflating the finding of declining neurocognitive scores for all survivors.

Another limitation is the heterogeneity in time since diagnosis at first assessment. While the majority of survivors (81%) underwent a first assessment within two years post-diagnosis, the remaining survivors underwent a first assessment three to 13 years post-diagnosis (Figure 2). Assuming that neurocognitive sequelae in survivors of PBTs are the result of multiple factors, whose influence may come at different time points before, during

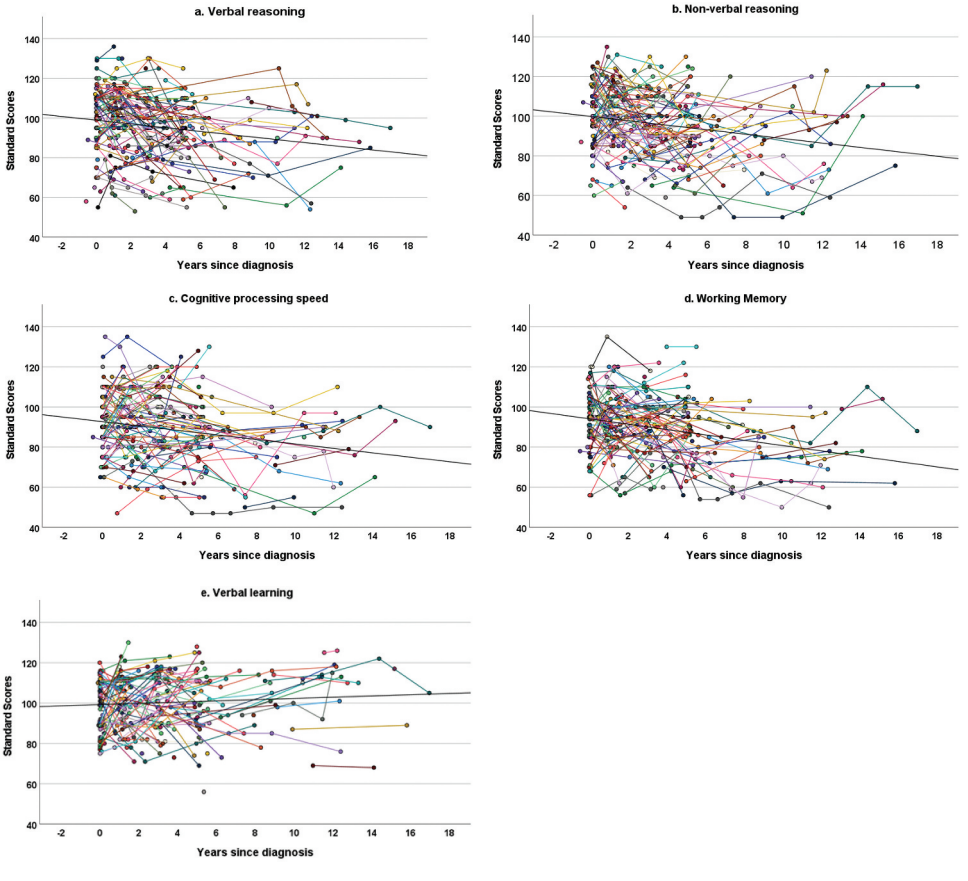

Figure 2. Spaghetti plots showing neurocognitive scores over time post-diagnosis. Each line represents one individual. All cognitive scores in standard scores (m=100, sd=15). Regression line unadjusted for clinical factors.

and after the PBT is diagnosed, the overall neurocognitive trajectory is likely to be highly idiosyncratic and develop very different, e.g., from pre-surgery to five years post-diagnosis compared to from 5 to 10 years post-diagnosis. For example, Stargatt et al. (Stargatt et al., 2007) propose different neurocognitive trajectories following a PBT, with one timeline for tumor/surgery-related injury (neurocognitive scores declining during the first year, then stable) and another for chemotherapy and CRT-related injury (later decline in neurocognitive scores). The heterogeneity in the present study might shadow declines in neurocognitive scores as most studies exploring not only linear but quadratic changes, find declines in neurocognitive scores to plateau several years post-diagnosis (Mabbott et al., 2005; Palmer et al., 2003; Spiegler et al., 2004). As the statistical models used here depict not only early development but also development several years post-diagnosis, declines in neurocognitive scores might not be as apparent. However, this heterogeneity is also a strength since the present data reflects a longer time span and survivorship in different post-treatment periods. Also, the use of MLM:s makes it possible to account for heterogeneity in assessment time points. Nevertheless, a related limitation is the fact that the size of the present sample limited model fitting to linear trends, while the development of neurocognitive sequelae in survivors of PBTs is likely to be non-linear. More studies are needed with larger samples, including more pre-diagnosis/pre-treatment data on cognitive functioning, follow-up periods extending into adulthood, and multiple statistical approaches to capture the varying trajectories of neurocognitive sequelae after a PBT is diagnosed and treated (Willard et al., 2019).

Overall, the present study finds that irrespective of treatment type, survivors of PBTs are at increased risk of significant declines in neurocognitive scores over time, except for verbal learning scores, which appeared to be stable or improving. Male sex and/or supra-tentorial lateral localization of tumor were associated with lower overall cognitive performance, but not with a faster decline in measures of neurocognitive functioning. Survivors who received WBRT together with focal CRT, chemotherapy, and surgery, and/or a VP shunt experienced the fastest rate of decline in neurocognitive scores. Further systematic, long-term neuropsychological follow-up studies of survivors of PBTs are needed, whether they are treated with CRT or not, to better identify individuals in need of neurocognitive rehabilitation interventions and to identify cancer treatment protocols that yield fewer and less severe neurocognitive sequelae, while maintaining high survival rates.

Acknowledgements

We would also like to acknowledge the survivors and their families, and the staff of the Pediatric Neuro-Oncology Service at Skåne University Hospital. Additional thanks are extended to Per-Erik Isberg for statistical guidance and Thomas Wiebe for helpful advice and inspiration.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The study was supported by the Swedish Childhood Cancer Fund under grant [NBCNSDoktBidr09/006], Skåne University Hospital Psychology Research and Development Grant [2020 and 2021], and the Jonas Foundation.

ORCID

Ingrid Tonning Olsson http://orcid.org/0000-0002-1643-8686
Lars Hjorth http://orcid.org/0000-0002-8302-7174
Per Munck Af Rosenschöld http://orcid.org/0000-0002-5988-8994
Åsa Hammar http://orcid.org/0000-0002-3852-8551
Sean Perrin http://orcid.org/0000-0002-5468-4706

Ethics

Data in this article were systematically recorded for clinical purposes and for internal monitoring. The ethical vetting board of Lund reviewed the project and waived the requirements for further informed consent from the patients (Dnr2013/68).

References

Aarsen, F. K., Van Dongen, H. R., Catsman-Berrevoets, C. E., Van Mourik, M., & Catsman-Berrevoets, C. E. (2004). Long-term sequelae in children after cerebellar astrocytoma surgery. *Neurology*, *62*(8), 1311–1316. https://doi.org/10.1212/01.WNL.0000120549.77188.36

Armstrong, G. T., Huang, S., Robison, L. L., Srivastava, D., Sanford, R., Ellison, D. W., Merchant, T. E., Hudson, M. M., Hoehn, M. E., Robison, L. L., Gajjar, A., & Morris, E. B. (2011). Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro-Oncology*, *13*(2), 223–234. https://doi.org/10.1093/neuonc/noq178

Armstrong, G. T., Sklar, C. A., Hudson, M. M., & Robison, L. L. (2007). Long-term health status among survivors of childhood cancer: Does sex matter? *Journal of Clinical Oncology*, *25*(28), 4477–4489. https://doi.org/10.1200/JCO.2007.11.2003

Ater, J. L., Moore, B. D., 3rd, Francis, D. J., Castillo, R., Slopis, J., & Copeland, D. R. (1996). Correlation of medical and neurosurgical events with neuropsychological status in children at diagnosis of astrocytoma: Utilization of a neurological severity score. *Journal of Child Neurology*, *11*(6), 462–469. https://doi.org/10.1177/088307389601100610

Bayley, N. (2006). *Bayley scales of infant and toddler development–third edition*. Pearson Education, Inc.

Beebe, D. W., Ris, M. D., Armstrong, F. D., Fontanesi, J., Mulhern, R., Holmes, E., & Wisoff, J. H. (2005). Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: Evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). *Journal of Clinical Oncology*, *23*(22), 5198–5204. https://doi.org/10.1200/JCO.2005.06.117

Brinkman, T. M., Krasin, M. J., Liu, W., Armstrong, G. T., Ojha, R. P., Sadighi, Z. S., Gupta, P., Kimberg, C., Srivastava, D., Merchant, T. E., Gajjar, A., Robison, L. L., Hudson, M. M., & Krull, K. R. (2016). Long-term neurocognitive functioning and social attainment in adult survivors of pediatric CNS tumors: Results from the St Jude lifetime cohort study. *Journal of Clinical Oncology*, *34*(12), 1358–1367. https://doi.org/10.1200/JCO.2015.62.2589

Carey, M. E., Barakat, L. P., Foley, B., Gyato, K., & Phillips, P. C. (2001). Neuropsychological functioning and social functioning of survivors of pediatric brain tumors: Evidence of non-verbal learning disability. *Neuropsychology Development Cognition C Child Neuropsychology*, *7*(4), 265–272. https://doi.org/10.1076/chin.7.4.265.8730

Dennis, M., Ross Hetherington, C., & Spiegler, B. J. (1998). Memory and attention after childhood brain tumors. *Medical and Pediatric Oncology*, *30* Suppl 1 , 25–33.

de Ruiter, M. A., van Mourik, R., Schouten van Meeteren, A. Y., Grootenhuis, M. A., & Osterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: A meta-analysis. *Developmental Medicine & Child Neurology*, *55*(5), 408–417. https://doi.org/10.1111/dmcn.12020

De Winter, A. E., BD, M., 3rd, JM, S., Ater, J. L., & Copeland, D. R. (1999). Brain tumors in children with neurofibromatosis: Additional neuropsychological morbidity? *Neuro-Oncology*, *1*(4), 275–281. https://doi.org/10.1093/neuonc/1.4.275

DiPinto, M., Conklin, H. M., Li, C., & Merchant, T. E. (2012). Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma. *International Journal of Radiation Oncology, Biology, Physics*, *84*(3), e363–9. https://doi.org/10.1016/j.ijrobp.2012.03.066

Ellenberg, L., McComb, J. G., Siegel, S. E., & Stowe, S. (1987). Factors affecting intellectual outcome in pediatric brain tumor patients. *Neurosurgery*, *21*(5), 638–644. https://doi.org/10.1227/00006123-198711000-00006

Fouladi, M., Chintagumpala, M., Laningham, F. H., Ashley, D., Kellie, S. J., Langston, J. W., McCluggage, C. W., Woo, S., Kocak, M., Krull, K., Kun, L. E., Mulhern, R. K., & Gajjar, A. (2004). White matter lesions detected by magnetic resonance imaging after radiotherapy and high-dose chemotherapy in children with medulloblastoma or primitive neuroectodermal tumor. *Journal of Clinical Oncology*, *22*(22), 4551–4560. https://doi.org/10.1200/JCO.2004.03.058

Fouladi, M., Gilger, E., Kocak, M., Wallace, D., Buchanan, G., Reeves, C., Robbins, N., Merchant, T., Kun, L. E., Khan, R., Gajjar, A., & Mulhern, R. (2005). Intellectual and functional outcome of children 3 years old or younger who have CNS malignancies. *Journal of Clinical Oncology*, *23*(28), 7152–7160. https://doi.org/10.1200/JCO.2005.01.214

Fraley, C. E., Thigpen, J. C., Pearson, M. M., Kuttesch, J. F., Desjardins, L., Hoskinson, K. R., Alvarado-Gonzalez, A., Esbenshade, A. J., Pastakia, D., Friedman, D. L., Wellons, J. C., McNally, C. M., Siciliano, R. E., & Compas, B. E. (2019). Predictors of cognitive function in pediatric brain tumor patients: Pre-surgery through 24-month follow-up. *Applied Neuropsychology Child*, *10*(4), 1–8. https://doi.org/10.1080/21622965.2019.1706179

Heitzer, A. M., Raghubar, K., Ris, M. D., Minard, C. G., Gragert, M. N., Stancel, H. H., Orobio, J., Xue, J., Whitehead, W., Okcu, M. F., Chintagumpala, M., & Kahalley, L. S. (2019). Neuropsychological functioning following surgery for pediatric low-grade glioma: A prospective longitudinal study. *Journal of Neurosurgery Pediatrics*, 1–9. https://doi.org/10.3171/2019.9.PEDS19357

IBM Corp, . (2020 IBM SPSS, statistics for Windows, Version 27.0 Computer software). (ed.). .

Jacobson, L. A., Mahone, E. M., Yeates, K. O., & Ris, M. D. (2019). Processing speed in children treated for brain tumors: Effects of radiation therapy and age. *Child Neuropsychology*, *25*(2), 217–231. https://doi.org/10.1080/09297049.2018.1456517

Kahalley, L. S., Conklin, H. M., Tyc, V. L., Hudson, M. M., Wilson, S. J., Wu, S., Xiong, X., & Hinds, P. S. (2013). Slower processing speed after treatment for pediatric brain tumor and acute lymphoblastic leukemia. *Psycho-Oncology*, *22*(9), 1979–1986. https://doi.org/10.1002/pon.3255

Kahalley, L. S., Douglas Ris, M., Mahajan, A., Fatih Okcu, M., Chintagumpala, M., Paulino, A. C., Whitehead, W. E., Minard, C. G., Stancel, H. H., Orobio, J., Xue, J. J., Warren, E. A., & Grosshans, D. R. (2019). Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. *Neuro-Oncology*, *21*(6), 809–818. https://doi.org/10.1093/neuonc/noz041

Kieffer-Renaux, V., Bulteau, C., Grill, J., Kalifa, C., Viguier, D., & Jambaque, I. (2000). Patterns of neuropsychological deficits in children with medulloblastoma according to craniospatial irradiation doses. *Developmental Medicine and Child Neurology*, *42*(11), 741–745. https://doi.org/10.1017/S0012162200001377

Kieffer-Renaux, V., Viguier, D., Raquin, M. A., Laurent Vannier, A., Habrand, J.-L., Dellatolas, G., Kalifa, C., Hartmann, O., & Grill, J. (2005). Therapeutic schedules influence the pattern of

intellectual decline after irradiation of posterior fossa tumors. *Pediatric Blood & Cancer*, *45*(6), 814–819. https://doi.org/10.1002/pbc.20329

Knight, S. J., Conklin, H. M., Palmer, S. L., Schreiber, J. E., Armstrong, C. L., Wallace, D., Bonner, M., Swain, M. A., Evankovich, K. D., Mabbott, D. J., Boyle, R., Huang, Q., Zhang, H., Anderson, V. A., & Gajjar, A. (2014). Working Memory abilities among children treated for medulloblastoma: Parent report and child performance. *Journal of Pediatric Psychology*, *39*(5), 501–511. https://doi.org/10.1093/jpepsy/jsu009

Korkman, M. (2000). *Nepsy handbok*. Psykologiförlaget.

Krull, K. R., Hardy, K. K., Kahalley, L. S., Schuitema, I., & Kesler, S. R. (2018). Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. *Journal of Clinical Oncology*, *36*(21), 2181–2189. https://doi.org/10.1200/JCO.2017.76.4696

Lannering, B., Sandstrom, P. E., Holm, S., Lundgren, J., Pfeifer, S., Samuelsson, U., Strömberg, B., & Gustafsson, G. (2009). Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984-2005. *Acta Paediatrica*, *98*(10), 1620–1627. https://doi.org/10.1111/j.1651-2227.2009.01417.x

Limond, J. A., Bull, K. S., Calaminus, G., Kennedy, C. R., Spoudeas, H. A., & Chevignard, M. P. (2015). Quality of survival assessment in European childhood brain tumour trials, for children aged 5 years and over. *European Journal of Paediatric Neurology*, *19*(2), 202–210. https://doi.org/10.1016/j.ejpn.2014.12.003

Limond, J., & Leeke, R. (2005). Practitioner review: Cognitive rehabilitation for children with acquired brain injury. *Journal of Child Psychology and Psychiatry*, *46*(4), 339–352. https://doi.org/10.1111/j.1469-7610.2004.00397.x

Limond, J., Thomas, S., Bull, K. S., Calaminus, G., Lemiere, J., Traunwieser, T., van Santen, H. M., Weiler, L., Spoudeas, H. A., & Chevignard, M. (2020). Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years. *European Journal of Paediatric Neurology*, *25*, 59–67. https://doi.org/10.1016/j.ejpn.2019.10.002

Mabbott, D. J., Spiegler, B. J., Greenberg, M. L., Rutka, J. T., Hyder, D. J., & Bouffet, E. (2005). Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *Journal of Clinical Oncology*, *23*(10), 2256–2263. https://doi.org/10.1200/JCO.2005.01.158

Merchant, T. E., Schreiber, J. E., Wu, S., Lukose, R., Xiong, X., & Gajjar, A. (2014). Critical combinations of radiation dose and volume predict intelligence quotient and academic achievement scores after craniospinal irradiation in children with medulloblastoma. *International Journal of Radiation Oncology*Biology*Physics*, *90*(3), 554–561. https://doi.org/10.1016/j.ijrobp.2014.06.058

Moxon-Emre, I., Bouffet, E., Taylor, M. D., Laperriere, N., Scantlebury, N., Law, N., Spiegler, B. J., Malkin, D., Janzen, L., & Mabbott, D. (2014). Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. *Journal of Clinical Oncology*, *32*(17), 1760–1768. https://doi.org/10.1200/JCO.2013.52.3290

Mulhern, R. K., Palmer, S. L., Merchant, T. E., Wallace, D., Kocak, M., Brouwers, P., Krull, K., Chintagumpala, M., Stargatt, R., Ashley, D. M., Tyc, V. L., Kun, L., Boyett, J., & Gajjar, A. (2005). Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *Journal of Clinical Oncology*, *23*(24), 5511–5519. https://doi.org/10.1200/JCO.2005.00.703

Netson, K. L., Conklin, H. M., Wu, S., Xiong, X., & Merchant, T. E. (2012). A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma. *International Journal of Radiation Oncology, Biology, Physics*, *84*(1), 217–223.e1. https://doi.org/10.1016/j.ijrobp.2011.10.043

Netson, K. L., Conklin, H. M., Wu, S., Xiong, X., & Merchant, T. E. (2013). Longitudinal investigation of adaptive functioning following conformal irradiation for pediatric craniopharyngioma and low-grade glioma. *International Journal of Radiation Oncology*Biology*Physics*, *85*(5), 1301–1306. https://doi.org/10.1016/j.ijrobp.2012.10.031

Oprandi, M. C., Oldrati, V., Cavatorta, C., Gandola, L., Massimino, M., Bardoni, A., & Poggi, G. (2022). The influence of Socioeconomic Status (SES) and processing speed on the psychological

adjustment and wellbeing of pediatric brain tumor survivors. *Cancers (Basel)*, *14*(13), 3075. https://doi.org/10.3390/cancers14133075

Oyefiade, A., Paltin, I., De Luca, C. R., Hardy, K. K., Grosshans, D. R., Chintagumpala, M., Mabbott, D. J., & Kahalley, L. S. (2021). Cognitive risk in survivors of pediatric brain tumors. *Journal of Clinical Oncology*, *39*(16), 1718–1726. https://doi.org/10.1200/JCO.20.02338

Packer, R. J., Sutton, L. N., Atkins, T. E., Radcliffe, J., Bunin, G. R., D'Angio, G., Siegel, K. R., & Schut, L. (1989). A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. *Journal of Neurosurgery*, *70*(5), 707–713. https://doi.org/10.3171/jns.1989.70.5.0707

Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., Schreiber, J., Swain, M., Chapieski, L., Mabbott, D., Knight, S., Boyle, R., & Gajjar, A. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: An international, prospective, and longitudinal study. *Journal of Clinical Oncology*, *31*(28), 3494–3500. https://doi.org/10.1200/JCO.2012.47.4775

Palmer, S. L., Goloubeva, O., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L., Merchant, T. E., & Mulhern, R. K. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *Journal of Clinical Oncology*, *19*(8), 2302–2308. https://doi.org/10.1200/JCO.2001.19.8.2302

Palmer, S. L., Mulhern, R. K., Gajjar, A., Glass, J. O., Kun, L. E., Wu, S., Xiong, X., & Mulhern, R. K. (2003). Predicting intellectual outcome among children treated with 35-40 Gy Craniospinal irradiation for medulloblastoma. *Neuropsychology*, *17*(4), 548–555. https://doi.org/10.1037/0894-4105.17.4.548

Patel, S. K., Fernandez, N., Dekel, N., Turk, A., Meier, A., Ross, P., & Rosenthal, J. (2015). Socioeconomic status as a possible moderator of neurocognitive outcomes in children with cancer. *Psycho-Oncology*, *25*(1), 115–118. https://doi.org/10.1002/pon.3797

Pulsifer, M. B., Sethi, R. V., Kuhlthau, K. A., MacDonald, S. M., Tarbell, N. J., & Yock, T. I. (2015). Early cognitive outcomes following proton radiation in pediatric patients with brain and central nervous system tumors. *International Journal of Radiation Oncology*Biology*Physics*, *93*(2), 400–407. https://doi.org/10.1016/j.ijrobp.2015.06.012

Raven, J., Raven, J. C., & Court, J. H. (2000). *Manual for Raven's standard progressive matrices*. Oxford Psychologists Press Ltd.

Reimers, T. S., Ehrenfels, S., Mortensen, E. L., Schmiegelow, M., Sønderkaer, S., Carstensen, H., Schmiegelow, K., & Müller, J. (2003). Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Medical and Pediatric Oncology*, *40*(1), 26–34. https://doi.org/10.1002/mpo.10211

Ris, M. D., & Beebe, D. W. (2008). Neurodevelopmental outcomes of children with low-grade gliomas. *Developmental Disabilities Research Reviews*, *14*(3), 196–202. https://doi.org/10.1002/ddrr.27

Ris, M. D., Beebe, D. W., Armstrong, F. D., Fontanesi, J., Holmes, E., Sanford, R. A., & Wisoff, J. H. (2008). Cognitive and adaptive outcome in extracerebellar low-grade brain tumors in children: A report from the Children's Oncology Group. *Journal of Clinical Oncology*, *26*(29), 4765–4770. https://doi.org/10.1200/JCO.2008.17.1371

Ris, M. D., Packer, R., Goldwein, J., Jones-Wallace, D., & Boyett, J. M. (2001). Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: A Children's Cancer Group study. *Journal of Clinical Oncology*, *19*(15), 3470–3476. https://doi.org/10.1200/JCO.2001.19.15.3470

Ris, M. D., Walsh, K., Wallace, D., Armstrong, F. D., Holmes, E., Gajjar, A., Zhou, T., & Packer, R. J. (2013). Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. *Pediatric Blood & Cancer*, *60*(8), 1350–1357. https://doi.org/10.1002/pbc.24496

Riva, D., Giorgi, C., Nichelli, F., Bulgheroni, S., Massimino, M., Cefalo, G., Gandola, L., Giannotta, M., Bagnasco, I., Saletti, V., & Pantaleoni, C. (2002). Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology*, *59*(1), 48–53. https://doi.org/10.1212/WNL.59.1.48

Robinson, K. E., Fraley, C. E., Pearson, M. M., Kuttesch, J. F., & Compas, B. E. (2013). Neurocognitive late effects of pediatric brain tumors of the posterior fossa: A quantitative review. *Journal of the International Neuropsychological Society*, *19*(1), 44–53. https://doi.org/10.1017/S1355617712000987

Schmahmann, J. D. (2020). Pediatric post-operative cerebellar mutism syndrome, cerebellar cognitive affective syndrome, and posterior fossa syndrome: Historical review and proposed resolution to guide future study. *Child's Nervous System*, *36*(6), 1205–1214. https://doi.org/10.1007/s00381-019-04253-6

Schmidt, M. (1996). *Rey auditory verbal learning test: a handbook*. Western Psychological Services.

Schreiber, J. E., Palmer, S. L., Gurney, J. G., Bass, J. K., Wang, M., Chen, S., Zhang, H., Swain, M., Chapieski, M. L., Bonner, M. J., Mabbott, D. J., Knight, S. J., Armstrong, C. L., Boyle, R., & Gajjar, A. (2014). Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. *Neuro-Oncology*, *16*(8), 1129–1136. https://doi.org/10.1093/neuonc/nou006

Spiegler, B. J., Bouffet, E., Greenberg, M. L., Rutka, J. T., & Mabbott, D. J. (2004). Change in neurocognitive functioning after treatment with cranial radiation in childhood. *Journal of Clinical Oncology*, *22*(4), 706–713. https://doi.org/10.1200/JCO.2004.05.186

Stargatt, R., Rosenfeld, J. V., Maixner, W., & Ashley, D. (2007). Multiple factors contribute to neuropsychological outcome in children with posterior fossa tumors. *Developmental Neuropsychology*, *32*(2), 729–748. https://doi.org/10.1080/87565640701376151

Stavinoha, P. L., Askins, M. A., Powell, S. K., Pillay Smiley, N., & Robert, R. (2018). Neurocognitive and psychosocial outcomes in pediatric brain tumor survivors. *Bioengineering*, *5*(3), 73. https://doi.org/10.3390/bioengineering5030073

Tonning Olsson, I., Alberts, N. M., Li, C., Ehrhardt, M. J., Mulrooney, D. A., Liu, W., Pappo, A. S., Bishop, M. W., Anghelescu, D. L., Srivastava, D., Robison, L. L., Hudson, M. M., Ness, K. K., Krull, K. R., & Brinkman, T. M. (2021). Pain and functional outcomes in adult survivors of childhood cancer: A report from the St. Jude lifetime cohort study. *Cancer*, *127*(10), 1679–1689. https://doi.org/10.1002/cncr.33303

Tonning Olsson, I., Perrin, S., Lundgren, J., Hjorth, L., & Johanson, A. (2014). Long-term cognitive sequelae after pediatric brain tumor related to medical risk factors, age, and sex. *Pediatric Neurology*, *51*(4), 515–521. https://doi.org/10.1016/j.pediatrneurol.2014.06.011

Tonorezos, E. S., Ford, J. S., Wang, L., Ness, K. K., Yasui, Y., Leisenring, W., Sklar, C. A., Robison, L. L., Oeffinger, K. C., Nathan, P. C., Armstrong, G. T., Krull, K., & Jones, L. W. (2019). Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the childhood cancer survivor study. *Cancer*, *125*(17), 3059–3067. https://doi.org/10.1002/cncr.32173

Wechsler, D. (2003). *Wechsler intelligence scale for children - fourth edition (Swedish version 2007)*. The Psychological Corporation.

Weil, M. D., Lamborn, K., Edwards, M. S., Wara, W.M., et al. (1998). Influence of a child's sex on medulloblastoma outcome. *JAMA*, *279*(18), 1474–1476. https://doi.org/10.1001/jama.279.18.1474

Weusthof, K., Lüttich, P., Regnery, S., König, L., Bernhardt, D., Witt, O., Herfarth, K., Unterberg, A., Jungk, C., Farnia, B., Combs, S. E., Debus, J., Rieken, S., Harrabi, S., & Adeberg, S. (2021). Neurocognitive outcomes in pediatric patients following brain irradiation. *Cancers (Basel)*, *13*(14), 3538. https://doi.org/10.3390/cancers13143538

Wilkening, G. N., Madden, J. R., Barton, V. N., Roberts, A., & Foreman, N. K. (2011). Memory deficits in patients with pediatric CNS germ cell tumors. *Pediatric Blood & Cancer*, *57*(3), 486–491. https://doi.org/10.1002/pbc.23096

Willard, V. W., Berlin, K. S., Conklin, H. M., & Merchant, T. E. (2019). Trajectories of psychosocial and cognitive functioning in pediatric patients with brain tumors treated with radiation therapy. *Neuro-Oncology*, *21*(5), 678–685. https://doi.org/10.1093/neuonc/noz010

Williams, A. M., Cheung, Y. T., Hyun, G., Liu, W., Ness, K. K., Ehrhardt, M. J., Mulrooney, D. A., Bhakta, N., Banerjee, P., Brinkman, T. M., Green, D. M., Chemaitilly, W., Huang, I.-C., Srivastava, D., Hudson, M. M., Robison, L. L., & Krull, K. R. (2021). Childhood neurotoxicity

and brain resilience to adverse events during adulthood. *Annals of Neurology*, *89*(3), 534–545. https://doi.org/10.1002/ana.25981

Winterkorn, E. B., Pulsifer, M. B., & Thiele, E. A. (2007). Cognitive prognosis of patients with tuberous sclerosis complex. *Neurology*, *68*(1), 62–64. https://doi.org/10.1212/01.wnl.0000250330.44291.54