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THE SUSPECT STUDY: GETTING INSIGHT INTO STRESS, SLEEP AND COGNITIVE FUNCTIONING.

Improving care for children with a brain tumor

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The research described in this thesis was performed at the Princess Máxima Center for Pediatric Oncology (Utrecht, The Netherlands)

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The SuSPeCT Study: Getting Insight into Stress, Sleep and Cognitive Functioning

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De SuSPeCT studie: inzicht krijgen in stress, slaap en cognitief functioneren
Het verbeteren van de zorg voor kinderen met een hersentumor

PROEFSCHRIFT

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1 Introduction

Pediatric brain tumors

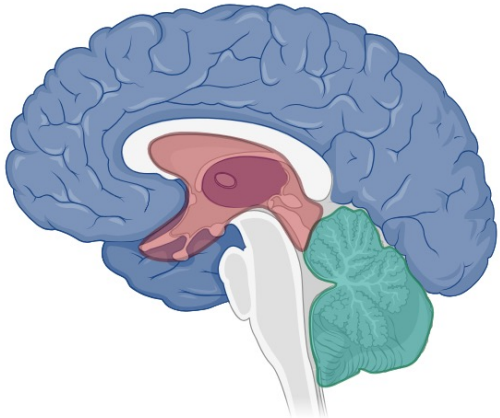
Brain tumors are the most common type of solid tumor in children, concerning about 28% of new pediatric cancer diagnoses [1]. Due to improvements in treatment, about 75% of pediatric brain tumor patients survive their disease [1]. However, survival comes with a cost: the tumor and its treatment are known to pose a high risk for cognitive and psychosocial late effects that can impact quality of life. For example, about 50% of survivors have cognitive problems in domains of attention, executive functioning, memory, and processing speed [2], and they also experience poorer psychological adjustment in areas of depression, anxiety, and distress [3, 4]. These types of difficulties can lead to lower functional and social independence in adulthood [5], and therefore has a significant impact on the survivor and their family. For these reasons, it is important to identify neuropsychological impairments early, in order to guide treatment though all phases of a child's development.

Individual or medical risk factors for cognitive outcome

Most research has focused on demographic, tumor, or treatment-related risk factors for cognitive problems in children with brain tumors. It is well established that younger age at treatment and cranial radiation therapy are risk factors for poorer outcomes [2, 6]; therefore, cranial radiation is avoided for the youngest children when possible. There is also evidence that children who receive surgery [7, 8] or chemotherapy only [9, 10] are at risk for cognitive problems, such as with attention or memory. These findings suggest that the tumor itself, but also treatments required for survival, can impact neural or cognitive performance in the long-term.

Additional risk factors have been explored, such as tumor location, obstructive hydrocephalus, or cerebellar mutism syndrome [6]. As shown in Figure 1, the effects of location are typically separated into cerebral lobes, supratentorial midline, or posterior fossa. However, findings of the impact of tumor location or tumor size on cognitive performance have been inconsistent [11, 12], and may depend on the specific cognitive domain or outcome of interest [13]. Hydrocephalus is increased pressure in the brain that can occur when the tumor is blocking flow of cerebral spinal fluid. Due to this increased pressure, patients may experience acute symptoms (e.g., headache) but it may also lead to long-term consequences including cognitive impairment. Surgery is often required to treat hydrocephalus, such as placement of an external ventricular drain or third ventriculostomy. In survivors, studies have shown that children who experience hydrocephalus at diagnosis [14] or who have persistent severe hydrocephalus [15] have poorer cognitive outcomes. Furthermore, in children with posterior fossa tumors, about 25% develop language, motor, or behavioral problems after surgery. This phenomenon is called cerebellar mutism syndrome (CMS) and although symptoms may improve over time, some children are left with permanent neuropsychological consequences [16]. These findings suggest that various medical complications, including hydrocephalus and CMS, can impact cognitive outcomes in children with brain tumors.

Figure 1 - Tumor location in cerebral lobes (blue), midline (red), or posterior fossa (green)



Overall, these studies suggest that tumor or treatment-related factors may lead to brain damage, thereby impacting brain or cognitive functioning in the long-term. For these reasons, it is important to include these factors when assessing cognitive performance in children with brain tumors. Methods to mitigate this damage, such as reducing radiation doses or radiation fields [17], are an ongoing field of research in pediatric oncology.

Psychological risk factors for cognitive outcome

Over the years, several interventions to diminish cognitive problems have been studied, but the effectiveness is inconsistent. For example, this has included cognitive training [18], pharmaceutical treatments [19], or neurofeedback [20] as an intervention. A recent review shows that, besides focusing on medical treatment as an explanation for cognitive problems, greater attention should be given to approaching childhood cancer as a disruptive event (adverse life event). For instance, this disruptive event may lead to traumatic stress symptoms, which then contributes to cognitive problems [21] and structural or functional changes in the brain [21, 22]. The importance of medical traumatic stress in pediatric cancer was already underlined by Price et al. [23] and could explain some of the cognitive vulnerabilities, especially attention problems. Other researchers [24] have linked pediatric medical traumatic stress to parental medical stress, and therefore, it is also important to consider parental stress when examining children's functioning.

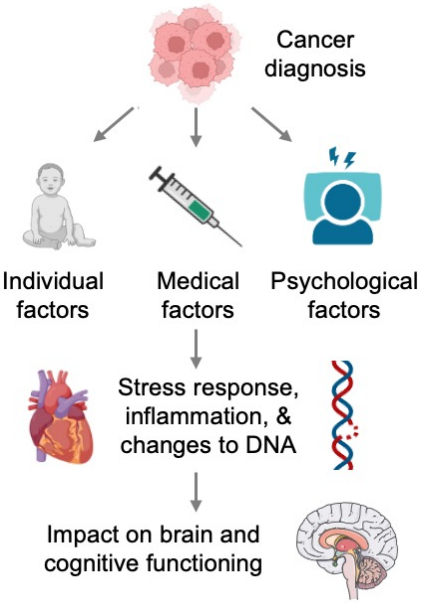
Sleep problems are also found to be highly prevalent in pediatric brain tumor patients. In a systematic review, our research group recently showed that children and young adults with brain tumors have significant daytime sleepiness, hypersomnia, or narcolepsy, with higher body mass index and hypothalamic involvement as potential risk factors for poorer sleep patterns [25]. It is known that poor sleep can impact both cognitive [26] or brain [27] function, which highlights the importance of healthy sleep for neuropsychological functioning. Furthermore, (traumatic) stress often leads to sleep problems, and stress is one of the most important maintaining factors of insomnia [28]. Therefore, these studies provide evidence for

the prevalence of sleep problems in pediatric brain tumors, and how medical or stress factors may further influence the quality of sleep in this population.

Recently, our group showed that sleep problems in childhood brain tumor survivors were independently associated with lower ratings of cognitive performance, particularly in executive functioning [26]. From clinical experience, it has become clear that children who are referred to the outpatient clinic because of sleep and cognitive complains often experience traumatic stress symptoms. A review by Rodenburg et al. [29] describes several studies in which eye movement desensitization and reprocessing (EMDR) treatment appears to be effective in treating a wide range of trauma-related symptoms in children. Furthermore, EMDR may also lead to improvement of cognitive problems, as shown in studies with adult trauma survivors [30]. Thus, targeting sleep or stress problems may also improve cognitive performance in other groups, including pediatric brain tumor.

Together, problems with sleep and stress can further exacerbate cognitive difficulties and brain dysfunction. Regardless of whether sleep problems arise as a result of childhood cancer or due to stress symptoms, sleep has been suggested as being a potential predictor of cognitive problems. In addition, both sleep and stress problems have been hypothesized to impact brain development in the long-term. It is important that both traumatic stress and sleep are further explored in relation to cognitive problems in pediatric brain tumors, as both may provide possible opportunities for interventions in this vulnerable patient group.

Figure 2 - Factors associated with cognitive problems in pediatric brain tumors



Mechanisms of cognitive impairment

There are various mechanisms that could explain why children with brain tumors experience cognitive impairment in the long-term. As noted above, there are various individual, medical, or psychological factors that are associated with cognitive outcomes. These factors can lead to heightened stress or inflammatory responses, which then alters gene expression and brain development [31, 32] (Figure 2). The use of non-invasive methods, such as neuroimaging, can help to identify these pathophysiological mechanisms of cognitive impairments, which can then be used to develop novel interventions. Various studies have shown that cranial radiation is associated with white matter alterations in the brain, and white matter metrics at an early phase may be able to predict the onset of cognitive problems [33, 34]. Furthermore, children with impaired sleep patterns may also have differences in brain functioning [27] that can impact their cognitive performance. These results suggest that neurobiological markers, such as white matter, may be useful for understanding or predicting cognitive impairments in the long-term. However, relationships between psychological factors (e.g., stress, sleep) and neurobiological mechanisms to predict cognitive outcome have been understudied in pediatric brain tumor groups.

Summary of literature

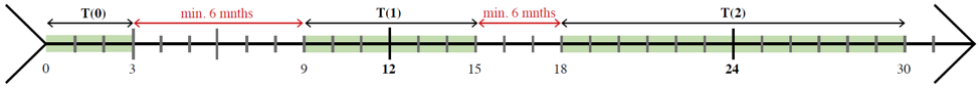
In summary, previous research has shown that children with brain tumors are at risk for cognitive and psychosocial problems, which are associated with poorer quality of life. This may be due to various individual, medical, or psychological factors that impacts cognitive and neural functioning (Figure 2). Therefore, neuropsychological monitoring is considered standard of care for children with brain tumors [35] and clinical guidelines for assessment and monitoring have been suggested [36]. However, the relationships between psychological factors and cognitive problems have not yet, or only minimally, been investigated in children with brain tumors. It is useful to investigate these relationships and underlying neural mechanisms because early screening could result in treating stress and sleep symptoms, which ultimately diminishes cognitive problems. Future interventions could consider psychological interventions in addition to cognitive and pharmaceutical approaches to improve cognitive functioning. Overall, these previous findings highlight the need for a multidimensional approach to assessment of cognition, stress and sleep in future research as well as in clinical practice.

The SuSPeCT study

The current thesis includes results from the stress, sleep and cognitive functioning (SuSPeCT) study, which is a longitudinal, prospective, observational study from the Princess Máxima Center for pediatric oncology in the Netherlands. The primary aim of the SuSPeCT study was to examine the relationships between sleep and posttraumatic stress symptoms (PTSS) with cognitive outcomes. A comprehensive assessment was used, which included neuropsychological assessments, sleep assessments, child and parent questionnaires, and brain magnetic resonance imaging (MRI) scans. The inclusion period for this study occurred between January 2019 and October 2021. During this period, children were invited to

complete assessments at three fixed time points: at 0-3 months after diagnosis (T0); one year after diagnosis (±3 months, T1); and two years after diagnosis (±6 months, T2). An overview of the study timeline is presented below (Figure 3).

Figure 3 - Timeline SuSPeCT study



Aims and outline of thesis

This thesis describes results from the SuSPeCT study in brain tumor patients. For this thesis, the primary aim was to examine sleep, posttraumatic stress symptoms (PTSS), and cognitive outcomes at an early phase after pediatric brain tumor diagnosis, and whether sleep or PTSS were associated with cognitive performance and white matter development in the brain. In **Chapter 2**, we examined the prevalence, associations, and risk factors of child's sleep shortly after brain tumor diagnosis, using questionnaires and sleep assessments. In **Chapter 3**, the prevalence, associations, and risk factors of child and parent PTSS shortly after brain tumor diagnosis were evaluated, using child and parent questionnaires. **Chapter 4** combines the topics of the previous chapters to examine the impact of child sleep's and PTSS on cognitive performance shortly after brain tumor diagnosis, using neuropsychological assessments, sleep assessments, and questionnaires. In **Chapter 5**, the effect of child's PTSS on cognitive functioning and white matter in the brain at one year after diagnosis was evaluated, using neuropsychological assessments, questionnaires, and brain MRI scans.

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2

Sleep problems and impact of obstructive hydrocephalus in newly diagnosed pediatric brain tumor patients

2

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Abstract

Background.

Pediatric brain tumor patients are at risk of developing sleep problems. Previous studies were conducted in longer-term survivors or without comprehensive sleep evaluations, therefore it remains unclear whether and when problems arise. Insights can facilitate timely interventions. The aim is to examine sleep problems and contributing factors shortly after diagnosis.

Methods.

Children 6-16 years with a primary brain tumor (diagnosed ≤3 months) were recruited for a prospective study. Sleep was measured at home using wrist-worn actigraphy and questionnaires (PROMIS Sleep Disturbanceand Sleep Related Impairment, self- and parent-reports). Mean PROMIS scores, prevalence of sleep problems (established by cut-off scores) and actigraphic outcomes were compared to norms (t-test, chi-square, linear regression). Risk factors were explored with multivariable linear regression models.

Results.

Sixty-nine children (68% male, mean age 11.6±2.8 years, 53±28 days after diagnosis) participated. Parents reported more child sleep disturbances (mean T=53.7, P<.01) compared to norms. Rates of self- and parent-reported severe sleep disturbances were elevated (11% versus 5% in norms, P<.04). Parents also reported higher rates of moderate child sleep disturbance (31%) and sleep related impairment (42%) than norms (25%, P<.03). Actigraphy was comparable to healthy controls. Obstructive hydrocephalus was associated with longer sleep times (B=41.04, 95%CI 11.41;70.68) and shorter time since diagnosis with self-reported sleep disturbances (B=-.11, 95%CI -0.19;-0.03).

Conclusion.

Sleep problems are more frequently reported shortly after pediatric brain tumor diagnosis, compared to healthy controls. Attention for sleep around brain tumor diagnosis and impact of obstructive hydrocephalus is important, as sleep is vital for recovery and health-related quality of life.

Keywords

Sleep, sleep problems, pediatric brain tumor, actigraphy

Introduction

Sleep problems are known to be highly prevalent in pediatric cancer patients and can be caused by biological and/or psychosocial factors such as treatment toxicity, pain, and anxiety [1, 2]. In the short term, sleep problems can lead to distress, cognitive problems, and lower quality of life in pediatric cancer patients [2-4]. In the long term, resulting from studies in the general population, sleep problems are associated with obesity, cardiovascular disease and lower life expectancy [2]. Sleep also plays a critical role in neuroimmune function and neuronal recovery in pediatric cancer patients. Moreover, fragmented sleep has increasingly been linked to tumor growth in mice [5-7]. Children with a brain tumor are especially prone to develop sleep problems. Neurosurgery, cranial radiation therapy and hypothalamic damage may further contribute to the onset of disturbances in sleeping patterns [1, 8].

Currently, little is known about the prevalence and extent of sleep problems of children with a brain tumor, in an early stage of their disease. Previous studies have mainly focused on patients with all types of cancer diagnoses, causing heterogeneity, or included only patients with hematologic malignancies, the most common type of pediatric cancer [9]. In addition, most studies focus on sleep during survivorship. Multiple physical, psychological, and therapeutic factors related to the period around diagnosis may impact sleep, such as high levels of distress or the requirement of one or multiple hospitalizations, which are characterized by frequent nightly awakenings [10]. Poor sleeping habits and maladaptive strategies may emerge in this period and persist over the course of the disease. Lastly, sleep is most often assessed by questionnaires only, which provide information on sleep behaviors and consequences of disrupted sleep. However, questionnaires do not measure sleep duration and sleep efficiency, and do not correlate well with polysomnography, the gold standard for measuring sleep [11]. Some questionnaire studies only assess parent-reported sleep, which inherently poses some reporting bias. Using several modes of sleep assessment is important as it provides complementary information and contributes to our understanding of sleep [11-14].

Sleep in the early phases of treatment in pediatric brain tumor patients has thus far not been studied comprehensively, despite strong recommendations by researchers and clinicians [5, 14-16]. Identifying which children are at risk is important, to provide effective, targeted sleep interventions in a timely manner, aiming to improve long-term negative health outcomes associated with poor sleep. In adult cancer patients, non-pharmacological interventions such as cognitive behavioural therapy have shown favorable results reducing sleep problems [17, 18]. In contrast, in hospitalized children with central nervous system tumors, a multicomponent sleep intervention modestly improved sleep outcomes [19]. Therefore, more insight into disrupted sleep and contributing factors in the earliest phase after brain tumor diagnosis is needed.

We performed a prospective, observational study into sleep within three months after primary pediatric brain tumor diagnosis. Our aim was to describe sleep estimates, patient- and parent-reported sleep problems and daytime consequences, and biological and psychological risk

factors for poor sleep. This study is part of a larger longitudinal study into sleep, post-traumatic stress, and neurocognitive functioning (SuSPeCT-study).

Materials and Methods

Participants and procedures

The Princess Máxima Center for Pediatric Oncology is a Dutch center where pediatric oncology care is centralized. A small number of low grade brain tumor patients, requiring neurosurgery only, are treated in former pediatric oncology centers. Between January 2019 and October 2021 all patients treated for a primary brain tumor were eligible if they were 6 to 16 years old, spoke Dutch sufficiently, had no pre-existing developmental delay and were not receiving endof-life care. All children and parents provided written informed consent. Sleep assessments took place one to three months after hospital entry. All assessments took place when the child slept at home. This study was approved by the Clinical Research Committee of the Princess Maxima Center and confirmed subsequently by the Medical Research Ethics Committee of the University Medical Center Utrecht.

Demographic and medical information

Children's demographic and medical information were abstracted from medical records. Parents provided sociodemographic information through a general survey. Information was provided on pre-existing sleep problems, use of sleep medications, daytime naps and whether they slept at home or in the hospital.

Sleep questionnaires

Subjective sleep was assessed with two eight-item questionnaires (both self-report and proxy-report) from the Patient-Reported Outcomes Measurement Information System (PROMIS) [20]. The Pediatric Sleep Disturbance shortform assesses satisfaction with sleep, including difficulties and concerns with falling asleep and staying asleep. The Pediatric Sleep Related Impairment shortform focusses on perceptions associated with sleep problems, such as impaired alertness, tiredness and sleepiness during usual waking hours. Both questionnaires assess sleep over the past seven days, and are generic rather than disease-specific. Strong internal consistency reliability and clinical validiy were demonstrated [21]. Raw scores are rescaled into T-scores (mean=50, standard deviation (SD)=10). Cut-off points for moderate (75–94th percentile) and severe (≥ 95th percentile) sleep problems were used [22].

Actigraphic measures

Sleep estimates were assessed using a wrist-worn actigraph (type wGT3XBT, Pensacola, FL). This device registers the occurrence and the intensity of arm movements and distinguishes the wake state from sleep. This low-cost measurement has been validated against polysomnography, and is well-tolerated during this intense stage of cancer therapy [23]. Participants were instructed to wear the actigraph for seven days and seven nights and keep a sleep log, to facilitate correct interpretation of the data.

Table 1 - Actigraphic sleep estimates

Sleep estimate	Definition
Sleep efficiency (SE)	Ratio between the time spent in bed and the total sleep time
Sleep onset latency (SOL)	Number of minutes between bedtime and onset of sleep
Wake after sleep onset (WASO)	Number of minutes awake after the onset of sleep
Total sleep time (TST)	Number of minutes sleeping during the time spent in bed
Total time spent in bed (TIB)	Number of minutes spent in bed
Number of awakenings (NA)	Total number of awakenings

Actigraphy software ActiLife (version 6.13.4, Sadeh algorithm) was used to process sleep outcomes (Table 1). To obtain reliable actigraphic measures, a minimum of five recorded nights was required [24]. Norm data of 47 healthy Dutch children were used to compare actigraphic sleep outcomes [25]. Actigraphic data of the healthy control participants were collected one year before this study; control participants were in the same age range and their average age did not differ from study participants (P=.26).

Statistical analysis

Baseline characteristics were descriptively reported. T-tests and chi-square tests were used to examine potential differences in age, sex and tumor location between participants and non-participants (active/passive refusal), and between participants and patients who were not approached (due to severe illness or logistical issues).

To examine differences in reported sleep between participants and healthy children, PROMIS scores were compared to a norm score of 50, using one-sided t-tests. The percentage moderate and severe sleep problems was described by using questionnaire-specific cut-offs [22] and compared to the general population with non- parametric chi-square tests.
Linear regression models were used for comparing actigraphic sleep estimates between participants and healthy children. Regression models were adjusted for age [25].

Risk factors were explored with linear regression models. Demographic (age, sex, highest parental educational level) and medical variables relevant for sleep outcomes were examined with univariable analyses. Medical variables were: tumor location (supratentorial midline versus other locations); treatment (neurosurgery, start of chemotherapy or radiotherapy before assessment); comorbidites (hormone deficiency, epilepsy, obstructive hydrocephalus); time since diagnosis; body mass index. Variables with a P-value of <.10 were subsequently added to a multivariable model.

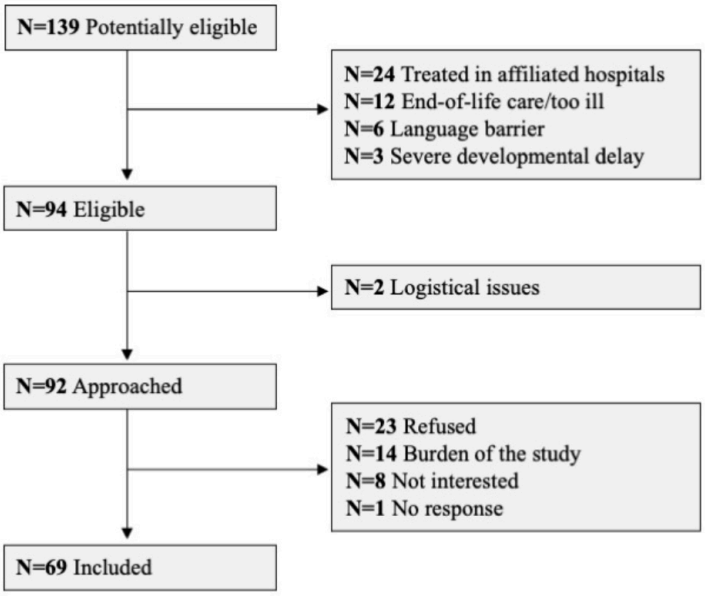
P-values of <.05 were considered significant. All analyses were carried out with IBM SPSS Statistics version 26.0.0.1.

Results

Demographic and medical information

In total, 69 (75%) children consented to the study; details of participant enrollment are described in Figure 1. Baseline characteristics of the participants and non-participants are described in Table 2. Of the children with supratentorial midline tumors (N=26, 38%), fifteen children (22%) had a tumor in the pituitary region, and none of the children had a tumor in the hypothalamus. Pre-existing sleep problems were reported by the parents of seven (10%) participants. During the assessment, six (9%) participants took daytime naps, two (3%) participants used melatonin and all actigraphy assessments took place when the children slept at home.

Figure 1 - Flowchart of participant enrollment.



Sleep questionnaires

Compared to norm data, parents reported significantly more child sleep disturbances (mean T=53.7, P<.01; Table 3). This was not reported by children themselves (mean T=50.6, P=.64). Sleep Related Impairment was not compared to norms as the data was not normally distributed.

Severe sleep disturbance was experienced by 11% of the children compared to 5% in the general population, according to both parent- and self-reports (P=0.03 and P=.04, respectively). Moderate sleep disturbance was also frequently reported by parents: 31% compared to 20% in the general population (P=.03). Rates of severe sleep related impairment were not significantly elevated. However, moderate sleep related impairment was more prevalent according to parents (42% vs 20%, P<.01).

Table 2 - Baseline characteristics of participants.

	Study participants (N=69)	Non-participants (N=23), P-value[3]	Not approached (N=14), P-value[3]
Child variables			
Male sex, N (%)	47 (68%)	14 (61%), P=.52	8 (57%), P=.44
Age at assessment, mean years (SD)	11.6 (2.8)	11.1 (4.3), P=.76	9.9 (2.3), P=.08
Time since diagnosis, mean days (SD)	53 (28)		
Body Mass Index, mean (SD)	18.7 (3.7)		
Parental education level[1]			
Low-Middle N (%)	33 (51%)		
High, N (%)	32 (49%)		
Medical variables			
Tumor type			
Low grade glioma, N (%)	33 (48%)		
Germ cell tumor, N (%)	10 (15%)		
Craniopharyngioma, N (%)	9 (13%)		
High grade glioma, N (%)	6 (8%)		
Medulloblastoma, N (%)	6 (8%)		
Ependymoma, N (%)	2 (3%)		
Other, N (%)[2]	3 (4%)		
Tumor location			
Posterior fossa, N (%)	29 (42%)	8 (35%), P=.54	6 (43%), P=.95
Supratentorial medial structures, N (%)	26 (38%)	5 (22%), P=.16	5 (36%), P=.89
Cerebral lobes, N (%)	14 (20%)	**10 (44%), P=.03***	3 (21%), P=.92
Started treatment			
Neurosurgery, N (%)	63 (91%)		
Started chemotherapy, N (%)	12 (17%)		
Started radiotherapy, N (%)	13 (19%)		
Proton therapy, N (%)	5 (7%)		
Photon therapy, N (%)	8 (12%)		
Obstructive hydrocephalus, N (%)	33 (48%)		
Hormone deficiency, N (%)	18 (26%)		
Epilepsy, N (%)	9 (13%)		

[1]Low =no education, primary school, lower secondary education; middle =upper secondary education, preuniversity education, intermediate vocational education; high =higher vocational education, university.
[2]ATRT (N =1), plexus tumor (N =1), meningioma (N =1).
[3]Compared to participant group.
*Statistically significant

Actigraphic sleep estimates

There were no statistical differences between participants and controls (Table 4). Based on the sleeplog, participants' bedtime (mean 21:36) was 30 minutes later, compared to controls (P=0.04). Also, participants' wake time (mean 07:57) was 32 minutes later, compared to controls (P<0.001).

Risk factors

Univariable analyses for risk factors are presented in Supplementary Tables 1 and 2. Multivariable analyses (Table 5 and 6) showed that shorter time after diagnosis (B=-.11, 95%CI -.19;-.03, P=<.01) remained the only independent significant determinant for self-reported sleep disturbance. Younger age remained associated with longer sleep onset latency (B=-1.73, 95%CI -3.12;-.35, P=.02), more total sleeping time (B=-8.63, 95%CI - 14.00;-3.26, P<.01) and more time in bed (B=-10.59, 95%CI -15.33;-5.85, P<.01). Finally, history of an obstructive hydrocephalus was independently associated with longer sleeping times (B=41.04, 95%CI 11.41;70.68, P<.01).

Table 3 - Patient- and parent-reported child sleep and prevalence of sleep problems.

	T-score[1]		Moderate sleep problems		Severe sleep problems		Any sleep problem	
	Mean (SD) or median [IQR]	P-value[2]	N (%)	P-value[3]	N (%)	P-value[4]	N (%)	P-value[5]
Self-report (n=53)								
Sleep disturbance	50.6 (9.5)	.64	8 (15%)	.37	6 (11%)	**.04**	14 (26%)	.81
Sleep related impairment	49.7 [40.1 - 54.2]	-	7 (15%)	.22	3 (6%)	.83	10 (19%)	.30
Proxy-report (n=65)								
Sleep disturbance	53.7 (10.0)	**<.01**	20 (31%)	**.03**	7 (11%)	**.03**	27 (42%)	**<.01**
Sleep related impairment	57.1 [37.9 - 61.8]	-	27 (42%)	**<.01**	5 (8%)	.32	31 (49%)	**<.01**

Abbreviations: SD =standard deviation, IQR =interquartile range.
Significant P-values are bold.
[1]Higher scores indicate more sleep problems
[2]Compared to norm population (mean=50, SD=10)
[3]Compared to percentage of moderate sleep problems in the norm population (20%)
[4]Compared to percentage of severe sleep problems in the norm population (5%)
[5]Compared to percentage of sleep problems (moderate or severe) in the norm population (25%)

Table 4 - Differences in actigraphic sleep estimates between participants and healthy controls.

	Participants (n=53)	Control group (n=47)	B (95% CI)	P-value
	Mean (SD)	Mean (SD)		
SE (%)	79.0 (7.1)	77.8 (7.3)	-1.1 (-3.9 – 1.8)	.47
SOL (min)	20.7 (14.8)	25.9 (15.4)	4.2 (-1.6 – 10.1)	.15
WASO (min)	107.3 (39.7)	113.9 (45.5)	4.5 (-12.2 – 21.2)	.60
TST (min)	480.9 (58.9)	479.1 (48.0)	-7.8 (-26.9 – 11.3)	.42
TIB (min)	608.9 (55.0)	618.6 (56.7)	.8 (-15.3 – 16.9)	.92
NA (N)	28.6 (6.9)	28.6 (6.2)	-.3 (-3.0 – 2.3)	.80

Abbreviations: SE =sleep efficiency, SOL =sleep onset latency, WASO =wake after sleep onset, TST =total sleep time, TIB =total time spent in bed, NA =number of awakenings, min =minutes.
Models were adjusted for age.
Significant values are in bold.

Table 5 - Multivariable regression models of risk factors for patient- and parent reported sleep outcomes

Questionnaires, B (95% CI)	PROMIS Self-report		PROMIS Proxy-report	
	Sleep Disturbance	Sleep Related Impairment	Sleep Disturbance	Sleep Related Impairment
Time since diagnosis *Continuous*	**-.11* (-.19 – -.03)**	-	-.07 (-.16 – .02)	-
Tumor location *Supratentorial midline vs. others*	-3.56 (-8.74 – 1.62)	-	-	-
Started radiotherapy[1] *Yes vs. no*	-	-	-4.60 (-10.96 – 1.76)	-

Only variables with a P-value of <.10 in univariable analyses (see Supplementary material) were added to the multivariable model.
[1]Proton and photon radiation therapy grouped together
* Statistically significant (P <0.05), Significant values are in bold.

Table 6 - Multivariable regression models of risk factors for actigraphic sleep outcomes

Actigraphic outcomes, B (95% CI)						
	SE	SOL	WASO	TST	TIB	NA
Age *Continuous*	-	**-1.73* (-3.12 – -.35)**	-	**-8.63** (-14.00 – -3.26)**	**-10.59** (-15.33 – -5.85)**	-
Neurosurgery *Yes vs. no*	-	-	-	-	-	4.68 (-1.26 – 10.61)
Started radiotherapy[1] *Yes vs. no*	-	-	-	-	-	3.63 (-1.37 – 8.64)
Obstr. hydrocephalus *Yes vs. no*	-	-7.28 (-14.93 - .37)	-	**41.04** (11.41 – 70.68)**	-	-

Only variables with a P-value of <.10 in univariable analyses (see Supplementary material) were added to the multivariable model.
Abbreviations: SE =sleep efficiency, SOL =sleep onset latency, TST =total sleep time, TIB =total time in bed, NA =number of awakenings, suprat. =supratentorial, obstr. =obstructive.
[1]Proton and photon radiation therapy grouped together
* Statistically significant (P <0.05), ** Statistically significant (P <0.01), Significant values are in bold.

Children with prior obstructive hydrocephalus slept on average 21 minutes longer (TST), and fell asleep 10 minutes sooner (SOL), compared to controls. In contrast, children without obstructive hydrocephalus slept on average 12 minutes shorter, and fell asleep equally fast compared to controls. On average, children with obstructive hydrocephalus went to bed 42 minutes later and rose 53 minutes later than the control group. Lastly, when corrected for age, the mean difference in TST with and without obstructive hydrocephalus was 41 minutes. Differences in age between the hydrocephalus and no hydrocephalus group were however not significant.

Body mass index, parental education level, start of chemotherapy, hormone deficiency and epilepsy were not significantly associated with any of the sleep outcomes.

Discussion

The results of this unique prospective nationwide cohort study of children with a recently diagnosed brain tumor demonstrate a higher prevalence of parent-reported sleep problems compared to a control group. Children more often reported severe sleep disturbances compared to healthy peers, but not more moderate sleep disturbances. Actigraphic sleep outcomes were not different from healthy controls. Shorter time since diagnosis was associated with more sleep disturbances and obstructive hydrocephalus was associated with longer sleep duration and shorter time to fall asleep.

We found high rates of parent-reported child sleep disturbance and sleep related impairment, with up to half of the parents reporting moderate or severe problems. Children themselves frequently reported severe sleep disturbances, especially more shortly after brain tumor diagnosis. These findings are consistent with our expectations, indicating sleep problems are experienced regularly and already at the earliest phase of cancer treatment, possibly arising as a result of factors such as distress and neurological damage. In children with ALL, high rates of sleep problems have also been reported in the first period after diagnosis [26]. Interestingly, alhough parents reported high rates of sleep related impairments, children did not report this and on average their scores did not differ from the general population.

Differences in self- and proxy-report are common in pediatric research and may be explained by several factors [26-28]. Firstly, children may underreport symptoms. This can be the result of "response shift", meaning symptoms are judged differently during cancer treatment than how they would be judged before diagnosis [29]. It could also be that neurocognitive-, stress- and sleep disturbances impact children's' capability of adequately recalling sleep experiences [30]. Second, parents may overreport symptoms due to feelings of stress and concern. Earlier research suggests that parental distress, parental sleep problems and parenting problems are related to parent reported child sleep [26]. Hence, differences in self- and proxy-reports emphasize the importance of using both types when measuring sleep, as they may provide complementary information.

We hypothesized that actigraphic outcomes would show lower sleep estimates compared to age-matched, healthy controls, due to the physical/psychosocial stressors associated with the period following brain tumor diagnosis. This was not seen in the overall group, however, it is important to note that sleep was measured at home. Sleep during hospitalization may have been impaired, as shown in previous studies [31]. Also, compared to controls, children without obstructive hydrocephalus slept shorter, and children with obstructive hydrocephalus slept longer and had shorter sleep onset times. Impact of obstructive hydrocephalus was not seen in earlier research amongst CNS tumor survivors [32] and is not previously investigated in any research into recently diagnosed pediatric brain tumor patients. Possibly, children with obstructive hydrocephalus are more ill and/or tired and therefore require more sleep to support physical recovery [5, 33, 34]. This is in line with comparable research in children with acute lymphoblastic leukemia (ALL), who showed longer sleeping times than healthy peers [26]. Another explanation could be poorer sleep quality, for example due to more sleep fragmentation with a destruction of the hypocretin system, biological clock or breathing disorders. The total group had later bed times and later rising times, possibly because they were all not going to school, however, this was particularly seen in children with obstructive hydrocephalus and could be related to altered sleep-wake rhythms.

Nevertheless, overall participant and control group sleep estimates were comparable. This study sample was however almost entirely assessed during the Covid-19 pandemic, while data of the control group were collected before. Possibly, children slept better during the pandemic, as due to lockdowns they were staying at home with limited social interactions and thus less exposed to stimuli [35]. In the healthy population, it was found that people with insomnia complaints experienced clinically meaningful alleviations of symptoms during the pandemic [36]. Lastly, sleep may be influenced by substantial efforts and strategies of parents, such as co-sleeping and comforting activities, as illustrated in parents of children with ALL [37]. Possibly, as parents put in a great deal of energy, parents do report sleep problems in their child, and yet these efforts seem relatively effective in terms of child sleep duration. This may also explain the different outcomes in parental reported sleep problems and actigraphy and has been described before in children with ALL [26].

Generally, little research has been done with actigraphy and children with cancer during treatment. However, sleep problems are well described and measured amongst brain tumor survivors [8, 14, 32]. Toxic treatmens effects such as radiation therapy or endocrine disturbances may lead to those sleep problems at a later stage. Longitudinal data from this current study should provide more insight into this matter [8, 38].

This study has several limitations. Although the participant group is relatively large for pediatric brain tumor research, there may not have been enough power to demonstrate sleep problems or specific predictors. In addition, not all children participated in all actigraphic sleep measurements, due to treatment toxicity or study burden, increasing the risk of participation bias. Subsequently, even though participants were recruited from a national pediatric

oncology hospital, specific tumor groups were underrepresented which may have lead to selection bias. Not invited for study participation were twenty-four children with low grade tumors, primarily treated in affiliated hospitals, and twelve children with high grade tumors, receiving palliative care. Finally, it would have been interesting to be informed on parental sleep, as previous work has shown the association between child and parents sleep in the first pahses after a childhood cancer diagnosis [39].

Actigraphy measures movement which is a well validated tool, but does not measure sleep phases (light, deep and REM sleep). Also, possible shifted circadian rhythms or inconsistent bedtimes are not reflected in the actual number of minutes asleep as reported here, but may still contribute to fatigue [4, 5, 40]. Future research should explore sleep phases and rhythms to gain more insight into sleep quality. Lastly, previous research suggested more knowledge of parents on sleep hygiene benefits child sleep, therefore education and support for parents may be an interesting intervention for future research [41, 42].

Conclusion

Sleep problems in children with a brain tumor are frequently reported in the first three months after brain tumor diagnosis, particularly sooner after diagnosis. History of obstructive hydrocephalus was related to longer sleeping times. Clinicians should be attentive to sleep problems and provide psycho-education on healthy sleep as part of regular care, as chronic problems may induce serious, negative consequences in this already vulnerable group. Systematic sleep monitoring with patient-reported outcomes is an important tool in early recognition of sleep problems. Increasing our understanding of sleep is of major importance because sleep is vital for recovery and health-related quality of life.

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Supplementary Table 1 - Univariable analyses risk factors for patient- and parent reported sleep outcomes

Questionnaires, B (95% CI)	PROMIS Self-report		PROMIS Proxy-report	
	Sleep Disturbance	Sleep Related Impairment	Sleep Disturbance	Sleep Related Impairment
Age *Continuous*	.39 (-.60 – 1.37)	.48 (-.49 – 1.44)	.47 (-.42 – 1.35)	.64 (-.35 – 1.63)
Sex F*emale vs. male*	1.16 (-4.30 – 6.61)	-2.69 (-7.99 – 2.62)	.56 (-4.79 – 5.92)	-3.06 (-9.02 – 2.90)
Time since diagnosis *Continuous*	**-.12*** **(-.20 – -.04)**	.01 (-.07 – .10)	**-.10*** **(-.18 – -.01)**	.03 (-.07 – 1.13)
BMI *Continuous*	.30 (-.44 – 1.04)	.15 (-.58 – .88)	.20 (-.46 – .86)	.03 (-.71 - .78)
Parental education *High vs. low/middle*	.66 (-4.65 – 5.96)	.67 (-4.53 – 5.86)	2.32 (-2.66 – 7.30)	.95 (-4.67 – 6.57)
Tumor location *Suprat. midline vs. rest*	**-4.56*** **(-10.01 – .88)**	1.10 (-6.57 – 4.37)	-4.14 (-9.27 – 1.00)	.19 (-5.70 – 6.06)
Neurosurgery *Yes vs. no*	8.44 (-2.78 – 19.65)	8.68 (-2.28 – 19.64)	1.24 (-8.16 – 10.64)	5.54 (-4.92 – 16.00)
Started chemotherapy *Yes vs. no*	-.51 (-7.28 – 6.26)	4.32 (-2.20 – 10.84)	-1.25 (-7.70 – 5.20)	3.31 (-3.89 – 10.50)
Started radiotherapy[1] *Yes vs. no*	-4.36 (-10.57 – 1.85)	3.78 (-2.33 – 9.89)	**-6.41*** **(-12.46 – -.35)**	3.32 (-3.64 – 10.30)
Hormone deficiency *Yes vs. no*	-3.35 (-9.29 – 2.58)	.24 (-5.64 – 6.13)	-.42 (-6.12 – 5.29)	4.09 (-2.22 – 10.40)
Epilepsy *Yes vs. no*	5.46 (-2.76 – 13.68)	3.21 (-4.93 – 11.35)	1.61 (-6.01 – 9.23)	-1.04 (-9.59 – 7.51)
Obstr. hydrocephalus *Yes vs. no*	-3.35 (-9.29 – 2.58)	.28 (-4.91 – 5.47)	-1.84 (-6.84 – 3.15)	-3.40 (-8.96 – 2.16)

Abbreviations: B = Beta, CI = confidence interval, SD = sleep disturbance, SRI = sleep related impairment, suprat. = supratentorial, obstr. = obstructive.
[1] Proton and photon radiation therapy grouped together
* P-value <.10, Significant values are in bold.

Supplementary Table 2 - Univariable analyses risk factors for actigraphic sleep outcomes

Actigraphic outcomes, B (95% CI)						
	SE	SOL	WASO	TST	TIB	NA
Age *Continuous*	.10 (-.62 – .83)	**-1.96*** **(-3.36 – -.56)**	-1.28 (-5.31 – 2.74)	**-7.35*** **(-12.98 – -1.73)**	**-10.59*** **(-15.33 – -5.85)**	-.19 (-.90 – .51)
Sex *Female vs. male*	**3.60*** **(-.60 – 7.78)**	-3.62 (-12.52 – 5.28)	-17.03 (-40.63 – 6.57)	18.96 (-16.36 – 54.27)	-1.70 (-35.06 – 31.66)	-.60 (-4.81 – 3.61)
Time since diagnosis *Continuous*	-.01 (-.08 – .06)	-.10 (-.25 – .039)	.083 (-.31 – .47)	-.14 (-.72 – .44)	-.16 (-.70 – .38)	.02 (-.05 – .09)
BMI *Continuous*	-.29 (-.88 – .31)	.62 (-.55 – 1.80)	.96 (-2.33 – 4.25)	-2.78 (-7.63 – 2.08)	-1.19 (-5.75 – 3.37)	.40 (-.17 – .96)
Parental education *High vs. low/middle*	2.13 (-1.88 – 6.14)	2.30 (-6.09 – 10.69)	-12.89 (-35.21 – 9.43)	12.63 (-20.69 – 45.94)	2.03 (-29.28 – 33.34)	-1.01 (-4.93 – 2.92)
Tumor location *Suprat. midline vs. rest*	-.75 (-4.88 – 3.38)	-5.83 (-14.25 – 2.59)	7.89 (-15.06 – 30.83)	-10.37 (-44.43 – 23.70)	-8.32 (-40.17 – 23.54)	-.72 (-4.75 – 3.31)
Neurosurgery *Yes vs. no*	-2.52 (-8.74 – 3.69)	-6.05 (-18.92 – 6.82)	26.68 (-7.38 – 60.75)	12.89 (-38.72 – 64.51)	33.52 (-13.89 – 80.93)	**5.37*** **(-.54 – 11.29)**
Started chemotherapy *Yes vs. no*	-.35 (-5.88 – 5.19)	-.47 (-11.96 – 11.02)	-1.78 (-32.65 – 29.09)	-18.19 (-63.70 – 27.32)	-20.44 (-62.83 – 21.95)	1.95 (-3.43 – 7.32)
Started radiotherapy[1] *Yes vs. no*	-.41 (-5.70 – 4.87)	-8.70 (-19.38 – 1.98)	9.41 (-19.91 – 38.73)	-10.04 (-53.61 – 33.53)	-9.33 (-50.03 – 31.38)	**4.27*** **(-.74 – 9.28)**
Hormone deficiency *Yes vs. no*	-1.90 (-6.27 – 2.46)	-6.49 (-15.44 – 2.45)	14.80 (-9.39 – 38.98)	-17.01 (-53.08 – 19.07)	-8.71 (-42.62 – 25.21)	-.27 (-4.57 – 4.02)
Epilepsy *Yes vs. no*	.25 (-5.61 – 6.10)	2.41 (-9.71 – 14.54)	-8.58 (-41.13 – 23.98)	-26.23 (-74.09 – 21.63)	-32.40 (-76.70 – 11.91)	-1.32 (-7.03 – 4.38)
Obstr. hydrocephalus *Yes vs. no*	2.47 (-1.47 – 6.41)	**-8.92*** **(-16.83 – -1.01)**	-2.86 (-25.15 – 19.43)	**32.86*** **(1.10 – 64.62)**	21.07 (-9.25 – 51.40)	2.01 (-1.86 – 5.87)

Abbreviations: B = Beta, CI = confidence interval, SE = sleep efficiency, SOL = sleep onset latency, WASO = wake after sleep onset, TST = total sleep time, TIB = total time spent in bed, NA = number of awakenings, suprat. = supratentorial, obstr. = obstructive.

[1] Proton and photon radiation therapy grouped together

* P-value <.10, Significant values are in bold.

3

Posttraumatic stress symptoms in children and parents shortly after pediatric brain tumor diagnosis: prevalence and risk factors

3

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Abstract

Background.

Children with brain tumors and their parents are at risk of developing posttraumatic stress symptoms (PTSS). Rates are high amongst survivors and parents, however early prevalence is unknown. This study aims to describe prevalence, associations and risk factors of child and parent PTSS shortly after diagnosis.

Procedures.

Sixty-nine children with brain tumors (6-16 years old) and their parents participated (response rate 75%). Child PTSS (CRIES-13 self- and proxy-report) and parent PTSS (PCL-5) were assessed one to three months after diagnosis. Prevalence of clinical PTSS was established using cut-offs, and compared to the general population (PCL-5; chi-square tests). Associations between child and parent PTSS (correlations) and risk factors (linear regression models) were explored.

Results.

Clinical child PTSS was reported by 29.4% of the children and 11.1% of their parents. Prevalence of clinical parent PTSS was higher than in the general population (13.8% mothers, 8.0% fathers, P<0.01). Child PTSS self-reports were associated to proxy-reports (r=0.49, P<0.01), but not to parent PTSS (mother r=0.22, father r=0.18). Risk factors for self-reported child PTSS were shorter time since diagnosis (B=-0.18, 95%CI -0.34 – -0.02, P=0.03) and cerebral hemisphere tumor (B=14.23, 95%CI 0.04–28.42, P=0.05). For mothers, their child receiving radiotherapy (B=9.95, 95%CI -0.40–20.30, P=0.05), and for fathers, less positive illness cognitions (B=20.93, 95%CI -0.50–42.37, P=0.05) were associated with higher parent PTSS.

Conclusions.

Prevalence of PTSS in children with a recently diagnosed brain tumor and their parents was high, highlighting the need for early monitoring, targeted interventions and studying changes of time, to optimize long-term health-related quality of life.

Keywords

Posttraumatic stress, PTSS, PTSD, pediatric brain tumor, parents

Introduction

Children with cancer are at risk of developing psychological problems on and off treatment, such as posttraumatic stress symptoms (PTSS) and disorder (PTSD) [1,2]. This may occur in response to the diagnosis of a life-threatening illness, pain, and invasive medical procedures [3,4], and may be reinforced by factors such as personality, preexisting psychological problems and genetic predisposition [5-7]. Children with a brain tumor have poorer prognoses than children with other cancer diagnoses and experience high morbidity resulting from factors like neurosurgery and cranial radiation, and could therefore be even more prone to developing psychological problems [1,8,9].

Experiencing stress in response to a life-threatening disease is common and often temporary. However, some children develop severe stress symptoms which can persist for a longer period of time or even become chronic [1,10,11]. These symptoms are often expressed as avoidance, hyperarousal and intrusive symptoms like recurrent nightmares or flashbacks, and are associated with lower quality of life, decreased educational performance, neurobiological changes, and in adults even degenerative and cardiovascular diseases [1,7,12-14].

Price and colleagues (2016) provide an updated integrative model of pediatric medical traumatic stress in which they describe different possible trajectories, depending on subjective appraisal of medical events. They underscore that the largest proportion of people are resilient to traumatic events, such that stress symptoms normalize shortly after an initial stress reaction. For those who are experiencing a prolonged stress reaction, it is proposed that this either recovers, remains stable or worsens over time [7]. Other research has also shown the possibility of experiencing posttraumatic growth, thus highlighting variability in responses [7,15,16]. To be able to timely intervene for those at risk, the need for early detection of PTSS has often been emphasized in pediatric oncology [10,17,18].

Not only children with cancer, but also their parents are prone to develop PTSS. Studies have shown that these symptoms are (sub)clinically common, during the child's cancer treatment and in the long term [4,11,19,20]. In addition to the impact PTSS has on parents themselves, it has been argued that stress complaints of parents can contribute to stress complaints of their children [21,22]. Therefore, it is important to assess the child's functioning within a family context. Previous research has shown promising family systems interventions to reduce both child and parent PTSS, but further development requires more knowledge on both child and parent PTSS, and potential risk factors [2,22,23].

Currently, the prevalence of early PTSS in children with a brain tumor and their parents has not been studied. Research has mainly focused on survivors or parents of survivors, whose complaints may have been present for a substantial period of time. In addition, the vast majority of studies include all cancer diagnoses, not adequately capturing the nuance of disease-specific factors. Consequently, it has been frequently argued to reduce heterogeneity by looking into specific diagnosis groups at specific time points [2,19,24].

Risk factors for child and parent PTSS during cancer treatment have thus far been studied to a limited extent. A recent review suggested that a poorer prognosis and cancer recurrence were related to higher levels of PTSS in children with cancer18. For parents of children with cancer, lower level of education, lower levels of emotion-focused coping, greater perceived uncertainty and shorter time since diagnosis were related to higher levels of PTSS [4,20,25]. For brain tumor survivors specifically, as well as their parents, lower perceived ability to resolve parent–child conflicts and more days spent in the hospital were related to higher levels of PTSS [26]. Factors associated with child and parent PTSS during brain tumor treatment are yet to be discovered, and it is important to consider both psychological as well as medical risk factors.

This prospective, longitudinal, observational study aims to provide a comprehensive overview of the prevalence of PTSS and risk factors in children and parents shortly after pediatric primary brain tumor diagnosis. Secondly, the relationship between parental and child PTSS is described. This study is part of a larger longitudinal study into sleep, PTSS, and neurocognitive functioning of children with a brain tumor (SuSPeCT-study).

Methods

Patients and procedures

In the Netherlands, since 2018 all pediatric cancer care is concentrated in The Princess Máxima Center for Pediatric Oncology. Active recruitment of new patients with a brain tumor took place between January 2019 and September 2021. Eligible patients had a primary brain tumor, age 6-16 at diagnosis, no evident developmental delay and sufficient understanding of the Dutch language. Written informed consent was provided by all participants and their parents or legally authorized representatives. As part of the larger longitudinal study, patients and their parents were asked to complete questionnaires at three time points. For the current study, we describe results from the first time point. Patients and parents completed online questionnaires between one and three months after diagnosis. The Institutional Review Board of the University Medical Center Utrecht classified this study as an exempt of the Medical Research Involving Human Subjects Act.

Patient and medical characteristics

Information on patient and medical characteristics was abstracted from the participants' medical records. This included sex, age, date of diagnosis, tumor type and tumor location. Also, information on neurosurgery, radiotherapy or chemotherapy treatment that had taken place at the time of assessment was collected, as well as information on medical complications that had occurred. In addition, information on premorbid psychological problems as documented by the center's psychologists was collected. Patients and their parents provided information on their country of birth and education through a general online survey.

Questionnaires

The Children's Revised Impact of Event Scale (CRIES-13) is a brief and validated measure to screen children for PTSS [27]. Both the self-report (8 years and older) and the similar proxy-report (6 years and older; completed by the parents) version were administered. Thirteen questions on a four-point Likert-scale (0-1-3-5) form three subscales (Re-experience N=4 items, Avoidance N=4 items, and Increased irritability N=5 items) and a total score (range 0-65). The total score is highly associated with fulfillment of the DSM-IV criteria for the diagnosis of PTSD [28]. Cut-off scores are 30 for the self-report and 31 for the proxy-report, and indicate a high risk of PTSD, for which further diagnostics and interventions are recommended [28,29]. There is no data available on the occurrence of PTSD amongst the general population of Dutch children. In the general population of American children PTSD according to DSM-IV criteria was estimated to be present in less than 0.5% of children [30]. As questionnaires do not yield official diagnoses, and we are merely interested in the presence of symptoms, we speak of PTSS only and describe scores above the cut-off as "clinical scores". Clinical scores can be considered severe PTSS (suggestive of PTSD). The Cronbach's α of the scales (subscales and total scale) in the current study ranged from 0.69 to 0.87.

The PTSD Checklist for DSM-5 (PCL-5) is an adult self-report checklist for posttraumatic stress symptoms, according to the DSM-5 criteria [31,32]. It was administered to both parents. The questionnaire consists of twenty questions on a five-point Likert-scale (range 0-80). Clinical scores can be obtained by either exceeding the cut-off score of 33 (established in several countries; subclinical scores 28-32) [33-35], or the DSM-5 diagnostic rule of fulfillment of at least one B-criterion (Re-experience, N=5 items), one C-criterion (Avoidance, N=2 items), two D-criterions (Negative cognitions/mood, N=7 items) and two E-criterions (Increased irritability, N=6 items) [36]. As described above, clinical scores are considered severe PTSS (suggestive of PTSD). Earlier research found clinical scores to be present in 5.3% of women and 2.2% of men in the general Dutch population, using the SRS-PTSD questionnaire [37]. The PCL-5 has evidence for adequate reliability and validity and the Cronbach's α of the scales (sub-scales and total scale) in the current study ranged from 0.80 to 0.94 [33-35].

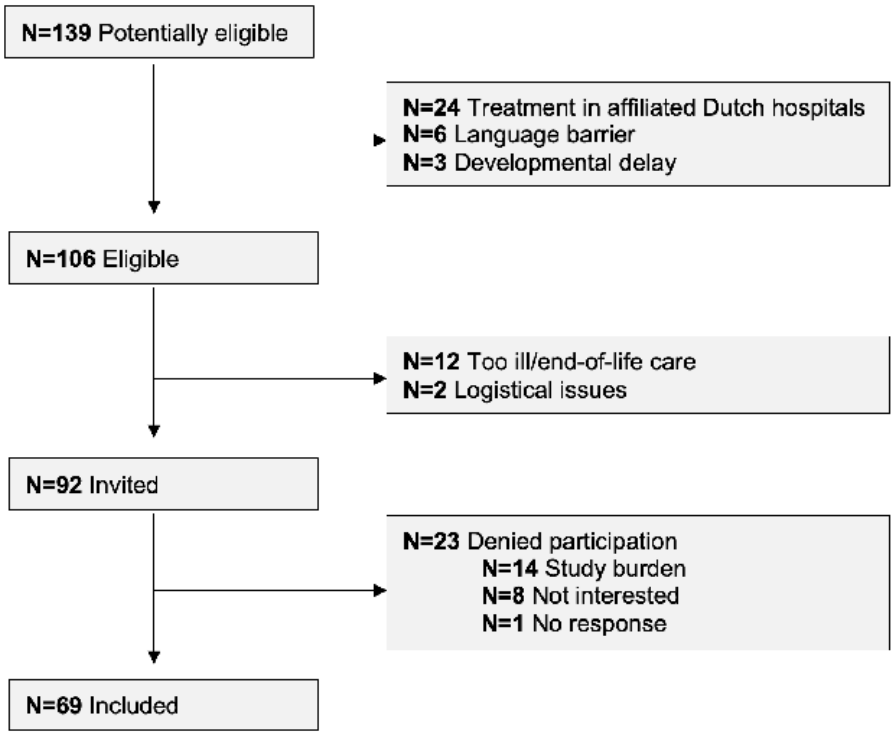
The Psychosocial Assessment Tool (PAT; version 2.0) is a validated brief screener for psychosocial risk in pediatric health [38]. It is completed by parents upon hospital entry as part of standard care. This parent-reported cancer-specific questionnaire identifies areas of risk and resilience across seven domains. The total PAT-score yields a three-level determination of family risk and associated care needs, based on the Pediatric Psychosocial Preventative Health Model: universal care (total score <1), targeted care (total score 1.0-1.9) or clinical care (total score $\geq$2) [39,40]. The domains family structure (e.g. parent marital status, financial difficulties), social support for parents (e.g. is emotional support and information provided), and illness cognitions (e.g. trust in physicians, trust in good outcome) were used here as potential risk factors for child and parent PTSS outcomes. Other domains contain questions which overlap with questions of the outcome questionnaires and were therefore not included as potential risk factors.

Statistical analyses

Baseline patient and tumor characteristics of the participants were reported, and T-tests and chi-square tests were used to examine potential differences between participants and non-participants (those who were invited to the study, but refused participation), and between participants and children who were eligible but not approached (due to severe illness or logistical issues).

The prevalence of PTSS was explored by describing the percentage of participants who obtained total scores higher than the cut-off scores (CRIES-13, PCL-5). The percentage of clinical scores in our sample was compared to the percentage of clinical scores in the general population, if available, by performing non-parametric chi-square tests (PCL-5). Odds ratios were calculated subsequently. Associations between parent and child PTSS (self- and proxy-reported) were explored with correlation tables. P-values of <0.05 were considered statistically significant. Subsequently, after assumptions were checked, risk factors for PTSS were explored with univariable linear regression models. Variables with a P-value of <0.10 were added to a multivariable model by performing a forward selection procedure. IBM SPSS Statistics version 26.0.0.1 was used for all analyses.

Figure 1 - Flowchart of participant enrollment



Results

Patient and medical characteristics

Consent was given by 69 (75%) children (see Figure 1 for participant enrollment). Compared to participants, non-participants (N=23) did not differ in sex (boy 68% vs. 61%, P=0.52) and age (mean age 11.6 (SD=2.8) vs. 11.1 (SD=4.3), P=0.76). Participants less often had a tumor in the cerebral lobes, compared to non-participants (20% vs. 44%, P=0.03), no significant differences were found for tumors in the posterior fossa (42% vs. 35%, P=0.54) or supratentorial medial structures (38% vs. 22%, P=0.16). Compared to participants, children who were eligible but not approached for the study due to end-of-life care or logistics (N=14) did not differ in sex (boy 68% vs. 57%, P=0.44), age (mean age 11.6 (SD=2.8) vs. 9.9 (SD=2.3), P=0.08) or tumor location; posterior fossa (42% vs. 43%, P=0.95), supratentorial medial structures (38% vs. 36%, P=0.89), cerebral lobes (20% vs. 21%, P=0.92).

Participants' baseline characteristics are described in Table 1. Premorbid psychological problems were present in 9 (13%) children, but these were not posttraumatic stress disorders. The PAT was filled out by the parents (N=49) and almost one quarter of the families were at psychosocial risk, based on the total scores (targeted or clinical; Table 1). Mean raw scores of the PAT's subscales that were used as predictors for the outcome measures could vary from zero to one, and were 0.11 for family structure, 0.03 for social support and 0.13 for illness cognitions (higher scores indicate more problems).

Table 1 - Baseline demographic, medical and psychosocial characteristics of participants and their family

	Study participants (N=69) Mean (SD), or N (%)
Child variables	
Boy	47 (68)
Age at assessment (years)	11.6 (2.8)
Time since diagnosis (days)	53 (28)
Premorbid psychological problems[1]	9 (13)
Parental education level[2]	
Low-Middle	33 (51)
High	32 (49)

Table 1 - Baseline demographic, medical and psychosocial characteristics of participants and their family

Medical variables	
Tumor type	
Low grade glioma	33 (48)
Germ cell tumor	10 (15)
Craniopharyngioma	9 (13)
High grade glioma	6 (8)
Medulloblastoma	6 (8)
Ependymoma	2 (3)
Other[3]	3 (4)
Tumor location	
Posterior fossa	29 (42)
Supratentorial medial structures	26 (38)
Cerebral lobes	14 (20)
Treatment	
Neurosurgery	63 (91)
Started chemotherapy	12 (17)
Started radiotherapy	13 (19)
Proton therapy	5 (7)
Photon therapy	8 (12)
Metastases	8 (12)
Obstructive hydrocephalus	33 (48)
Hormone deficiency	18 (26)
Epilepsy	9 (13)
CMS	5 (8)
Psychosocial risk (PAT) (N=49)	
Universal score	37 (76)
Targeted score	10 (20)
Clinical score	2 (4)

Abbreviations: SD = standard deviation, CMS = cerebellar mutism syndrome, PAT = Psychosocial Assessment Tool
[1] Attention deficit/hyperactivity disorder (N=4), depression (N=2), autism (N=1), oppositional defiant disorder (N=1), panic disorder (N=1)
[2] Low = no education, primary school, lower secondary education; middle = upper secondary education, preuniversity education, intermediate vocational education; high = higher vocational education, university
[3] ATRT (N=1), plexus tumor (N=1), meningioma (N=1)

Table 2 - Child and parent PTSS scores

	Mean score[1] (SD) Participants	Clinical score[2], % (N) Participants	Clinical score[2], % Reference group	OR
Child PTSS				
CRIES-13 self-report (N=51)[3]				
Re-experience	5.2 (4.2)	-	-	-
Avoidance	6.3 (5.8)	-	-	-
Increased irritability	8.3 (5.9)	-	-	-
Total PTSS	19.9 (13.5)	29.4% (15)	NA	-
CRIES-13 proxy-report (N=63)[3]				
Re-experience	4.7 (4.1)	-	-	-
Avoidance	4.7 (5.2)	-	-	-
Increased irritability	6.4 (5.2)	-	-	-
Total PTSS	15.8 (12.3)	11.1% (7)	NA	-
Parent PTSS				
PCL-5 mothers (N=58)[4]				
Re-experience (criterion B)	4.08 (3.59)	-	-	-
Avoidance (criterion C)	1.00 (1.47)	-	-	-
Negative cognitions/mood (criterion D)	3.97 (5.17)	-	-	-
Increased irritability (criterion E)	5.25 (4.41)	-	-	-
Total PTSS	14.4 (13.4)	**13.8% (8)***	5.3%	2.86
PCL-5 fathers (N=50)[4]				
Re-experience (criterion B)	3.16 (3.22)	-	-	-
Avoidance (criterion C)	0.86 (1.47)	-	-	-
Negative cognitions/mood (criterion D)	3.48 (4.2)	-	-	-
Increased irritability (criterion E)	4.16 (3.58)	-	-	-
Total PTSS	11.7 (11.0)	**8.0% (4)***	2.2%	4.09

Abbreviations: SD = standard deviation, OR = odds ratio, CRIES = Children's Revised Impact of Event Scale, PTSS = posttraumatic stress symptoms, PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5

[1] Higher scores indicate more problems.

[2] According to questionnaire cut-off points

[3] Possible score ranges: Re-experience 0-20, Avoidance 0-20, Increased irritability 0-25, Total PTSS 0-65

[4] Possible score ranges: Re-experience 0-20, Avoidance 0-8, Negative cognitions/mood 0-28, Increased irritability 0-24, Total PTSS 0-80

* Statistically significant (P<0.01)

Table 3 - Correlations between child and parent PTSS scores

	Child PTSS self-report (CRIES-13)	Child PTSS proxy-report (CRIES-13)	Mother PTSS (PCL-5)	Father PTSS (PCL-5)
Child PTSS self-report (CRIES-13)	-	**0.49** (N=50)**	0.22 (N=47)	0.18 (N=41)
Child PTSS proxy-report (CRIES-13)	-	-	0.24 (N=58)	**0.42** (N=48)**
Mother PTSS (PCL-5)	-	-	-	**0.35* (N=43)**

Abbreviations: PTSS = posttraumatic stress symptoms, CRIES = Children's Revised Impact of Event Scale, PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5
* Statistically significant (P<0.05)

** Statistically significant (P<0.01)

Outcome questionnaires

Results on all outcome questionnaires are presented in Table 2 and 3. A total of 29.4% of the children reported clinical PTSS scores, whereas according to their parents only 11.1% of the children experienced clinical PTSS. Self- and proxy-reports were significantly correlated (r=0.49, P<0.01).

For parent PTSS, 13.8% (OR=2.86) of the mothers and 8.0% (OR=4.09) of the fathers reported scores above the cut-off, both significantly higher compared to the general population (P<0.01). Scores of parents were significantly correlated (r=0.35, P=0.02).
Parental PTSS was not associated with self-reported child PTSS (mothers (r=0.22, P=0.13), fathers (r=0.18, P=0.26)). For proxy-reported child PTSS, child and father PTSS scores were associated (r=0.42, P<0.01), but not child and mother PTSS scores (r=0.24, P=0.07).

Risk factors

Results on univariable analyses of risk factors for child and parent PTSS are presented in Table 4. Children self-reported more PTSS more shortly after diagnosis (B=-0.13, 95%CI -0.25 – -0.01, P=0.04), when diagnosed with a tumor in the cerebral hemispheres (B=16.43, 95%CI 6.47 – 26.39, P<0.01), after having had one or multiple epileptic seizures (B=12.93, 95%CI 1.61 – 24.26, P=0.03), and when more problems were reported on family structure (B=27.76, 95%CI 6.10 – 49.41, P=0.01; PAT questionnaire). In the multivariable models (Table 5), shorter time since diagnosis (B=-0.18, 95%CI -0.34 – -0.02, P=0.03) and a tumor in the cerebral hemispheres (B=14.23, 95%CI 0.04 – 28.42, P=0.05) were the two remaining contributing factors associated with more PTSS.

Parents reported more child PTSS when their child had a tumor in the posterior fossa (B=5.91, 95%CI -0.92 – 12.76, P=0.03), when their child had cerebral mutism syndrome (B=15.22, 95%CI 2.97 – 27.47, P=0.02), and when they experienced less positive illness cognitions (B=25.28, 95%CI 4.93 – 45.63, P=0.02; PAT questionnaire). However, no associations were found in multivariable models.

Table 4a -Univariable analyses of risk factors for child and parent PTSS

B (95%CI)	Child PTSS self-report (CRIES-13)	Child PTSS proxy-report (CRIES-13)
Sex *Girl vs. boy*	1.13 (-6.81 – 9.07)	-1.83 (-8.54 – 4.89)
Age *Continuous*	0.21 (-1.27 – 1.68)	0.42 (-0.72 – 1.56)
Time since diagnosis *Continuous*	**-0.13 (-0.25 – -0.01)****	-0.08 (-0.19 – 0.03)
Premorbid psychological problems *Yes vs. no*	6.68 (-3.56 – 16.91)	0.79 (-7.63 – 9.21)
Parental education *High vs. low/middle*	0.14 (-7.58 – 7.86)	1.12 (-5.15 – 7.29)
Tumor location *Supratentorial midline (ref.)* *Cerebral hemispheres* *Posterior fossa*	 **16.43 (6.47 – 26.39)**** **6.86 (-1.06 – 14.79)**	 **-1.92 (-10.29 – 6.46)** **5.91 (-0.92 – 12.76)****
Neurosurgery *Yes vs. no*	3.10 (-13.19 – 19.40)	-0.06 (-11.65 – 11.53)
Started chemotherapy *Yes vs. no*	-6.50 (-15.99 – 3.00)	-1.90 (-10.14 – 6.35)
Started radiotherapy[1] *Yes vs. no*	0.91 (-8.42 – 10.24)	-5.53 (-13.66 – 2.60)
Metastases *Yes vs. no*	-1.73 (-12.88 – 9.42)	-1.71 (-11.12 – 7.69)
Obstr. hydrocephalus *Yes vs. no*	-4.16 (-11.74 –3.43)	0.87 (-5.40 – 7.14)
Hormone deficiency *Yes vs. no*	-6.19 (-14.82 – 2.44)	0.83 (-6.23 – 7.89)
Epilepsy *Yes vs. no*	**12.93 (1.61 – 24.26)****	-3.41 (13.34 – 6.52)
CMS *Yes vs. no*	1.17 (-13.11 – 15.45)	**15.22 (2.97 – 27.47)****
Family structure[2] *Continuous*	**27.76 (6.10 – 49.41)****	3.01 (-16.15 – 22.26)
Social support[2] *Continuous*	9.14 (-44.52 – 62.81)	9.73 (-38.40 – 57.86)
Illness cognitions[2] *Continuous*	1.38 (-25.13 – 27.89)	**25.28 (4.93 – 45.63)****

All outcomes are raw scores.
Abbreviations: PTSS = posttraumatic stress, CRIES = Children's Revised Impact of Event Scale, PCL-5 = PTSS Checklist voor de DSM-5, ref. = reference, obstr. = obstructive, CMS = cerebellar mutism syndrome
[1] Proton and photon radiation therapy grouped together
[2] Higher values reflect more problems (PAT questionnaire).
** Statistically significant (P<0.05) and added to the multivariable models
* P-value <0.10 and added to the multivariable models

Table 4b -Univariable analyses of risk factors for child and parent PTSS

B (95%CI)	Mother PTSS (PCL-5)	Father PTSS (PCL-5)
Sex *Girl vs. boy*	-5.31 (-12.74 – 2.11)	-2.44 (-9.15 – 4.27)
Age *Continuous*	0.32 (-0.98 – 1.62)	0.78 (-0.31 – 1.87)
Time since diagnosis *Continuous*	0.02 (-0.11 – 0.16)	0.03 (-0.07 – 0.14)
Premorbid psychological problems *Yes vs. no*	4.73 (-4.65 – 14.11)	**7.90 (-0.43 – 16.23)***
Parental education *High vs. low/middle*	-2.52 (-9.58 – 4.55)	1.00 (-5.29 – 7.29)
Tumor location *Supratentorial midline (ref.)* *Cerebral hemispheres* *Posterior fossa*	 -0.60 (-10.32 – 9.12) -0.24 (-8.42 – 7.94)	 3.58 (-5.37 – 12.53) -0.44 (-7.41 – 6.53)
Neurosurgery *Yes vs. no*	3.88 (-10.09 – 17.85)	-9.58 (-22.54 – 3.38)
Started chemotherapy *Yes vs. no*	4.83 (-4.88 – 14.55)	**8.36 (1.16 – 15.56)****
Started radiotherapy[1] *Yes vs. no*	**11.04 (2.13 – 19.96)****	**6.07 (-0.88 – 13.03)***
Metastases *Yes vs. no*	5.17 (-6.40 – 16.74)	2.47 (-7.19 – 12.13)
Obstr. hydrocephalus *Yes vs. no*	-0.68 (-7.79 – 6.43)	-2.39 (-8.65 – 3.87)
Hormone deficiency *Yes vs. no*	3.83 (-4.21 – 11.87)	-3.72 (-3.06 – 10.51)
Epilepsy *Yes vs. no*	-0.57 (-11.47 – 10.32)	-2.90 (-10.78 – 10.20)
CMS *Yes vs. no*	10.62 (-3.09 – 24.33)	2.84 (-1.39 – 16.07)
Family structure[2] *Continuous*	-2.18 (-25.99 – 21.64)	11.98 (-10.64 – 34.60)
Social support[2] *Continuous*	-5.20 (-60.35 – 49.95)	14.19 (-34.82 – 63.20)
Illness cognitions[2] *Continuous*	**20.91 (-4.91 – 46.72)***	**21.87 (2.25 – 41.49)****

All outcomes are raw scores.
Abbreviations: PTSS = posttraumatic stress, CRIES = Children's Revised Impact of Event Scale, PCL-5 = PTSS Checklist voor de DSM-5, ref. = reference, obstr. = obstructive, CMS = cerebellar mutism syndrome
[1] Proton and photon radiation therapy grouped together
[2] Higher values reflect more problems (PAT questionnaire).
** Statistically significant (P<0.05) and added to the multivariable models

* P-value <0.10 and added to the multivariable models

Mothers reported more PTSS themselves when their child had started radiotherapy (proton/photon; B=11.04, 95CI 2.13 – 19.96, P=0.02) and when they experienced less positive illness cognitions (B=20.91, 95%CI -4.91 – 46.72, P=0.10; PAT questionnaire). In multivariable models, having started radiotherapy remained significantly associated to maternal PTSS (B=9.95, 95%CI -0.40 – 20.30, P=0.05).

Fathers reported more PTSS themselves when their child had premorbid psychological problems (B=7.90, 95%CI -0.43 – 16.23, P=0.06), when their child had started chemotherapy (B=8.36, 95%CI 1.16 – 15.56, P=0.02) or radiotherapy (proton/photon, B=6.07, 95%CI -0.88 – 13.03, P=0.09), and when they experienced less positive illness cognitions (B=21.87, 95%CI 2.25 – 41.49, P=0.03, PAT questionnaire). Illness cognitions was the only remaining contributing factor in multivariable models (B=20.93, 95%CI -0.50 – 42.37, P=0.05).

Sex of the child, age of the child, level of parental education, history of neurosurgery, metastases, obstructive hydrocephalus, hormone deficiency and level of social support (PAT questionnaire) were not significantly associated to any of the outcomes.

Table 5 -Multivariable analyses of risk factors for child and parent PTSS

B (95%CI)	Child PTSS Self-report (CRIES-13)	Child PTSS Proxy-report (CRIES-13)	Mother PTSS (PCL-5)	Father PTSS (PCL-5)
Time since diagnosis	**-0.18 (-0.34 – 0.02)***	-	-	-
Premorbid psychological problems	-	-	-	4.39 (-5.82 – 14.60)
Tumor location Supratentorial midline (ref.) Cerebral hemispheres Posterior fossa	 **14.23 (0.04 – 28.42)*** -	 - 1.84 (-5.20 – 8.87)	 - -	 - -
Started chemotherapy	-	-	-	5.37 (-4.41 – 15.14)
Started radiotherapy[1]	-	-	**9.95 (-0.40 – 20.30)***	1.00 (-9.40 – 11.40)
Epilepsy	-1.56 (-20.47 – 17.36)	-	-	-
CMS	-	13.90 (-2.06 – 29.87)	-	-
Family structure[2]	15.93 (-4.70 – 36.57)	-	-	-
Illness cognitions[2]	-	15.53 (-6.79 – 37.84)	16.74 (-8.67 – 42.16)	**20.93 (-0.50 – 42. 37)***

All outcomes are raw scores.
Time since diagnosis, Family structure and Illness cognitions are continuous,
Premorbid psychological problems, started chemotherapy, started radiotherapy, epilepsy, and CMS is yes vs. no.
Abbreviations: PTSS = posttraumatic stress, CRIES = Children's Revised Impact of Event Scale, PCL-5 = PTSS Checklist voor de DSM-5, ref. = reference, obstr. = obstructive, CMS = cerebellar mutism syndrome.
[1] Proton and photon radiation therapy grouped together
[2] Higher values reflect more problems (PAT questionnaire).
* Statistically significant (P-value <0.05)

Discussion

This comprehensive overview demonstrates a high prevalence of PTSS, for both children and their parents, one to three months after pediatric brain tumor diagnosis. Children report more symptoms earlier after diagnosis and when the tumor is in the cerebral hemispheres. Mothers report more symptoms themselves when their child has started radiotherapy, fathers when they experience less positive illness cognitions.

Almost three out of ten children report scores suggestive of a posttraumatic stress disorder. Reference numbers are not available, and to date, there have been no earlier studies examining PTSS in children during brain tumor treatment. Two studies investigated PTSS during treatment for any type of childhood cancer, and found self-reported clinical child PTSS to be present in 10% and 11% of the sample [41,42]. A possible explanation for the higher percentage of clinical child PTSS in our sample may be that the medical interventions and the medical symptomatology – as a consequence of tumor or treatment – are more impactful for brain tumors than for other types of childhood cancer.

Of the 29.4% of children in our sample reporting clinical PTSS, it is expected that some will recover, and some will develop chronic symptoms [7,43]. However, several previous studies failed to reliably correlate time since diagnosis with cancer-related PTSS in childhood cancer survivors, and PTSS prevalence was similar after six and twelve months post-diagnosis2,9. Longitudinal data of our study will provide insight into the course of PTSS in this sample of children with brain tumors. Lastly, as expected, the majority of children in our sample seem resilient, providing further evidence for resilience as the predominant adjustment outcome and possibly as a result of strengthened psychosocial care provided for children and families in our pediatric cancer center.

Interestingly, although self- and proxy-reports were associated, children seem to experience more symptoms than parents are aware of, underlining the importance of the use of self-reported outcome measures. Phipps and colleagues previously described no observed differences in PTSS between informants [25]. Nonetheless, differences in self- and proxy-reported outcomes are common, although usually parents consistently overestimate their children's symptoms during cancer treatment [44,45]. A possible explanation for why the parents in our sample seem to underestimate the symptoms of their children may be that, in this very early phase, they are so overwhelmed themselves that they fail to notice some (perhaps more covert) symptoms in their children. Another explanation is that parents may – possibly rightly so – interpret certain symptoms in their children as direct consequences of the brain tumor or the medical treatment instead of as signs of posttraumatic stress, and therefore choose not to report them (e.g. increased irritability after neurosurgery). This latter explanation is in line with our clinical impression that behavioral changes in children shortly after diagnosis and start of treatment are partly stress-related and partly tumor- or treatment-related. This warrants careful interpretation of both self- and proxy-reported child PTSS scores in this early phase.

Clinical PTSS scores were observed in 13.8% of the mothers and 8.0% of the fathers, and rates were higher than in the general Dutch population [37]. As expected, mothers experience more symptoms, which has already been seen in parents of children with cancer, as well as in the general population [20,37,41]. An earlier meta-analysis described PTSS rates in parents of children with cancer or childhood cancer survivors between 4 and 75%, with a pooled prevalence of 26% [19]. A longitudinal study of Sharp and colleagues showed 28.5% of parents having moderately high PTSS in the first few months after their child's cancer diagnosis, with significantly increasing symptoms over time [42]. Comparing rates of PTSS across studies should however be done with caution, as heterogeneity due to significant methodological differences in measurement tools and defined thresholds complicates valid interpretation.

It was hypothesized that self-reported child PTSS and parental PTSS were associated. This relationship was not found, though earlier studies showed significant associations between parent and child PTSS amongst childhood cancer survivors [21]. Possibly, high parental distress levels will impact children only when it is present for a significant amount of time, and longitudinal results of our study will reveal longer term parent-child associations.

Interestingly, risk factors for PTSS were different for children with brain tumors compared to their parents. Also, different risk factors for PTSS were observed in child self-reports and child proxy-reports. Nevertheless, for both parents and children there were psychological as well as medical risk factors associated to PTSS outcomes, and these insights contribute further to our understanding of who is most at risk.

Regardless of what factors contribute to the onset and continuation of symptoms, previous literature underlines that subjective experience is a critical predictor [7,26,43]. Future research should look into psychological interventions aiming to change subjective appraisal of cancer-related events in an early phase of pediatric brain tumor treatment.

This prospective, observational study was the first to assess PTSS in children with a brain tumor and their parents, within three months after diagnosis, and the sample and participation rate were relatively high. Also, few research has included fathers specifically. Methodological limitations are small numbers (e.g. CMS, epilepsy), lack of information on recent psychological care, and limited norm data. Furthermore, even though clinical PTSS scores are indicative of PTSD, an official diagnosis is obtained by clinical interviews. To speak of PTSD, symptoms should be present for at least one month, and although the questionnaires were filled out at least one month after diagnosis, it asks for symptoms of the last seven days and symptoms could consequently be the result of recent events. Also, the questionnaires ask for general posttraumatic stress symptoms, not specific cancer-related events, and symptoms could be a result of other current or past life events.

In conclusion, children with a recently diagnosed brain tumor frequently experience PTSS, and seem to experience more symptoms than parents are aware of. Parents frequently

experience PTSS as well, especially mothers. For both children and parents, the majority seem to show resilience, although symptoms of re-experiencing, avoidance and/or irritability may still be present to some extent. Longitudinal data of this study will provide valuable insights in the course of PTSS over time, longer-term risk factors and parent-child associations. Given the significant negative health consequences of chronic posttraumatic stress symptoms, there should be early systematic monitoring in place for children with a brain tumor and their parents. Healthcare staff should be aware of posttraumatic stress symptoms, actively assess distress, encourage and empower families to talk and seek comfort, identify family strengths and coping resources and timely refer to hospital or community-based mental health interventions when appropriate [46].

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4

Posttraumatic stress, sleep and neurocognitive problems in children newly diagnosed with a pediatric brain tumor

4

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Abstract

Purpose.

Children diagnosed with a pediatric brain tumor are at risk to develop cognitive problems. Posttraumatic stress and sleep have been associated with poorer cognitive outcomes in the general population, and could be potential targets for intervention in brain tumor patients. Therefore, this study examined cognitive functioning in children newly diagnosed with a pediatric brain tumor and the association of posttraumatic stress and sleep on cognitive outcomes.

Methods.

Children 6-16 years old who were newly diagnosed with a brain tumor completed questionnaires on posttraumatic stress and sleep, actigraphy for sleep, and tests for neuropsychological outcomes. One-sample t-tests were used to compare cognition with age norms and multivariable regression analyses examined associations between posttraumatic stress and sleep on cognitive functioning. Models were adjusted for age, sex, time since diagnosis, hydrocephalus, and tumor location.

Results.

Of all eligible children, 69 patients with newly diagnosed brain tumors were included (32% female, mean=11.6 years). Compared to age norms, patients with brain tumors scored lower on attention (mean Z [SD]=-0.61 [1.26], P<0.01), executive functioning (mean Z [SD]=-0.41 [1.10], P<0.01), processing speed (mean Z [SD]=-0.61 [1.10], P<0.01) and long-term auditory memory (mean Z [SD]=-0.39 [1.38], P=0.03). Hydrocephalus and posterior fossa tumor diagnosis were associated with lower scores on attention and processing speed (P<0.05). A significant association was found between the posttraumatic stress and sleep self-report questionnaires (P<0.001), however, posttraumatic stress or sleep were not associated with cognitive outcomes at this phase (P>0.10).

Conclusion.

Children newly diagnosed with a brain tumor show deficits in cognitive functioning. Medical factors, but not posttraumatic stress and sleep, are associated with poorer cognitive performance at this phase. Longitudinal research will be important for identifying early risk factors that may be associated with poorer cognitive skills on the longer term.

Keywords

Brain tumor, posttraumatic stress, sleep, cognition, pediatric

Introduction

Due to improved medical care, more children who are diagnosed with cancer survive [1] and therefore greater attention is needed on health-related quality of life in this vulnerable group. Of all children diagnosed with childhood cancer, survivors of a pediatric brain tumor are especially prone to develop neurocognitive problems [2]. Domains such as attention and working memory are particularly sensitive to impairment [3, 4], which can then impact psychosocial and academic performance [5-7]. Medical factors have been the most widely studied risk factors for poorer neurocognitive outcome. For example, this has included direct medical factors such as the location of the tumor and type of treatment, but also secondary medical effects such as hydrocephalus and epilepsy [8-10].

Previous research has studied the relationship between demographic or psychosocial factors and neurocognitive outcomes in survivors of a pediatric brain tumor, such as posttraumatic stress symptoms [11]. A diagnosis of childhood cancer is obviously a stressful life event for children and their parents. Therefore, post-traumatic stress symptoms have been extensively studied in children treated for childhood cancer, during hospitalization but also after treatment and in childhood cancer survivors [9, 12-15]. Children with brain tumors are particularly vulnerable to develop posttraumatic stress symptoms, partly due to the uncertain future regarding long-term and ongoing problems [13, 16-18]. Furthermore, persisting posttraumatic stress symptoms may negatively influence neurobiological mechanisms in the brain in the longer term [19].

Aside from posttraumatic stress symptoms, increased sleep problems are associated with worse neurocognitive functioning in childhood cancer survivors [20]. Previous studies have shown that pediatric brain tumor survivors have increased sleep problems, which are associated with cognitive complaints [21]. For example, higher levels of sleep disturbance were associated with more cognitive problems, including sluggish cognitive tempo [22], attention deficits [22] or executive functioning deficits [21].

Whereas most research focusses on vulnerabilities in long-term survivors of a pediatric brain tumor, it is important to monitor problems in an early phase to prevent persisting problems that can impede development. Also, most studies include a variety of cancer diagnoses due to the small percentage of children diagnosed with a brain tumor which causes heterogeneity in the sample, although these children specifically face challenges on neurocognitive functioning. Therefore, it is important to understand more of the underlying factors (such as posttraumatic stress and sleep) that contribute to neurocognitive problems in children newly diagnosed with a brain tumor, to develop possible targets for interventions.

Therefore, in the current study, we aim to investigate the associations between posttraumatic stress symptoms and sleep on neurocognitive problems in children with a newly diagnosed brain tumor. We hypothesize that higher amounts of posttraumatic stress and sleep problems will be associated with increased neurocognitive problems. We will operationalize

neurocognitive problems by focusing primarily on the domain of attention, which has been shown to be mostly associated with posttraumatic stress symptoms and sleep in other pediatric groups [23, 24], including survivors of a pediatric brain tumor [19]. Furthermore, we will investigate the effect of posttraumatic stress and sleep on domains such as executive functioning, processing speed and memory, as these domains are also impacted in pediatric brain tumor survivors [21].

Methods

Participants and procedures

The Princess Máxima Center is a Dutch nationwide pediatric oncology center where all pediatric cancer patients are treated. A small number of children with low-grade brain tumors are treated with surgery only in former pediatric oncology centers. For this study, children who were diagnosed with a primary brain tumor and who received treatment primarily in the Princess Máxima Center were eligible if they were between 6-16 years of age at diagnosis, had no evident developmental delay (as reported by physicians) and had sufficient understanding of the Dutch language. We actively recruited participants between January 2019 and November 2021. Children and parents provided written informed consent. The Institutional Review Board of the University Medical Center Utrecht classified this study as exempt from the Medical Research Involving Human Subjects Act. This study is part of a larger longitudinal study examining sleep, posttraumatic stress, and neurocognitive functioning of children with a brain tumor (SuSPeCT-study). For the current study, we used data from the first time point, which was between four weeks and three months after brain tumor diagnosis.

Demographic and medical information

Demographic and medical factors of participants were extracted from the medical records, including information on sex, age, date of diagnosis, tumor type, tumor location, treatment details, history of obstructive hydrocephalus, hormone deficiency, epilepsy and cerebellar mutism syndrome. Information on pre-morbid child psychological functioning and psychological treatment, as well as information on their parents' educational level was collected through a general survey.

Neurocognitive functioning

Several neurocognitive tests of attention, executive functioning, processing speed and memory were administered by a qualified psychologist during a one-hour neuropsychological assessment.

The Amsterdam Neuropsychological Tasks (ANT) program is a computerized neurocognitive test battery. Previous research shows the ANT has sufficient sensitivity and validity [25, 26]. The subtest 'Sustained Attention Dots' (SAD) measures visual sustained attention. The outcome variables 'average completion time' and the 'standard deviation of the completion time' were included as indicators of attention, namely speed and fluctuation of speed. Because the target rate (four-dot pattern) was 33%, the no-button should be pressed twice as often

as the yes-button. With increasing time on the task, this difference in response probability is expected to invoke a response bias during the task, or an increasing number of targets missed. Therefore, number of misses was included as a measure of inhibition [27]. The subtest 'Baseline Speed' (BS) measures reaction time where the child presses a button as quickly as possible. The outcome variable of reaction time was examined. All outcomes are represented as Z-scores.

The '15-word test' (15WT) child (up to 12 years old) or adult (13 years and older) version was used to measure auditory verbal memory [28]. Children were asked to remember fifteen words that were read to them 5 consecutive times, and after every repetition the examiner asked the child to name the words that were remembered (immediate recall). After 20 minutes, the child was asked to recall the list of words (delayed recall). Scores of immediate recall and delayed recall were analyzed as measures of short-term and long-term memory. Decile scores (child version) and T-scores (adult version) were converted to Z-scores.

The Dutch version of the Wechsler Intelligence Scale for Children, 5th edition (WISC-V-NL, up to 15 years old) or the Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV-NL, 16 years and older) were partly administered [29, 30]. The subtest 'Digit Span' measures working memory, where the child had to repeat a series of numbers in a specific order. During subtests 'Symbol Search' and 'Coding', the child was asked to search and cross out as many figures possible, and to draw as many figures possible within a certain time. Both subtests measure processing speed and the processing speed index score was converted to a Z-score.

Neurocognitive composite scores were calculated by calculating the mean of two subscores: average completion time (ANT SAD) and the standard deviation of the completion time (ANT SAD) for attention, number of misses (ANT SAD) and Digit Span (WISC-V-NL/WAIS-IV-NL) for executive functioning, reaction speed (ANT BS) and processing speed index (WISC-V-NL/WAIS-IV-NL) for processing speed, and immediate and delayed recall (15-WT) for memory.

Posttraumatic stress symptoms and sleep

All posttraumatic stress and sleep outcomes were comprehensively described in preliminary work where children in our sample showed higher stress- and sleep problems compared to the general population [31, 32]. For example, 13.5% (self-report) and 12.3% (proxy) reported stress problems and 11% (self-report) and 5% (proxy) reported sleep problems [31, 32].

Posttraumatic stress was assessed with the Children's Revised Impact of Event Scale (CRIES-13) self-report. The total score consists of the 3 subscales 'increased irritability', 're-experience', and 'avoidance'. A clinical cut-off score of 30 in total was used, based on a diagnostic interview for DSM-IV criteria for PTSD [33]. Sleep was assessed by a self-report questionnaire and actigraphy. The PROMIS Pediatric Sleep Related Impairment short form 8a has eight items and focuses on perceptions associated with sleep problems, such as tiredness, impaired alertness and sleepiness during usual waking hours. The questionnaire is generic and not disease-specific

and assesses sleep over the past 7 days. The American version has strong clinical validity and internal consistency [34, 35]. The outcome is a T-score, where cut-off points are used to assess moderate (75–94th percentile) and severe (≥ 95th percentile) sleep problems [36]. Actigraphs (type wGT3XBT, Pensacola, FL) were wrist-worn for 7 nights, which registered the occurrence and intensity of arm movements. Actigraphy is low-cost, well-tolerated and validated against polysomnography [37]. The sleep efficiency (SE) was calculated, which is the ratio between the time spent in bed and the total sleep time, and is considered a relevant outcome for estimating sleep [38].

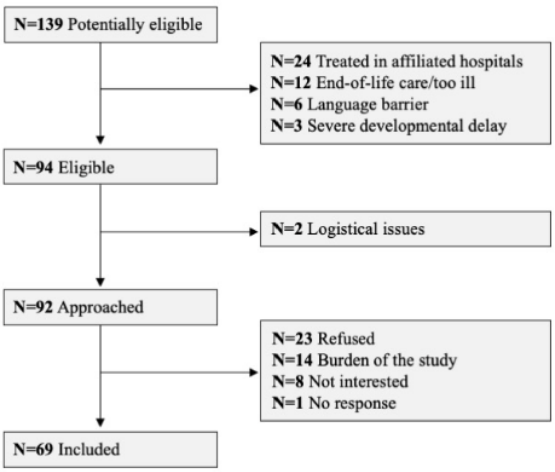
Statistical analyses

All analyses were performed in SPSS, version 26.0.01. One-sample t-tests were performed to compare Z-scores of attention, memory, executive functioning and processing speed with an average norm score of zero. The percentage of participants who scored >1SD below the norms was calculated, and compared to 16% (average population) by using non-parametric chi-square tests.

Univariable regression analyses were performed to explore if age (continuous), sex (female vs. male), time since diagnosis (continuous), tumor location (posterior fossa vs. elsewhere) and obstructive hydrocephalus (yes vs. no) were associated with cognitive outcomes. Predictors with a P-value lower than .05 were subsequently added into the multivariable analyses.

For the primary aim, multivariable regression models were conducted to investigate the effect of sleep disturbance, sleep efficiency and posttraumatic stress symptoms on cognitive outcomes. These models included variables that were significant from univariable regression (as above, per cognitive outcome). Sleep disturbance, sleep efficiency and posttraumatic stress were examined in separate models due to multicollinearity (based on Pearson correlation analyses).

Figure 1 - Flowchart of participant enrollment.



Results

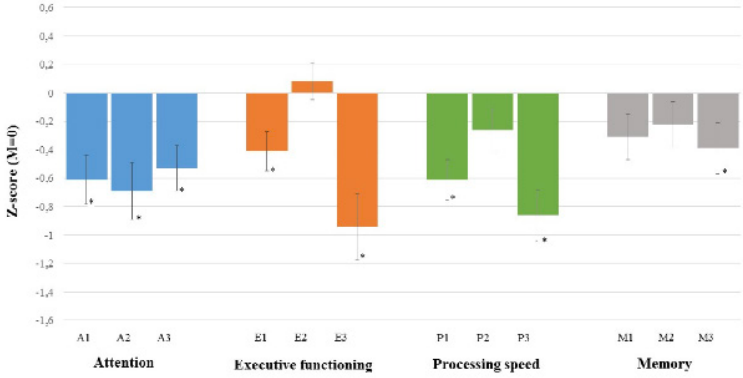
Of all eligible children and adolescents to participate in the study (N=94), 69 children participated (73.4%) with a mean age of 11.6 (SD=2.6) years (Figure 1). Reasons for not participating were logistical issues, burden or no interest in the study. Potential response bias was explored by using independent samples t-tests and non-parametric chi-square tests, and there were no differences in age (P=0.52), sex (P=0.76) or tumor location (P=0.95) between participants and non-participants (Table 1).

A description of participants is represented in Table 1. Of all participants, a total of 29 (42%) had a diagnosis of a posterior fossa tumor (versus other structures) and 33 (48%) had obstructive hydrocephalus. Furthermore, 63 (91%) were treated with neurosurgery, 12 (17%) had started with chemotherapy and 13 (19%) had started with radiotherapy.

Cognitive functioning

Cognitive results are presented in Table 2 and Figure 2. Participants scored significantly lower compared to the norm group on attention (mean Z (SD)= -0.61 (1.26), P<0.01), executive functioning (mean Z (SD)= -0.41 (1.10), P<0.01) and processing speed (mean Z (SD)= -0.61 (1.10), P<0.01). Regarding memory, participants did not show significantly lower scores on the average memory composite score (mean Z (SD)= -0.31 (1.23), P=0.06), however, the subscore of long-term memory was significantly lower compared to the general population (mean Z (SD)= -0.39 (1.38), P< 0.05). For attention and processing speed, impairments were shown in 26% and 29% of the children, respectively, which was significantly more than the percentage of impairments seen in the general population (16%, P≤.05). Higher rates of impairment were not seen in overall executive functioning and memory scores, however, difficulties were seen on the subtests of impulsivity and short-term memory (33% and 31%, P<.01).

Figure 2 - Cognitive outcomes in newly diagnosed patients with brain tumors



* P<.05, Compared to norm Z-score of zero using one-sample t-tests.:
A1: Attention composite score: mean of A2 and A3, A2: ANT SAD average completion time, A3: ANT SAD SD
E1: Executive functioning composite score: mean of E2 and E3 E2: ANT SAD number of misses, E3: WISC-V-NL/WAIS-IV-NL digit span
P1: Processing speed composite score: mean of P2 and P3, P2: ANT BS reaction speed, P3: WISC-V-NL/WAIS-IV-NL processing speed index
M1: Memory composite score: mean of M2 and M3, M2: 15WT immediate recall, M3: 15WT delayed recall

Table 1- Participant characteristics

	Study participants (N=69)	Non-participants (N=23)	P-value[1]
Male sex, N (%)	47 (68%)	14 (61%)	P=.52
Age at assessment, mean years (SD)	11.6 (2.8)	11.1 (4.3)	P=.76
Time since diagnosis, mean days (SD)	53 (28)		
Preferred hand			
Right, N (%)	46 (81%)		
Left, N (%)	9 (16%)		
Ambidextrous, N (%)	2 (4%)		
Glasses, N (%)	9 (15%)		
Hearing aid, N (%)	1 (2%)		
Parental education level[2]			
Low-Middle N (%)	33 (51%)		
High, N (%)	32 (49%)		
Tumor location			
Posterior fossa, N (%)	29 (42%)	8 (35%)	P=.95
Other structures, N (%)	40 (58%)	15 (65%)	
Tumor type			
Low grade glioma, N (%)	33 (48%)		
Germ cell tumor, N (%)	10 (15%)		
Craniopharyngioma, N (%)	9 (13%)		
High grade glioma, N (%)	6 (8%)		
Medulloblastoma, N (%)	6 (8%)		
Ependymoma, N (%)	2 (3%)		
Other, N (%)[3]	3 (4%)		
Treatment			
Neurosurgery, N (%)	63 (91%)		
Started chemotherapy, N (%)	12 (17%)		
Started radiotherapy, N (%)	13 (19%)		
Proton therapy, N (%)	5 (7%)		
Photon therapy, N (%)	8 (12%)		
Obstructive hydrocephalus, N (%)	33 (48%)		
Hormone deficiency, N (%)	18 (26%)		
Epilepsy, N (%)	9 (13%)		
Cerebellar mutism syndrome, N (%)	5 (7%)		

[1] Compared to participant group.
[2] Low = no education, primary school, lower secondary education; middle = upper secondary education, preuniversity education, intermediate vocational education; high = higher vocational education, university.
[3] ATRT (N=1), plexus tumor (N=1), meningioma (N=1).

Table 2 - Cognitive performance compared to age norms

	Mean Z (SD)	P-value[1]	Impaired N (%)[2]	P-value[3]
Attention (N=55)	-0.61 (1.26)	**<.01**	14 (26%)	.05
Completion time (ANT SAD)	-0.69 (1.51)	**<.01**	17 (31%)	**<.01**
Fluctuations (ANT SAD)	-0.53 (1.18)	**<.01**	14 (26%)	.06
Executive functioning (N=58)	-0.41 (1.10)	**<.01**	12 (21%)	.33
Digit Span (WISC/WAIS)	0.08 (.98)	.54	10 (17%)	.80
Misses (ANT SAD)	-0.94 (.1.75)	**<.01**	18 (33%)	**<.01**
Processing speed (N=58)	-0.61 (1.1)	**<.01**	17 (29%)	**<.01**
PSI (WISC/WAIS)	-0.26 (1.12)	.10	11 (20%)	.38
Reaction speed (ANT BS)	-0.86 (1.40)	**<.01**	19 (34%)	**<.01**
Memory (N=59)	-0.31 (1.23)	.06	14 (24%)	.11
Immediate recall (15WT)	-0.22 (1.23)	.17	18 (31%)	**<.01**
Delayed recall (15WT)	-0.39 (1.38)	**.03**	16 (27%)	**.02**

Composite scores include mean of two sub-scores per domain.
[1] Compared to normative Z-score of zero using one-sample t-tests.
[2] Percentage scoring >1SD below the mean norm score.
[3] Compared to 16% (1SD in norm group) using chi-square tests.
Significant values (P<.05) are in bold.
Abbreviations:
ANT = Amsterdam Neuropsychological Tests, BS = Baseline Speed, PSI = Processing Speed Index, SAD = Sustained Attention Dots, WAIS = Wechsler Adult Intelligence Scale 4th edition, WISC = Wechsler Intelligence Scale for Children 5th edition

Associations between posttraumatic stress symptoms, sleep and cognitive functioning

The primary aim of this study was to assess the association between posttraumatic stress symptoms and sleep with cognitive functioning. There was a significant positive association between self-reported posttraumatic stress and sleep disturbance (r=0.68, P<0.001), and therefore, analyses for sleep and stress were conducted in separate models.

Univariable analyses are represented in Table 3 and show a significant association of hydrocephalus (B=-0.94, P<0.05) and tumor location (B=-0.70, P<0.05) on attention. Also, significant associations between hydrocephalus (B=-0.56, P<0.05) and tumor location (B=-0.57, P<0.05) were found on processing speed. No significant relationships were found regarding age, sex and time since diagnosis on cognitive outcomes.

In multivariable analyses, we investigated the association between sleep efficiency, sleep disturbance and posttraumatic stress on attention, executive functioning, processing speed and memory domains in separate models. Significant covariates from the univariable analyses (above) were added to the models, where applicable. Hydrocephalus remained a significant predictor of attention performance (B= -0.84, P<0.02) in the sleep efficiency analyses. However, no significant effect of posttraumatic stress or sleep on cognitive outcomes was found (P>0.10), as shown in Table 4.

Table 3 - Univariable regression models for cognitive outcomes

Predictor	Outcome			
	Attention	Executive functioning	Processing speed	Memory
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Age *Continuous*	-0.10 (-0.22 – 0.03)	-0.02 (-0.13 – 0.09)	-0.10 (-0.20 – 0.01)	0.03 (-0.08 – 0.15)
Sex *Female vs. male*	0.17 (-0.55 – 0.90)	0.12 (-0.50 – 0.74)	0.24 (-0.37 – 0.85)	0.15 (-0.54 – 0.84)
Time since diagnosis *Continuous*	0.01 (-0.01 – 0.02)	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)
Obstr. hydrocephalus *Yes vs. no*	**-0.94 (-1.58 – -0.31)**	-0.17 (-0.75 – 0.41)	**-0.56 (-1.11 – 0.00)**	-0.52 (-1.15 – 0.12)
Tumor location *Posterior fossa vs. other*	**-0.70 (-1.36 – -0.03)**	-0.52 (-1.09 – 0.01)	**-0.57 (-1.13 – -0.01)**	-0.20 (-0.85 – 0.45)

Univariable models were examined for each predictor and outcome separately. Significant values (P<.05) are in bold.

Abbreviations: CI = Confidence Interval, Obstr. = obstructive.

Discussion

The aim of this study was to examine predictors associated with cognitive problems in children newly diagnosed with a pediatric brain tumor, in order to target possible interventions in this vulnerable group. Various cognitive interventions have been studied in pediatric brain tumor survivors, for example neurofeedback and working memory training, but significant effects are scarce and do not seem to generalize to daily life functioning [39, 40]. Other factors, such as posttraumatic stress and sleep, may be effective in preventing cognitive problems on the longer term. Therefore, we specifically studied whether posttraumatic stress and sleep were associated with cognitive outcomes in an early phase.

The results of our study showed that children newly diagnosed with a pediatric brain tumor have more cognitive problems than peers of the general population on various neurocognitive domains (attention, executive functioning, processing speed and long-term auditory memory). This is in line with previous research where cognitive vulnerabilities were found on neurocognitive outcomes shortly after pediatric brain tumor diagnosis which were associated with several medical risk factors, such as longer time after radiotherapy, epilepsy, increased intracranial pressure and larger tumors [10, 41]. Furthermore, these deficits have been shown in children treated for a pediatric brain tumor in the long term and seem to increase over time [2, 9, 10, 42].

No significant associations were found between posttraumatic stress or sleep with cognitive functioning in this study. In other clinical groups such as children and adults following traumatic brain injury (TBI), heightened stress levels shortly after diagnosis have shown to be associated with cognitive functioning [24, 43-45]. Also, previous research in adults finds some evidence for improvement in cognitive functioning after trauma-based therapy reducing

Table 4 - Multivariable models for the associations between sleep, posttraumatic stress, and cognitive functioning

		Outcome									
		Attention (N=46)		Executive functioning (N=49)		Processing speed (N=49)		Memory (N=49)			
Sleep or stress model	Predictor	B (95% CI)	P	B (95% CI	P	B (95% CI)	P	B (95% CI)	P		
Sleep efficiency (Actigraphy)	Sleep efficiency	-0.01 (-0.06 – 0.04)	.60	0.00 (-0.04 – 0.05)	.84	-0.01 (-0.06 – 0.03)	.57	0.00 (-0.05 – 0.05)	.94		
	Obstr. hydrocephalus	-0.84 (-1.56 – -0.13)	.02	-	-	-0.49 (-1.15 – 0.18)	.15	-	-		
	Tumor location	-0.20 (-0.91 – 0.51)	.57	-	-	-0.29 (-0.95 – 0.37)	.38	-	-		
Sleep disturbance (Questionnaire)	Sleep disturbance	0.02 (-0.02 – 0.06)	.24	0.01 (-0.03 – 0.04)	.59	0.01 (-0.02 – 0.05)	.49	0.01 (-0.02 – 0.05)	.44		
	Obstr. hydrocephalus	-0.67 (-1.42 – 0.09)	.08	-	-	-0.39 (-1.07 – 0.29)	.25	-	-		
	Tumor location	-0.66 (-1.41 – 0.09)	.08	-	-	-0.46 (-1.13 – 0.22)	.18	-	-		
PTSS (Questionnaire)	PTSS	-0.01 (-0.03 – 0.02)	.68	-0.01 (-0.03 – 0.02)	.61	0.01 (-0.02 – 0.03)	.49	0.01 (-0.02 – 0.03)	.45		
	Obstr. hydrocephalus	-0.72 (-1.50 – 0.07)	.07	-	-	-0.37 (-1.07 – 0.32)	.29	-	-		
	Tumor location	-0.61 (-1.39 – 0.17)	.12	-	-	-0.46 (-1.16 – 0.23)	.19	-	-		

Multivariable models were examined for sleep efficiency, sleep disturbance, and PTSS separately. Predictors in models were included based on univariable results (Table 3). Significant values (P<.05) are in bold.

Abbreviations: CI = Confidence Interval, Obstr = obstructive, PTSS = posttraumatic stress symptoms.

posttraumatic stress symptoms [46, 47] and stress has been related to cognition [11, 19]. The finding that no significant effects were found of posttraumatic stress or sleep on cognition at an early phase in this study can be due to several reasons. First, in this study, children did not report severe sleep problems, which might have resulted in no associations between sleep and cognition. Second, this early time point shortly after diagnosis may not (yet) show the potentially detrimental effects of sleep and stress. Children at this early time point may not have ongoing sleep- and posttraumatic stress problems that can impact the brain and cognitive functions on the longer term which was found in several pediatric groups [11, 19, 48, 49]. For example, previous research has proposed to focus on prolonged exposure to stress as a risk factor for neurodevelopmental problems [11, 19]. Finally, at this time point, children might show acute stress levels, but not meet the criteria for posttraumatic stress disorder (PTSD) but rather may develop over time [50]. In other pediatric groups, PTSD was a risk factor for developing more severe cognitive problems [48], and therefore reducing PTSD symptoms may be also able to reduce cognitive deficits.

There was a positive association found between posttraumatic stress and sleep on the self- report questionnaires. This result is consistent with previous research, which showed experiencing a stressful event (such as the diagnosis with childhood cancer) may impact day- and nighttime functioning including sleep [21, 51]. Studies in children with PTSD or in childhood cancer survivors showed that sleep problems contribute to developing affective disorders [51, 52]. These results highlight the importance of early intervention to reduce problems in the long-term. Furthermore, this can give direction to clinical interventions, such as monitoring both posttraumatic stress and sleep after diagnosis to determine targets for clinical treatment in an individual child.

In addition, there was a significant association between medical factors such as hydrocephalus and diagnosis of a posterior fossa tumor on attention and processing speed, which is consistent with previous research in children treated for a pediatric brain tumor in the long-term [42]. For clinical purposes at this early time after diagnosis, it thus seems important to focus on primarily targeting and improving medical risk factors (such as reducing radiotherapy fields where possible) to prevent the development of cognitive problems.

This study has many strengths, including the systematic monitoring of neuropsychological functioning at an early time point, which can provide determinants of severe cognitive deficits on the longer term. Also, we thoroughly investigated various risk factors, which provides a more holistic approach on targets for psychological treatment in thus vulnerable group. However, several limitations of our study need to be mentioned. First, quality of sleep might have been difficult to report for children and may have given an underrepresentation compared to proxy reported sleep outcomes [53]. Regarding the neuropsychological tests, children might have been more alert and showed better results in a testing situation, compared to cognitive functioning in daily life. Also, we had missing data in the study partly due to burden and severity of disease, which might have contributed to response bias and underestimated

the severity of complaints in our sample. Finally, our study was partly conducted during the COVID-19 pandemic, which might have influenced the outcomes [54]. Future research should therefore focus on including more children to increase the sample size. Also, longitudinal follow-up is needed to examine the relationship between posttraumatic stress and sleep and cognitive problems on the longer term, to target potential interventions in this vulnerable group.

Conclusion

Children newly diagnosed with a pediatric brain tumor show more cognitive problems on the domains of attention, executive functioning, long term auditory memory and processing speed compared to peers of the general population. No significant associations were found between posttraumatic stress and sleep on cognitive outcomes at this time point. Shortly after diagnosis, medical factors including hydrocephalus and diagnosis with a posterior fossa tumor seem to be the most important risk factors associated with early cognitive problems. Future research is needed to investigate the long-term effects of posttraumatic stress and sleep on cognition, to target possible interventions in this vulnerable group.

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5

Unraveling the relations between post-traumatic stress symptoms, neurocognitive functioning and limbic white matter in pediatric brain tumor patients

5

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Abstract

Background.

Pediatric brain tumor patients (PBTP) are at risk of developing neurocognitive impairments and associated white matter alterations. In other populations, post- traumatic stress symptoms (PTSS) impact cognition and white matter, although these relationships in PBTP remain unclear. The aim is to investigate the effect of PTSS on neurocognitive functioning and limbic white matter in pediatric brain tumor patients.

Methods.

Sixty-six PBTP (6-16 years) completed a neuropsychological assessment and brain MRI (one-year post-diagnosis) and parents completed PTSS proxy questionnaires (CRIES-13; 1-3 months and one-year post-diagnosis). Mean Z-scores and percentage impaired (>1SD) for attention, processing speed, executive functioning, and memory were compared to norms (t-tests, chi-square tests). Multi-shell diffusion MRI data were analyzed for white matter tractography (fractional anisotropy/axial diffusivity). Effects of PTSS on neurocognition and white matter were explored with linear regression models, including age at diagnosis, treatment intensity, and tumor location as covariates. Neurocognition and limbic white matter associations were explored with correlations.

Results.

Attention (M=-.49, 33% impaired; P<.05) and processing speed (M=-.57, 34% impaired; P<.05) were significantly lower than healthy peers. PTSS was associated with poorer processing speed (β=-0.64, P<.01). Treatment intensity, age at diagnosis, and tumor location, but not PTSS, were associated with limbic white matter metrics. Neurocognition and white matter metrics were not associated.

Conclusion.

Higher PTSS was associated with poorer processing speed in PBTP, highlighting the need for monitoring and timely referrals to optimize psychological well-being and neurocognitive functioning. Future research should focus on longitudinal follow-up and explore the impact of PTSS interventions on neurocognitive performance.

Keywords

Neurocognition, white matter, limbic system, pediatric brain tumor, PTSS.

Key points

- Higher post-traumatic stress symptoms (PTSS) in pediatric brain tumor patients are associated with poorer processing speed one year after diagnosis
- Limbic white matter integrity was related to treatment intensity, age at diagnosis, and tumor location (not PTSS)

Importance of the study

Of all pediatric cancers, children with a brain tumor are at highest risk for developing neurocognitive impairments, which may worsen over time and impact educational attainment and employment rates. These cognitive impairments have been associated with changes in age- expected white matter growth, but interventions to prevent or reverse cognitive declines are limited. In other populations, post-traumatic stress symptoms (PTSS) are linked to both neurocognition and white matter, and has not been researched in pediatric brain tumor patients. This study provides insights into these relationships and demonstrates that higher PTSS negatively impacts processing speed, independent of treatment intensity, age at diagnosis, and tumor location. This suggests that interventions targeting PTSS may be able to enhance cognitive functioning and health-related quality of life, which is a suggested target for future research. Future longitudinal studies to examine relationships with brain metrics in the long- term is suggested.

Introduction

Survivors of pediatric brain tumors report the poorest health-related quality of life amongst childhood cancer survivors [1,2], and commonly experienced neurocognitive problems can contribute to this poorer quality of life. Furthermore, these problems may continue to worsen over time after cancer treatment, negatively impacting educational attainment and employment rates [3,4]. Earlier research has shown that declines are mostly seen in the domains of attention, executive functioning, processing speed and memory [5–8]. Also, these impairments have been associated with altered brain structure, such as abnormalities in white matter, including a loss of white matter volume and a deficit in age-expected white matter growth [9–11]. Neurocognition and white matter integrity impairments can be caused by factors such as the tumor itself, neurosurgery, and radiotherapy, and greater risk is associated with higher intensity therapies [8,12–16]. To date, interventions to prevent or reverse impairments are limited [7].

Besides medical factors, there is increasing evidence that psychological factors can also influence both neurocognition and structure and function of the brain. In typically developing children, it was seen that post-traumatic stress symptoms (PTSS) negatively impacted neurocognitive functioning on overall IQ and several domains such as executive functioning [17]. The diagnosis of a life-threatening disease, undergoing intensive medical procedures, and a high degree of morbidity inevitably causes stress responses in children with a brain tumor. Although stress is a normal response and many children and families are resilient, research has shown that PTSS is common and can even become chronic in some children [18–21]. For example, a significant number of survivors are at risk of developing symptoms of post-traumatic stress [19]. The traumatic stress model of Price et al. [22] proposes that, on average, stress levels peak at the beginning after a medical diagnosis and decrease over time. However, some people (30%) have higher than average rates of stress levels close to a medical diagnosis, and this group may experience persistent stress for a longer period. After some time, in this patient group, stress levels can either increase even further, be persistent (chronical), or decrease. Due to ongoing concerns about a potential long-term effects or new knowledge acquired on diagnosis, some patients may experience persistent or increased stress levels over time [18]. It has been suggested that early life experiences, particularly persistent stress, can increase the risk of cognitive dysfunction [23]. However, the early relationship between PTSS and neurocognitive functioning in children with a brain tumor remains unclear.

Chronic PTSS has also been linked to abnormalities in the structure and function of the brain, such as changes in white matter in the limbic regions, which are crucial for emotional regulation and cognitive processing [17,18,24–26]. In typically-developing children, PTSS has been associated with altered white matter fractional anisotropy (FA) and axial diffusivity (AD) metrics, suggesting potential disruptions in connectivity and structural integrity in these areas after exposure to stressful events [17]. Relationships between PTSS and limbic white matter integrity have not been previously investigated in pediatric brain tumor patients.

Considering the challenges of physical and psychological burden faced by children with brain tumors, it is important to gain insight into the impact of PTSS on neurocognitive functioning and limbic white matter integrity at an early stage during treatment. Understanding the relationships could be a starting point in developing timely, much-needed tools and interventions for healthcare practitioners that target PTSS, to improve long-term neurocognitive functioning and health-related quality of life. The overall aim of this research is to examine relationships between PTSS, neurocognitive functioning, and limbic white matter in pediatric brain tumor patients within the first year after diagnosis. First, we investigate the occurrence of PTSS in PBT patients. Secondly, we investigate the neurocognitive performance of our sample and how it relates to what would be expected in and age-matched healthy population. This is followed by an investigation into the effect of PTSS on neurocognition and PTSS on limbic white matter. Finally, we evaluate the relationship between PTSS and neurocognition. Gaining further knowledge of the possible relationship between between post- traumatic stress symptoms, neurocognitive functioning and limbic white matter in pediatric brain tumor patients may be of great importance in improving the quality of life.

Materials and Methods

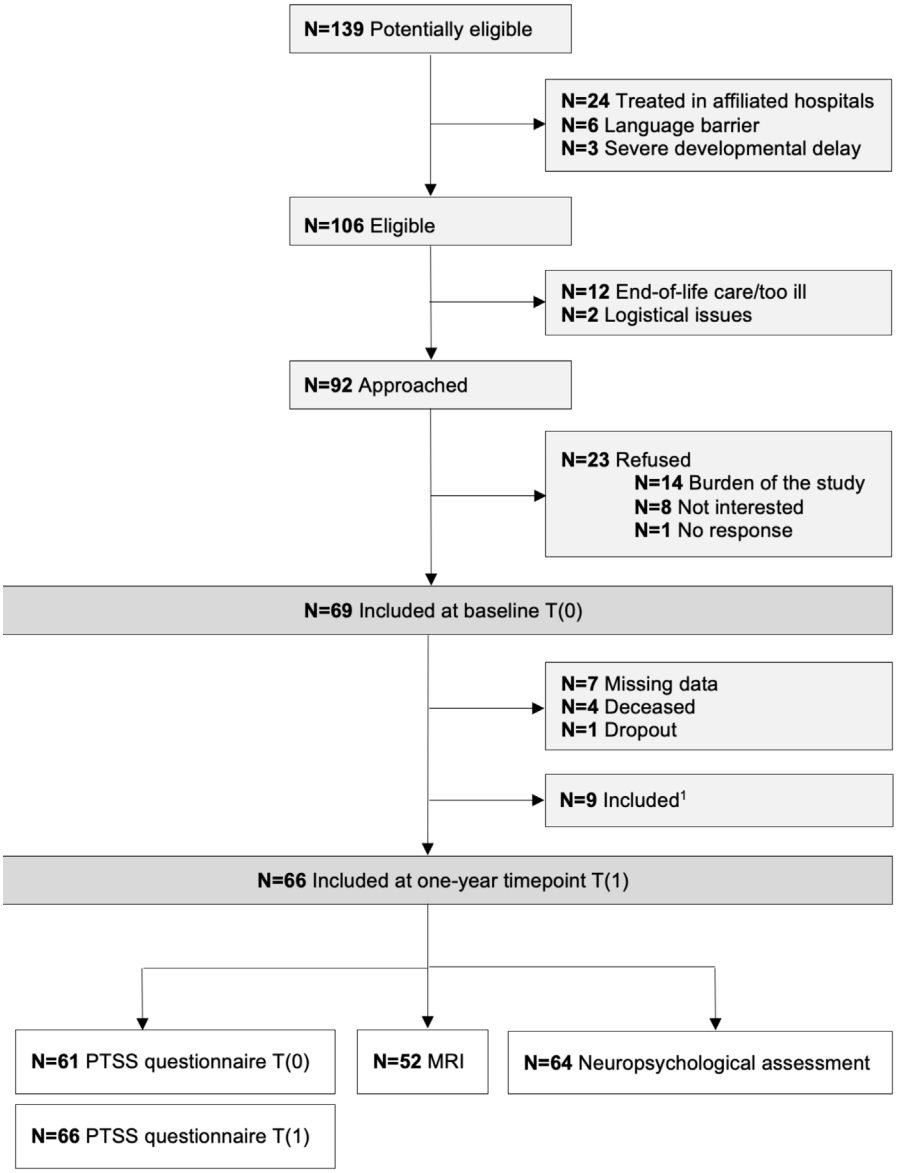
Participants

The SuSPeCT-study is a longitudinal, prospective, observational study at the Princess Máxima Center for Pediatric Oncology in the Netherlands. Between January 2020 and December 2021, children with a newly diagnosed primary brain tumor were invited for study participation. All children and parents provided written informed consent. This study was approved by the Clinical Research Committee of the Princess Maxima Center (PMC CRC 2019-065) and confirmed subsequently by the Medical Research Ethics Committee of the University Medical Center Utrecht (19/728). The Institutional Review Board of the University Medical Center Utrecht classified this study as exempt from the Medical Research Involving Human Subjects Act. Eligible patients were between 6 and 16 years old at the time of diagnosis, spoke Dutch sufficiently, did not have a developmental delay, and were not receiving end-of- life care. See Figure 1 for flowchart of patient enrollment.

Procedure

All patients were followed for two years and completed three testing moments, consisting of neuropsychological assessments, actigraphic sleep measures, questionnaires, and a brain MRI. Measures of interest for this study were at the time points shortly after diagnosis (one-three months; T0) and one year later (nine-fifteen months; T1). For T0, proxy report PTSS questionnaires were administered. For T1, the same proxy report PTSS questionnaires were administered, plus a multi-shell diffusion MRI scan (standard care) and neuropsychological assessment (standard care for a part of the participants) were completed.

Figure 1 - Flowchart of participant enrollment.



[1]Patients who were initially treated at shared care centers, and continued treatment at the Princess Máxima Center, were invited for participation for the one-year timepoint.

Proxy reported PTSS

PTSS was assessed using the Children's Revised Impact of Event Scale (CRIES-13) proxy report [27]. The CRIES-13 is a brief measure designed to screen children at risk for post- traumatic stress disorder (PTSD). It has good face and construct validity, a stable factor structure, correlates well with other indices of distress, and has been used to screen very large samples of at-risk

children following a wide range of traumatic events. The internal consistency and test-retest reliability of the CRIES are high: α= .89 and a test-retest reliability of .85 [28]. The questionnaire is completed by parents, using the online "KLIK PROM" portal (www.hetklikt.nu). It contains 13 questions on three subscales; re-experience, avoidance, and increased irritability; these can be captured in a total score range of 0-65. The clinical threshold for children at risk for PTSD is established at 31, however, to examine the effect of proxy reported PTSS, rather than a PTSD diagnosis, we used a subclinical threshold of 25. Patients were split into two groups based on their scores: the "no PTSS" group obtained scores ≤ 25 on both time points, and patients who obtained a score >25 on at least one of the two time points were allocated to the "PTSS" group.

Neuropsychological assessment

Neuropsychological assessments were administered by a trained neuropsychologist around one year after diagnosis, N=24 (36%) were completed within standard care (called Brain CARE program). We tested the domains of attention, executive functioning, processing speed, and memory, using norm-referenced Dutch tests (see below). All scores were converted to Z-scores (higher scores indicate better performance). For each neurocognitive domain, composite scores were calculated by averaging two sub-scores. When only one of the two domain scores was available for calculating domain scores, only one score was used. For this analysis, we used the same composite scores as our other papers of the SuSPeCT-study (unpublished manuscript, Hooft van Huijsduijnen, E.).

Attention was measured with the sustained attention dots (SAD) task of The Amsterdam Neuropsychological Tasks (ANT), a computerized test battery [29]. The neurocognitive composite attention score was calculated by calculating the mean of the average completion time (ANT SAD) and the standard deviation of the completion time (ANT SAD). Executive functioning was measured by the number of misses of the ANT SAD, as an indicator of inhibition, and the Digit Span task (WISC-V-NL/WAIS-IV-NL), as an indicator for working memory [30,31]. The processing speed composite score consisted of the mean reaction speed (ANT Baseline Speed) and the Processing Speed Index (WISC-V-NL/WAIS-IV-NL, subtests 'Symbol Search' and 'Coding') [30,31]. Memory was measured by averaging the immediate recall (short-term memory) and delayed recall (long-term memory) scores of the 15-word task (15WT). For children up to 12 years old, the child version was administered, and for adolescents, there was the 15WT adult version [32].

MRI image acquisition and processing

MRI data was acquired one year (±3 months) after diagnosis using a standard clinical protocol. Data acquisition included an anatomical 3D T1 scan and multi-shell diffusion MRI from a 3.0T Philips MR scanner (Philips Healthcare, Best, Netherlands).

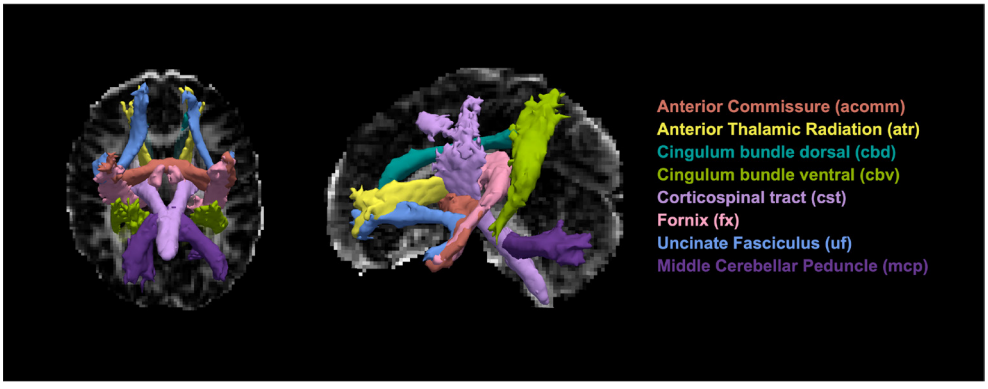
Whole-brain multi-shell diffusion MRI was collected with a single-shot echo-planar imaging sequence. 56 directions; 4x b0, 52x b=1000 s/mm^2 and 56x b=2000 s/mm^2; TE=8.9 ms, TR=323.97ms; 66 slices; slice acquisition matrix=112x112 with FOV=224×224 mm^2; voxel-

size=2x2x2mm^3. Slices were acquired on the axial plane, with a total scan duration of 5 min and 57s.

We used FreeSurfer 7.3.2 to define cortical and subcortical regions in the T1-weighted images of each individual [33]. Briefly, this processing included motion correction and averaging [34], removal of non-brain tissue using a hybrid watershed/surface deformation procedure [35], automated Talairach transformation, and segmentation of the subcortical white matter and deep gray matter volumetric structures [33,36]. Freesurfer morphometric procedures have been shown to have good test-retest reliability across scanner manufacturers and field strengths [37,38].

We then performed global probabilistic tractography with anatomical priors using TRACULA (Tracts Constrained by Underlying Anatomy). This tool reconstructs major white- matter pathways by incorporating prior information on the structural segmentation labels that each pathway goes through or next to as a function of position along the length of the pathway. We used the ball and stick single-shell model in the bedpostx step [39]. TRACULA generated averaged fractional anisotropy (FA) and axial diffusivity (AD) of all seven tracts around the limbic system and the Middle Cerebellar Peduncle as control. We chose to only look into FA and AD, since we wanted to reduce the number of comparisons and radial diffusivity (RD) and mean diffusivity (MD) were both highly negatively correlated with FA. Additionally, we generated head motion data, of which we calculated the Total Motion Index (TMI) for quality control. One participant had >3SD deviance for the TMI and therefore was excluded from the analysis, resulting in a sample size of N=52. FA and AD scores were averaged across left and right. AD values were multiplied by 1000 (to help with interpretation). The eight tracts were Anterior Commissure, Anterior Thalamic Radiation, Cingulum Bundle Dorsal, Cingulum Bundle Ventral, Corticospinal tract, Fornix, Uncinate Fasciculus, and Middle Cerebellar Peduncle (Figure 2).

Figure 2 - White matter tracts that were constructed using TRACULA. 7 tracts are in/ around the limbic system and the MCP is added as control tract. FA and AD scores were averaged across left and right.



Medical variables

The Neurological Predictor Scale (NPS) indicates treatment intensity by combining cumulative neurological risk factors and tumor treatments into a single total score [40,41]. The NPS considers information on radiotherapy, chemotherapy, neurosurgery, and the presence of hydrocephalus, endocrine dysfunction, and seizure medications. The score ranges from 0 (lowest level of risk) to 11 (highest level of risk). Studies have established the reliability and validity of this measure in childhood cancer survivors. For example, the total NPS score is significantly associated with intelligence, processing speed, working memory, attention, and adaptive functioning, which was independent of individual risk factors [40].

Statistical analysis

Participant characteristics were descriptively reported. Demographics were compared between participants and non-participants, and the PTSS group and no PTSS group (t-tests for sex, age at assessment, days since diagnosis, NPS score and TMI) to assess potential dempgraphic differences between the groups of interest. For each neurocognitive domain, the percentage impaired (participants scoring >1SD lower than norm scores) was compared to 16% (as expected in the general population) by using non-parametric chi-square tests. Average Z- scores were compared to a norm score of zero with one sample t-tests. These tests were performed for the complete sample and subsequently for the separate PTSS groups. We built four linear regression models to test the effect of PTSS (dichotomous) on the four neurocognitive domains (attention, executive functioning, processing speed, and memory; continuous) and corrected for multiple testing using false discovery rate (FDR) [42]. For the limbic white matter outcomes, sixteen linear regression models were built and corrected for multiple testing using FDR. We tested the effect of PTSS (dichotomous) on FA and AD (continuous) in the seven different white matter tracts around the limbic system and the MCP. For all linear regression models, covariates were age at diagnosis (continuous), NPS score (continuous), and whether the tumor was in the limbic system area or not (supratentorial medial structures vs. other locations; dichotomous) and corrected for multiple testing using FDR. We reported on significant effects of covariates in the linear models on both neurocognition and the limbic white matter. To explore the relation between limbic white matter and neurocognitive functioning, Pearson correlation tests were performed and corrected for multiple testing using FDR.

Results

Sample characteristics

Ninety-two patients and parents were approached for the study; 69 (75%) participated at T0, and 66 (72%) at T1 (Figure 1). Demographics and medical characteristics are shown in Table 1. Participants (35% male, mean age 12.53 (SD=2.81) years, 33% supratentorial medial structure tumors) did not differ from non-participants (N=42; 40% male, mean age 10.61 (SD=3.41) years, 33% supratentorial medial structure tumors, all P>.10). Furthermore, there were no differences in demographics and medical variables between the PTSS and no PTSS groups (Table 1). Of the participants, 64 (91%) had data on PTSS and neuropsychological functioning, and 52 (74%) patients had proxy data on PTSS and limbic white matter structure.

Table 1 - Demographic and medical variables

N (%) or mean (SD)	Overall (N=66)	No PTSS (N=43)	PTSS (N=23)	P-value[1]
Female sex	23 (35)	15 (35)	8 (35)	>0.99
Age at assessment (years)	12.53 (2.81)	12.04 (2.83)	13.40 (2.62)	0.06
Time since diagnosis (days)	393 (76)	390 (86)	400 (52)	0.57
NPS score	4.11 (2.11)	4.00 (2.06)	4.30 (2.22)	0.59
Tumor location				
Cerebral lobes	12 (18)	10 (23)	2 (9)	
Supratentorial medial structures	22 (33)	15 (35)	7 (30)	
Posterior fossa	32 (48)	18 (42)	14 (61)	
Tumor type				
Low grade glioma	31 (47)	21 (49)	10 (43)	
High grade glioma	2 (3)	1 (2)	1 (4)	
Medulloblastoma	7 (11)	4 (9)	3 (13)	
Ependymoma	2 (3)	1 (2)	1 (4)	
Germ cell tumor	10 (15)	7 (16)	3 (13)	
Craniopharyngioma	10 (15)	7 (16)	3 (13)	
Other[2]	4 (6)	2 (5)	2 (9)	
Neurosurgery				
No	8 (12)	6 (14)	2 (9)	
Biopsy only	5 (8)	4 (9)	1 (4)	
One resection	48 (73)	31 (72)	17 (74)	
Several resections	5 (8)	2 (5)	3 (13)	
Radiotherapy				
No radiotherapy	43 (65)	31 (72)	12 (52)	
Focal radiotherapy	11 (17)	5 (12)	6 (26)	
Whole brain or craniospinal	4 (6)	2 (5)	2 (9)	
Whole brain + boost	8 (12)	5 (12)	3 (13)	
Radiotherapy type				
Photon	7 (11)	2 (5)	5 (22)	
Proton	16 (24)	10 (23)	6 (26)	
Chemotherapy	18 (27)	11 (26)	7 (30)	
Cerebellar mutism syndrome	5 (8)	2 (5)	3 (13)	
Metastases at diagnosis	9 (14)	7 (16)	2 (9)	
Hormone deficiency	20 (31)	15 (35)	5 (23)	
Epilepsy with seizure medication	7 (11)	6 (14)	1 (4)	
Obstructive hydrocephalus	30 (45)	19 (44)	11 (48)	
Total Motion Index (MRI)	1.10 (2.06)	1.28 (2.16)	0.75 (1.85)	0.35

[1] Independent t-tests between no PTSS and PTSS group. T-tests were only performed on variables that influenced the sample selection.

[2] Choroid plexus tumor, atypical teratoid rhabdoid tumor, mesenchyoma, meningioma

Proxy reported PTSS

Twenty-three (34%) patients had PTSS above the threshold of 25 at either T0 and/or T1, reported by their parents. This included 15 (22%) patients at T0, 12 (18%) patients at T1, and 4 (6%) patients at both T0 and T1. Of note, 54 (82%) participants had PTSS data on both time points. Of the 12 participants that had data at either one of both time points, 3 scored above the subclinical threshold. There were 9 patients who were not included at T0, and this was mostly because of burden at that time. At T1, PTSS scores for these patients suggest that stress may have also played a role (3 out of 9 later included patients have >25 score at T1). This is a limitation to our study, however, we chose not to exclude these patients from analyses because they are an especially vulnerable group.

Neurocognition

Results on neuropsychological performance are presented in Table 2. Mean Z-scores included attention (M=-0.49, SD=1.12), executive functioning (M=-0.21, SD=1.02), processing speed (M=-0.57, SD=0.98) and memory (M=-0.23, SD=1.42). Attention (t(57)=- 3.29, P<.01) and processing speed (t(60)=-4.55, P<.001) deviated significantly from 0, indicative of lower performance compared to healthy peers. Additionally, attention (33% impaired; χ^2=5.98, P=.01) and processing speed (34% impaired; χ^2 =7.27, P<.01) had a significantly higher proportion of impaired patients (>1SD) compared to what would be expected in the healthy, age-matched population (16%). In the overall group, 59% of patients were impaired on at least one domain.

In the PTSS group specifically, attention (38% impaired; χ^2=5.33, P=.02) and processing speed (48% impaired; χ^2=11.06, P<.001) had an even higher proportion of impaired children. Average scores of attention (M=-0.67, SD=1.14, t(20)=-2.68, P=.01), executive functioning (M=-.47, SD=.99, t(21)=-2.22, P=.04), and processing speed (M=-1.04, SD=0.92, t(22)=-5.43, P<.001) were lower than expected compared to what would be expected in the healthy, age-matched population (16%). In the no PTSS group, only attention (M=-0.38, SD=1.11, t(36)=-2.09, P=.04) was significantly lower than expected, but the percentages impaired were not different from the general population

Table 2 - Neurocognitive performance

	Overall group (N=66)		No PTSS group (N=43)		PTSS group (N=23)	
	Z-score, M (SD)[1]	Impaired, N (%)[2]	Z-score, M (SD)[1]	Impaired, N (%)[2]	Z-score, M (SD)[1]	Impaired, N (%)[2]
Attention (N=58)	-0.49 (1.12)	19 (33)	-0.38 (1.11)	11 (30)	-0.67 (1.14)	8 (38)
Executive functioning (N=63)	-0.21(1.02)	11 (17)	-0.06 (1.01)	5 (12)	-0.47 (0.99)	6 (27)
Processing speed (N=61)	-0.57 (0.98)	21 (34)	-0.29 (0.92)	10 (26)	-1.04 (0.92)	11 (48)
Memory (N=59)	-0.23 (1.42)	16 (27)	-0.17 (1.58)	9 (24)	-0.34 (1.07)	7 (32)

Significant numbers (P<.05) are in bold.
[1]One-sample t-test for testing mean Z-scores against 0
[2]Chi square tests to compare impaired patient proportions with those expected in a healthy, age-matched population.

Table 3 - Multivariable regression models of PTSS and neurocognitive functioning

B (95% CI)	Attention (N=58)	Executive functioning (N=63)	Processing speed (N=61)*	Memory (N=59)
(Intercept)	0.54 (-0.85 – 1.94)	0.86 (-0.30 – 2.02)	0.41 (-0.66 – 1.48)	-0.36 (-1.97 – 1.25)
PTSS group Yes vs. no	-0.13 (-0.78 – 0.52)	-0.22 (-0.77 – 0.32)	**-0.64 (-1.12 – -0.15)****	-0.13 (-0.89 – 0.62)
Age at diagnosis Continuous	-0.05 (-0.16 – 0.06)	-0.08 (-0.17 – 0.01)	-0.03 (-0.11 – 0.05)	0.07 (-0.06 – 0.19)
NPS score Continuous	-0.11 (-0.25 – 0.04)	-0.04 (-0.17 – 0.08)	**-0.12 (-0.24 – -0.01)***	-0.16 (-0.34 0.01)
Tumor location Suprat. vs. rest	0.14 (-0.50 – 0.77)	0.41 (-0.13 – 0.95)	0.44 (-0.06 – 0.93)	0.16 (-0.60 – 0.93)

Abbreviations. Suprat. = supratentorial medial structures.
* Significant at the P<.05 level

** Significant at the P<.01 level

PTSS and neurocognition

Results on the effect of proxy reported PTSS on neurocognitive functioning are presented in Table 3. The overall model for processing speed was statistically significant (R2=0.24, F(4,56)=4.30, PFDRcorrected=.017). It was found that the PTSS group (β=-0.64, P=.01) and higher NPS score (β=-0.12, P=.03) were significantly related to lower processing speed. Models for the other three neurocognitive domains demonstrated no significant effects of PTSS, and overall models were not statistically significant.

PTSS and limbic white matter

Results on the effect of PTSS on FA and AD in eight white matter tracts are presented in Table 4. After FDR correction for multiple testing, models were not statistically significant. There was no effect of PTSS group in any of the white matter regression models.

For exploratory reasons, we report the effects of the individual predictors. Older age at diagnosis was associated with higher FA of the Anterior Thalamic Radiation (β=0.01, P=.03) and Corticospinal tract (β=0.01, P=.03), and lower AD of the Anterior Commissure (β=-0.01, P<.01), Anterior Thalamic Radiation (β=-0.00, P=.02), ventral part of the Cingulum Bundle (β=-0.01, P=.02), and Fornix (β =-0.01, P=.03). Higher NPS (treatment intensity) score was associated to lower FA of the Anterior Thalamic Radiation (β=-.01, P=.05) and higher FA of the dorsal part of the Cingulum Bundle (β=0.01, P<.01). Tumors in the supratentorial medial structures were related to lower FA in the Fornix (β=-0.04, P<.01) and Uncinate Fasciculus (β=-.03, P=.04), and lower AD of the Uncinate Fasciculus (β=-0.03, P=.03) and Middle Cerebellar Peduncle (β=-0.04, P<.01).

Neurocognition and limbic white matter

To explore the relation between neurocognitive functioning and limbic white matter integrity, we calculated Pearson correlations. After correction for multiple testing, no significant correlations were found.

Table 4 - Multivariable regression models of FA and AD of the eight white matter tracts

B (95%CI)	Fractional Anisotropy (N=52)			
	ACOMM	ATR	CBD	CBV
(Intercept)	**0.28 (0.23 – 0.34)*** **	**0.30 (0.23 – 0.36)*** **	**0.35 (0.27 – 0.43)*** **	**0.34 (0.23 – 0.45)*** **
PTSS group *Yes vs. no*	0.01 (-0.02 – 0.04)	-0.00 (-0.04 – 0.03)	0.03 (-0.00 – 0.07)	0.00 (-0.05 – 0.06)
Age at diagnosis *Continuous*	0.00 (-0.00 – 0.00)	**0.01 (0.00 – 0.01)***	-0.01 (-0.01 – 0.00)	-0.00 (-0.01 – 0.01)
NPS score *Continuous*	0.00 (-0.00 – 0.01)	**-0.01 (-0.01 – -0.00)***	**0.01 (0.00 – 0.02)****	0.01 (-0.00 – 0.02)
Tumor location *Suprat. vs. rest*	-0.03 (-0.05 – 0.00)	-0.02 (-0.05 – 0.01)	-0.01 (-0.05 – 0.02)	-0.01 (-0.06 – 0.04)
	CST	FX	UF	MCP
(Intercept)	**0.49 (0.43 – 0.55)*** **	**0.37 (0.31 – 0.42)*** **	**0.31 (0.26 – 0.36)*** **	**0.42 (0.36 – 0.48)*** **
PTSS group *Yes vs. no*	0.00 (-0.02 – 0.03)	-0.01 (-0.03 – 0.02)	0.01 (-0.02 – 0.03)	0.02 (-0.01 – 0.04)
Age at diagnosis *Continuous*	**0.01 (0.00 – 0.01)***	0.00 (-0.00 – 0.01)	0.00 (-0.00 – 0.01)	0.00 (-0.00 – 0.01)
NPS score *Continuous*	0.00 (-0.00 – 0.01)	-0.00 (-0.01 – 0.00)	0.00 (-0.01 – 0.01)	0.00 (-0.00 – 0.01)
Tumor location *Suprat. vs. rest*	-0.01 (-0.04 – 0.02)	**-0.04 (-0.06 – -0.01)****	**-0.03 (-0.05 – -0.00)***	0.01 (-0.02 – 0.04)

	Axial Diffusivity (N=52)			
	ACOMM	ATR	CBD	CBV
(Intercept)	**0.88 (0.82 – 0.94)*** **	**0.88 (0.84 – 0.93)*** **	**0.87 (0.75 – 0.99)*** **	**0.92 (0.84 – 1.00)*** **
PTSS group *Yes vs. no*	0.00 (-0.02 – 0.03)	0.00 (-0.02 – 0.03)	0.02 (-0.04 – 0.07)	0.02 (-0.02 – 0.06)
Age at diagnosis *Continuous*	**-0.01 (-0.01 – -0.00)** **	**-0.00 (-0.01 – -0.00)***	-0.01 (-0.02 – 0.00)	**-0.01 (-0.01 – -0.00)***
NPS score *Continuous*	0.00 (-0.00 – 0.01)	0.00 (-0.00 – 0.01)	0.01 (-0.00 – 0.03)	0.00 (-0.01 – 0.01)
Tumor location *Suprat. vs. rest*	-0.01 (-0.04 – 0.02)	-0.01 (-0.03 – 0.01)	0.05 (-0.00 – 0.11)	-0.01 (-0.04 – 0.03)
	CST	FX	UF	MCP
(Intercept)	**0.87 (0.79 – 0.94)*** **	**0.99 (0.94 – 1.05)*** **	**0.90(0.84 – 0.97)*** **	**0.80 (0.74 – 0.86)*** **
PTSS group *Yes vs. no*	0.01 (-0.03 – 0.04)	0.00 (-0.02 – 0.03)	0.02 (-0.01 – 0.05)	0.00 (-0.02 – 0.03)
Age at diagnosis *Continuous*	-0.00 (-0.01 – 0.00)	**-0.00 (-0.01 – -0.00)***	-0.00 (-0.01 – 0.00)	-0.00 (-0.01 – 0.00)
NPS score *Continuous*	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)	0.00 (-0.01 – 0.01)	0.00 (-0.00 – 0.01)
Tumor location *Suprat. vs. rest*	-0.01 (-0.05 – 0.02)	-0.01 (-0.04 – 0.01)	**-0.03 (-0.06 – -0.00)***	**-0.04 (-0.07 – -0.01)** **

Abbreviations. Suprat. = supratentorial medial structures, ACOMM = Anterior Commissure, ATR = Anterior Thalamic Radiation, CBD = Cingulum Bundle Dorsal, CBV = Cingulum Bundle Ventral, CST = Corticospinal Tract, FX = Fornix, UF = Uncinate Fasciculus, MCP = Middle Cerebellar Pedunclue.

* Significant at the P<.05 level

** Significant at the P<.01 level

*** Significant at the P<.001 level

Discussion

This study aimed to investigate the effect of PTSS on neurocognitive functioning and limbic white matter integrity during the first year after pediatric brain tumor diagnosis. Higher PTSS was associated with poorer processing speed, and no effect of PTSS on limbic white matter integrity was found. White matter integrity was, however, associated with treatment intensity, age at diagnosis, and tumor location.

In general, the overall group had poorer attention and processing speed performance compared to healthy peers, and in the PTSS group, executive functioning was also lower than peers. In our sample, per domain, between 17% and 34% experienced these problems, and 59% of the patients were impaired in at least one neurocognitive domain. These neurocognitive impairments amongst pediatric brain tumor patients are common and frequently described, highlighting the need to develop targeted interventions to prevent or reverse deterioration in a timely manner [16].

Relationship between PTSS and neurocognition

The finding that PTSS was associated with poorer processing speed suggests that children with PTSS are at risk for declines in intellectual and psychosocial functioning [3]. In our clinic, we have observed that slow movements and reaction speeds are often seen in pediatric brain tumor patients, and potentially there are interventions that could reduce the processing speed problems. For example, processing speed has been associated with PTSS in the literature in different populations [43,44]. Earlier research [44] in trauma survivors showed significant, small- to medium-sized improvements in several cognitive domains, including processing speed, after trauma-focused psychotherapy such as EMDR (Eye Movement Desensitisation and Reprocessing [45]). This earlier research has not been done in a childhood population. Still, EMDR is known to be helpful as a trauma intervention in children [46], and therefore, trauma therapy such as EMDR could potentially help cognitive problems.

It is possible that attention, executive functioning, and memory domains may also be impacted by PTSS, if PTSS levels are present for a longer period and with severe symptoms [43]. In the first three months after diagnosis, we found no relationship between PTSS and neurocognitive performance, including processing speed, suggesting that time is an important factor (unpublished manuscript, Hooft van Huijsduijnen, E.). Also, cognitive domains seem to deteriorate years after cancer treatment, and PTSS may play a role in this, underlining the importance for future research to look at these associations over time [16].

We hypothesized PTSS to induce both neurobiological changes in limbic white matter as well as neurocognitive problems, in which it is assumed that neurocognitive problems could be (partly) caused by those white matter alterations. Our findings, however, suggest that PTSS is related to neurocognition and not white matter, at least in the short term on processing speed. This phenomenon is in line with the limited capacity model of working memory [47], where cognitive representations of stressful life events compete with task demands

for attentional resources. In other words, these unwanted thoughts from stressful life events compete for limited activation resources, hindering normal cognitive functioning [47]. When working memory is compromised, it can potentially affect other aspects of neurocognitive performance as well. The lower processing speed scores in the PTSS group, compared to the no PTSS group that we found in our sample, could point to this mechanism.

Relationship between PTSS and white matter

In this study, there was no effect of PTSS on either FA or AD of the limbic white matter tracts. Earlier research with seventeen maltreated children with PTSD showed reduced FA in the medial and posterior corpus callosum compared to controls, and in pediatric acute lymphoblastic leukemia survivors, higher re-experiencing PTSS was linked to increased functional connectivity of the amygdala [48,49]. Possibly, effects in our sample can occur in the long-term, and/or different brain regions are impacted by PTSS. Limbic areas play a key role in the fear neural circuitry. However, other regions, such as the ventral anterior cingulate cortex and ventromedial prefrontal cortex, can extinguish fear responses of the amygdala by inhibitory control50. Processing speed, for example, is known to be related to prefrontal processes in the brain43. An alternative explanation is that children with lower processing speed may be more irritable, which resulted in higher PTSS scores. In this case, the relationship between processing speed and PTSS may be due to irritability, and therefore, a relationship between irritability and limbic white matter may not be found (due to different underlying mechanisms).

In addition, it could be that the changes in white matter integrity are not reflected in changes in FA or AD, but could be a change in connectivity and reflect in for example shorter tracts and is therefore could be examined in future research. Finally, earlier neuroimaging studies propose exposure to childhood trauma, even in the absence of PTSS, alters neurodevelopment fundamentally, and changes in the fear neural circuitry induce susceptibility to the development of PTSS/PTSD up to decades later. This further emphasizes the importance of unraveling the pathophysiology of PTSS in this vulnerable patient group [18] using longer-term follow-up.

Strengths and limitations

Strengths of this study are a relatively large sample size within a specific patient group, namely children with the highest risk of developing neurocognitive problems from all cancer diagnoses. It provides insight into different neurocognitive domains, where earlier research often focuses on global intellectual functioning and considers many different white matter tracts [16]. In earlier research, neuropsychological deficits, medical factors, and white matter alterations resulting from cancer treatment are well-described as opposed to psychological factors. Psychological factors such as PTSS may be more targetable with interventions compared to white matter alterations and neuropsychological deficits. This study contributes to our understanding of the effect of PTSS on the white matter alterations and neuropsychological deficits. Additionally, the study highlights the importance of early

testing on cognitive performance and PTSS. This was also the first study using the NPS score in brain tumor patients at an early phase, as previous studies focused on survivors [40,51]. The NPS score is used as an indicator for treatment intensity and has been validated for survivors. Our analysis shows that the NPS is useful at an earlier stage in treatment and survivorship, particularly within the first year after diagnosis. However, future research is needed to validate the validity and reliability of using the NPS at different time points.

Limitations may be the estimates of PTSS, which were completed by proxy (parent) reported questionnaires. We know from our unpublished manuscript that proxy-reports and self-reports for child PTSS are correlated, but that proxy-reports yield lower PTSS scores than self-reports and this may be underestimating PTSS (unpublished manuscript, Hooft van Huijsduijnen, E). This could potentially induce a group bias where the 'no PTSS' group may then in fact contain participants with considerable PTSS symptoms. That could in turn explain why no relation was found between PTSS scores and limbic white matter integrity. In this analysis, we chose to focus on proxy reported scores because of sample size and to limit data imputation. Additionally, patients who were included at T1 (and not T0) may be because they were experiencing stress; the fact that 3 out of 9 later included patients had subclinical scores (>25) at T1 endorse this statement. Some participants only completed the PTSS questionnaire at one time point, and therefore, changes over time are unknown. Additionally, no data on psychosocial care was collected. Consequently, we do not know to what extent the patients had anxiety problems or received psychotherapy or other psychological interventions regarding their medical traumatic stress.

The MRI TRACULA pipeline may have been negatively impacted by the tumor, tumor cavities, and potentially disrupted white matter pathways due to neurosurgery. Studies utilizing TRACULA with pediatric brain tumor patients have not been conducted before, making it difficult to determine how this has impacted the outcomes. We do, however, replicate findings from the literature on the covariates (age, tumor, treatment), indicating reliable processing of the MRI analysis pipeline.

Lastly, as mentioned above, we were interested in early brain changes caused by heightened PTSS, although one year after diagnosis may be too early to detect subtle changes, and thus, we recommend longer follow-up designs for future research. Furthermore, we recommend PTSS questionnaires to be administered more frequently, including self-reports and/or objective stress measures such as hair cortisol. MRI analyses can include grey matter volumetric analyses of limbic areas such as the hippocampus and amygdala. Finally, it will be important to assess the effect of trauma interventions on neurocognitive functioning [18,52].

Conclusions

In conclusion, PTSS during the first year after pediatric brain tumor diagnosis was associated with lower processing speed performance, but not with limbic white matter integrity. Ongoing efforts to unravel the relationship of psychological wellbeing with neurocognitive

and neurobiological outcomes are important, as it may guide the development of targeted interventions to prevent or reverse functional decline and optimize health-related quality of life. PTSS and neurocognitive impairments were frequently observed in this sample and therefore regular screening and timely referrals for psychological and educational support are important throughout brain tumor treatment and survivorship.

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Appendices 6

ABOUT THE AUTHOR

Eva Adriane Barbara Kremer - Hooft van Huijsduijnen was born on March 7th 1993 in Voorburg, the Netherlands. She attended highschool at Het Vrijzinnig Christelijk Lyceum in The Hague, where she finished *Voortgezet Wetenschappelijk Onderwijs* in 2011.

In 2015, Eva obtained her Bachelor's degree in Cognitive Neuroscience at the Universiteit of Amsterdam. During her studies, she had parttime jobs as a research assistant at the University and as a volunteer for *Stichting De Kindertelefoon*. In 2018, she obtained her Master's degree in Clinical Neuropsychology, at Leiden University. She followed both the clinical and the research track of the program. Eva did her clinical internship at the Noordwest Ziekenhuisgroep in Alkmaar, where she worked at the geriatric and neurology department. At this internship, she obtained her *Basis Aantekening Psychodiagnostiek*. She also did a research internship at the Dienst Justitiele Inrichtingen (Ministerie van Veiligheid en Justitie), where she studied psychosocial criminogenic and neurobiological features of male detainees. Here, she wrote her Master's Thesis under supervision of dr. Ilse Schuitema.

After briefly working as an Assistant Neuropsychologist at DC VerzuimDiagnostiek, Eva quickly found her way to the Princess Máxima Center, where she could combine her interests in both psychological and neurological problems, in particular in cognition affected by medical conditions. Starting as a junior researcher in January 2019, Eva began working on a neuropsychological guideline as part of the International Guideline Harmonization Group (IGHG) guidelines under supervision of Prof. dr. Leontien C.M. Kremer. At the same time, she helped set up a PhD project, that she started later that year, under supervision of Prof. dr. Martha A. Grootenhuis, dr. Marita H. Partanen, dr. Raphaele R.L. van Litsenburg and Prof. dr. Eelco W. Hoving. This longitudinal project about sleep, stress, and cognition in pediatric brain tumor patients, titled the SuSPeCT-study, provided the data described in the current thesis. During her time as a PhD student, Eva was the secretary for the M4C Research and Care meetings and continued working on the IGHG guidelines. She attended the ISLCCC congress in Atlanta in 2019 and presented her own findings at SIOP in 2021. That year, Eva also participated in the 'Slimme Gasten' program, where she presented her work as a researcher to elementary school children. To explore a more clinical career path, she worked as a psychologist for one year from December 2021 until November 2022, at the neuro-oncology department of the Princess Máxima Center.

During her PhD Eva suffered from serious health issues which hampered her in finalizing her manuscript with a general discussion. She passed away November 19th 2023.

Eva lived in Amsterdam, with her husband Jeroen.

PHD PORTFOLIO*

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PhD training
Courses
Clinical Trial Development Course
CTO Introduction course
Writing a Patient Information Letter
Writing a Scientific Paper
Introductory Biostatistics for Researchers
eBROK
WISC-V course
Base course ANT
Master course 2.3- Neuro-oncology
Seminars and Workshops
Clinical and Translational Oncology PhD retreat
Research Retreat Princess Máxima Center
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Amsterdam Kindersymposium
ECRN Research Day
LATER Research Day
Quality of life symposium
KWF Vermoeidheidsbijeenkomst
NASLCCC congress Atlanta
SIOP (two virtual editions)

* Non exhaustive overview