Improve the night, improve the day

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Chapter 7

High occurrence of sleep problems in survivors of a childhood brain tumor with neurocognitive complaints: The association with psychosocial and behavioral executive functioning

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Abstract

Background: Survivors of childhood brain tumors are prone to sleep and neurocognitive problems. Effective interventions to improve neurocognitive functioning are largely lacking. In general, sleep problems are negatively related to neurocognitive functioning, but this relationship is unclear in survivors of childhood brain tumors. Therefore, the occurrence of sleep problems, potential risk factors, and the relation between sleep and executive functioning were evaluated.

Procedure: Baseline data of a randomized controlled trial on the effectiveness of neurofeedback were used. Childhood brain tumor survivors 8-18 years of age with parent-reported neurocognitive complaints ≥ 2 years after treatment were eligible. Parents completed the Sleep Disturbance Scale for Children. Executive functioning was assessed by parents and teachers (Behavior Rating Inventory of Executive Functioning). Multiple linear regression analyses were used to examine sociodemographic and medical characteristics and emotional difficulties and hyperactivity / inattention (Strength and Difficulties Questionnaire) as potential risk factors for sleep problems, and to assess the association between sleep and executive functioning.

Results: Forty-eight percent of survivors (n = 82, 7.0 ± 3.6 years post diagnosis, age 13.8 ± 3.2 years) had sleep problems and scored significantly worse than the norm on the subscales Initiating and Maintaining Sleep, Excessive Somnolence and the total scale (effect sizes .58 - .92). Emotional problems and / or hyperactivity / inattention were independent potential risk factors. Sleep problems were associated with worse parent-reported executive functioning.

Conclusions: Sleep problems occur among half of childhood brain tumor survivors with neurocognitive problems, and are associated with worse executive functioning. Future studies should focus on the development of sleep interventions for this population, to improve sleep as well as executive functioning.

Introduction

The prevalence and nature of sleep problems varies with the different developmental stages of childhood.[1] Sleep problems involve disturbances in quality, timing, or amount of achieved sleep, which cause daytime problems.[2] Up to 50% of children experience a sleep problem at some point during childhood, characterized mostly by problems with falling and staying asleep.[1,3,4] Sleep problems are related to a lower quality of life in children.[3-5] In longitudinal studies, children with emotional problems such as anxiety and attention problems tend to have more sleep problems.[6-8] Alternatively, behavioral problems and mood disturbances are negative psychosocial consequences of sleep problems too, as is daytime sleepiness, which can lead to difficulties with focus and attention.[1,5,9] The relationship between sleep and psychosocial issues therefore seems to be bidirectional.

Children with a brain tumor are more prone to sleep disturbances than survivors of other pediatric malignancies. The hypothalamus and the hypothalamic-pituitary axis located in the brain are main regulators of sleep and play a key role in identifying sleep debt and regulating the circadian rhythm.[10] These brain structures can be damaged primarily if the tumor is located in this region or secondarily if radiotherapy and surgery affect the area, often resulting in sleep-wake disturbances.[11] Sleep problems are one of the most frequently reported symptoms after finishing treatment for a pediatric brain tumor.[12] Children and adolescent survivors self report sleep problems in 20-38% of cases, and the majority perceives these problems as severe or distressing.[12,13] Verberne et al. reported that survivors of a brain tumor and other pediatric malignancies, experience more problems with initiating and maintaining sleep, which affects their daytime functioning. Survivors of a brain tumor also experience more sleepiness, compared to children with other malignancies and compared to healthy children.[14] Besides tumor location and treatment, behavioral aspects may also play an important role in the susceptibility for sleep problems. For example, almost 20% of survivors experience clinically relevant inattention problems.[15] Inattention is one of the core symptoms of Attention Deficit Hyperactivity Disorder (ADHD), which has been linked to a higher prevalence of several sleep problems.[16,17] This makes inattention a factor worth investigating in relation to sleep problems in survivors of a brain tumor.

A pediatric brain tumor and its treatment also has a negative influence on neurocognitive functioning. The deficits mostly arise in attention, working memory and processing speed. Intelligence Quotient (IQ) decreases after treatment for a brain tumor.[18] On average, survivors have almost one standard deviation (SD) lower IQ than the norm population.[19] Younger age at diagnosis and treatment with cranial

radiotherapy are strongly associated with worse neurocognitive outcomes, as is longer time since diagnosis, since developmental demands increase with age and damage to neural cells can challenge normal development.[20-22]

Significant associations between neurocognitive functioning and various aspects of sleep have been reported in healthy and chronically sick children - worse sleep is associated with worse neurocognitive outcomes.[1,5,23-30] Neurocognitive outcomes were measured in different ways in these studies - academic performance was frequently used as an indicator of neurocognitive functioning,[1,5,23,24] and a more comprehensive perspective was given by neurocognitive performance tasks.[25-27,30] However, ecologically valid measures, such as questionnaires assessing the real-world behavioral manifestations of executive dysfunction, were used less often.[28,29] These type of measures have become increasingly important for clinical translation of research results.[31]

As pediatric brain tumor survivors are at risk both for sleep problems and neurocognitive impairment, improvement of sleep could be a way to benefit neurocognitive functioning in these children, for which proper interventions are currently scarce.[32] Exploring the extent of sleep problems in a vulnerable subgroup of brain tumor survivors - children with neurocognitive complaints - and subsequently examining the relation between sleep and behavioral executive functioning in this specific population is an important step towards developing and implementing sleep interventions. Therefore, this study aimed to determine (a) the rate of occurrence of sleep problems (based on a questionnaire that addresses domains similar to the six main categories of the International Classification of Sleep Disorders-3:[33] Insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders, disorders of somnolence and circadian rhythm sleep-wake disorders); (b) potential risk factors (sociodemographic, medical, and psychosocial) for sleep problems; and (c) the relation between sleep problems and behavioral executive functioning in survivors of a brain tumor with parent-reported neurocognitive complaints.

Methods

Participants and procedure

Baseline data of a randomized controlled trial (RCT) on the effectiveness of neurofeedback to improve neurocognitive functioning are used for the current study.[32] Survivors of a brain tumor with parent-reported neurocognitive complaints, aged 8-18 years, who completed tumor treatment at least 2 years ago, were approached

through their oncologist or psychologist for participation in the RCT. If interested in the RCT, parents / caregivers filled out a screening questionnaire concerning their child's neurocognitive functioning. The questionnaire included the attention subscale of the Disruptive Behavior Disorders Rating Scale (DBDRS[34]) and items on problems with attention, memory, information processing, and speed. Patients were eligible for inclusion if parents/caregivers reported cognitive problems, defined as a DBDRS-score indicative of subclinical functioning (14 or higher), and / or reported at least two problems with respect to attention, memory, speed, and information processing. Exclusion criteria for the RCT were diagnosis with ADHD / ADD, a mental or physical condition that could prohibit neurocognitive assessment, and insufficient mastery of the Dutch language. Participants filled out written informed consent forms and Dutch versions of the questionnaires described in the following sections online, at home.

Participating hospitals were the Emma Children's Hospital / Academic Medical Center in Amsterdam, VU Medical Center in Amsterdam, University Medical Center Utrecht/ Wilhelmina Children's Hospital in Utrecht, Radboud University Medical Center in Nijmegen and University Medical Center Maastricht in Maastricht.

Primary outcomes

Sleep problems

Sleep was assessed with the Sleep Disturbance Scale for Children (SDSC).[35] The SDSC is a parent-reported questionnaire, developed and validated by Bruni et al, in a large group of healthy children (aged 6.5-15.3 years) and a clinical subsample of children with known insomnia, hypersomnia, parasomnias, and respiratory problems during sleep.[35] The objective was to provide a standardized measure of sleep disturbance in childhood and adolescence. The SDSC reached a good test-retest reliability ($r = .71$) and good diagnostic accuracy (area under the curve .91).[35] Since then, the SDSC has been used in studies with survivors of a brain tumor, children with pineal cysts, neurofibromatosis, and other neuropsychological conditions.[14,36-38]

The SDSC contains 26 questions that assess sleep behavior and disturbances in the previous 6 months and are divided in the following six subscales: disorders of initiating and maintaining sleep (DIMS, seven items, e.g., 'the child has difficulty going to sleep at night'), sleep breathing disorders (SBD, three items, e.g., 'the child has difficulty breathing at night'), disorders of arousal / nightmares (DA, three items, e.g., 'you have observed the child sleepwalking'), sleep wake transition disorders (SWTD, six items, e.g., 'the child jerks parts of the body while falling asleep'), disorders of excessive somnolence (DOES, six items, e.g., 'the child is unusually difficult to wake up in the morning'), and sleep hyperhidrosis (SHY, two items, e.g., 'the child sweats excessively

while falling asleep'). Items (problems) are answered on a 5-point Likert scale: 1 = never, 5 = always. For two items in the DIMS subscale, the Likert scale reflects an amount of hours ('how many hours of sleep does your child get on most nights': 1 = 9-11 h, 5 = less than 5 h; and 'how long after going to bed does your child usually fall asleep': 1 = less than 15 minutes, 5 = more than 60 minutes). The total score range is 26-130, a higher score reflects worse symptoms. Norm values have been established for Italian children aged 6.5-15.3 years. A score above the upper quartile (39) of the norm is considered clinically relevant.[35] In our population, all subscales except for DA reached a satisfying Cronbach's alpha ≥ .60 (DIMS .61, SBD .60, DA .38, SWTD .66, DOES .61, SHY .87, and total score .79), therefore the DA subscale was excluded from analysis.

Behavioral executive functioning

One important subset of neurocognitive functions is encompassed in executive functioning, that is, functions necessary for the cognitive control and adaptation of behavior. Daily behavioral executive functioning was assessed with the Behavior Rating Inventory of Executive Functioning (BRIEF).[39] The BRIEF is a parent- and teacher-rated questionnaire. The questionnaire comprises 75 items divided in eight subscales (inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials, and monitor), two indices (behavioral index and metacognition index), and a total score. Items are answered on a 3-point Likert scale: 1 = never, 3 = often. A higher score indicates worse behavioral executive functioning. The raw scores are transformed to age and gender-specific standardized T-scores with a mean of 50 and an SD of 10.[40] In this study, the indices and total score are used. In our population Cronbach's alphas for the BRIEF parent ranged from .66 to .94, and for the BRIEF teacher from .82 to .97.[39]

Independent variables

Demographic and medical variables

Medical characteristics were retrieved from medical records. Variables of interest were time since diagnosis, tumor location, treatment type, and history of hydrocephalus. Parents / caregivers provided information on sociodemographic characteristics. Variables of interest were child's age at assessment and gender, as gender has previously been shown to be associated with sleep problems and its consequences,[4,9,41-43] and highest level of parent education as a reflection of the family's socioeconomic status, which has been associated with both sleep and neurocognitive functioning.[41,43,44]

Psychosocial functioning

To assess the child's psychosocial functioning, the parent form of the Strength and Difficulties Questionnaire (SDQ) was used.[45,46] The SDQ assesses behaviors, emotions, and relationships of children in the previous 6 months. The questionnaire comprises a total of 25 items divided into four problem subscales (emotional symptoms, conduct problems, hyperactivity / inattention, and peer problems) and a strength subscale (prosocial behavior). Items are answered on a 3-point Likert scale: 0 = not true, 2 = certainly true. In this study, the following two problem subscales were used: emotional symptoms (five items) and hyperactivity / inattention (five items). The emotional problems subscale of the SDQ measures the presence of worries, fears, nervousness, other mood disturbances, and physical complaints often present with anxiousness. The hyperactivity / inattention subscale measures indications of behaviors such as restlessness, being overactive or easily distracted, and the ability to think before acting.[45,46] In our population, Cronbach's alpha for the emotional symptoms subscale was .60 and for the subscale hyperactivity / inattention .72.

Statistical analyses

To assess sleep problems, SDSC subscale scores and the total score were compared to the scores in the norm population using a one-sample t-test.[35] Effect sizes (ES) were calculated and interpreted following Cohen: 0.2 as small, 0.5 as medium and 0.8 as large.[47,48] Descriptive statistics were used to determine the occurrence of clinically relevant sleep problems. We considered a P-value < .008 significant, .05 divided by the number of (sub)scales.

To determine the potential risk factors for sleep problems, we performed multiple linear regression analyses. Separate regression models were estimated for each SDSC subscale and for the total score, predicted by medical variables (time since diagnosis, radiotherapy, and tumor location), sociodemographic variables (age, gender, and educational level of parents), and the SDQ subscales emotional symptoms and hyperactivity/inattention. We considered a P-value < .008 significant (.05 divided by the six regression models). Tumor location was divided in three categories (supratentorial, infratentorial, and supratentorial midline). Supratentorial midline tumors served as the reference category because it is known that children with a tumor located at the supratentorial midline have a higher prevalence of sleep problems, since key regulators of sleep, such as the hypothalamus, are situated in this region.[49-51] Previous research suggests influence on sleep of all the variables mentioned above. The association between hydrocephalus and sleep is unclear.[14] Univariate regression analysis revealed no significant relationship between the prior presence of hydrocephalus and the SDSC subscales and total score (P = .18 – .80). We therefore did not use this variable in the prediction models.

Finally, to determine the relation between sleep problems (as reflected by the SDSC total score) and behavioral executive functioning (BRIEF), we performed multiple linear regression analyses with BRIEF scores as the dependent variable and the SDSC total score as the independent variable. The regression analyses were corrected for medical variables (time since diagnosis, radiotherapy, and tumor location) and sociodemographic variables (age, gender, and educational level of parents). SDQ subscale scores were not included in the models because of multicollinearity with the BRIEF scores. Separate association models were estimated for the indices and the total score of the BRIEF parent and teacher, resulting in three regression models for parents and three for teachers. We considered a P-value < .017 significant (.05 divided by the three regression models).

Beta values were interpreted following Cohen: For dichotomous predictors 0.2 as small, 0.5 as medium and 0.8 as large; for continuous predictors 0.1 as small, 0.3 as medium and 0.5 as large.[47,48] IBM SPSS version 21 was used for all analyses.

Results

Population

A total of 249 patients were approached for the study: 96 did not meet the inclusion criteria, 71 declined participation before the inclusion criteria could be assessed and a total of 82 patients met inclusion criteria and participated in the study (mean age 13.8 years, SD 3.2 years, 49% males). This resulted in a participation rate of 54%. Demographic and medical characteristics are shown in Table 1. Participants did not differ from the survivors who declined participation (n = 71) regarding age at assessment, gender, radiotherapy, and tumor location. Participants more often received chemotherapy (43% vs 27%) and the time since diagnosis was longer (mean 7.0, SD 3.6 vs mean 6.1, SD 3.3 years).[32]

Rate of occurrence of sleep problems

In our population, 48.8% reported scores indicative of a clinically relevant sleep problem, which is significantly (P < .001) higher than the 25% in the norm population. As shown in Table 2, mean scores of the survivors were significantly higher than the norm, indicating more sleep problems. Medium to large effects sizes were found on the subscale DIMS (P < .001, ES = 0.92), DOES (P < .001, ES = 0.58), and on the total score (P < .001, ES = 0.74). Scores did not differ on SBD (P = .13, ES = 0.19), SWTD (P .02, ES = 0.32), and SHY (P = .70, ES = 0.04).

Table 1 Description of the study population

	Total sample (n=82)
Age at assessment (mean years, SD)	13.8 (3.2)
Time since diagnosis (mean years, SD)	7.0 (3.6)
Gender (n, % male)	40 (48.8)
Highest education parent (n, %)[a]	
Low or intermediate	39 (47.6)
High	43 (52.4)
Tumor location (n, %)	-
Supratentorial midline	16 (19.5)
Infratentorial	36 (43.9)
Supratentorial	30 (36.6)
Tumor type and grade (n, %)	-
High grade	34 (41.5)
Medullablastoma	12 (14.6)
Supratentorial PNET	8 (9.8)
Ependymoma	5 (6.1)
Astrocytoma gr III	5 (6.1)
Germ cell tumor	4 (4.9)
Low grade	48 (58.5)
Low-grade glioma	35 (42.7)
Craniopharyngioma	7 (8.5)
Plexus papilloma	6 (7.3)
Treatment (n, %)	-
Radiotherapy	30 (36.7)
Chemotherapy	35 (42.7)
Surgery	72 (87.8)
History of hydrocephalus (n, %)	39 (47.6)
Questionnaire scores	-
BRIEF parent total score (mean, SD; range)	54 (8); 37-76
BRIEF teacher total score (mean, SD; range)	51 (13); 31-103
SDQ parent emotional symptoms subscale (mean, SD; range)	3 (2); 0-9
SDQ parent hyperactivity/inattention subscale (mean, SD; range)	4 (2); 0-10

Abbreviations: BRIEF = Behavior Rating Inventory of Executive Functioning; PNET = Primitive Neuro-Ectodermal Tumor; SD = Standard Deviation; SDQ = Strength and Difficulties Questionnaire

[a] Low or intermediate - primary education, general secondary education and secondary vocational education; high - higher vocational education and university.

Table 2 SDSC scores of study population compared to norm values[35]

SDSC subscale[a]	Mean (SD) study population	Mean (SD) norm population	P-value	Effect size
DIMS	**12.8 (3.4)**	**9.9 (3.1)**	**< 0.001**	**-0.92**
SBD	4.1 (1.6)	3.8 (1.5)	0.13	-0.19
SWTD	8.9 (2.9)	8.1 (2.4)	0.02	-0.32
DOES	**8.6 (2.5)**	**7.1 (2.6)**	**< 0.001**	**-0.58**
SHY	2.9 (1.6)	2.9 (1.7)	0.70	-0.04
Total score	**40.7 (8.2)**	**35.1 (7.7)**	**< 0.001**	**-0.74**

Abbreviations: DIMS = Disorders of Initiating and Maintaining Sleep; DOES = Disorders Of Excessive Somnolence; SBD = Sleep Breathing Disorders; SD = Standard Deviation; SDSC = Sleep Disturbance Scale for Children; SHY = Sleep Hyperhidrosis; SWTD = Sleep-Wake Transition Disorders
[a] Significant results (P < .008) are presented in bold.

Table 3 Prediction models for sleep problems as measured with the SDSC (n=82)

Dependent variable	Predictors[a]	B	Bèta	P-value	R^2
DIMS	Age	0.26	0.24	.04	0.32
	Female gender	0.85	0.13	.25	
	Time since diagnosis	-0.12	-0.12	.26	
	SDQ emotion	**0.64**	**0.39**	**< .001**	
	SDQ hyperactivity/inattention	**0.49**	**0.34**	**.002**	
	High educational level parents[b]	0.49	0.07	.49	
	Radiotherapy	- 0.18	- 0.03	.81	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	0.80	0.12	.39	
	Supratentorial	0.06	0.01	.96	
SBD	Age	- 0.11	- 0.20	.11	0.17
	Female gender	- 1.02	- 0.31	.01	
	Time since diagnosis	0.06	0.13	.31	
	SDQ emotion	- 0.06	- 0.08	.51	
	SDQ hyperactivity/inattention	0.06	0.09	.46	
	High educational level parents[b]	- 0.39	- 0.12	.30	
	Radiotherapy	0.72	0.21	.06	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	0.20	0.06	.68	
	Supratentorial	0.06	0.02	.91	
SWTD	Age	0.00	0.01	.97	0.21
	Female gender	- 0.76	- 0.13	.25	
	Time since diagnosis	- 0.02	- 0.03	.81	
	SDQ emotion	0.23	0.17	.12	
	SDQ hyperactivity/inattention	0.34	0.28	.02	
	High educational level parents[b]	- 0.79	- 0.14	.22	
	Radiotherapy	- 0.23	- 0.04	.73	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	0.23	0.04	.78	
	Supratentorial	- 0.31	- 0.05	.72	

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DOES	Age	0.14	0.18	.16	0.17
	Female gender	- 0.21	- 0.04	.72	
	Time since diagnosis	- 0.06	- 0.09	.47	
	SDQ emotion	0.32	0.27	.02	
	SDQ hyperactivity/inattention	0.09	0.09	.49	
	High educational level parents[b]	0.89	0.18	.12	
	Radiotherapy	- 0.95	- 0.19	.10	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	- 0.98	- 0.20	.19	
	Supratentorial	- 0.46	- 0.09	.55	
SHY	Age	- 0.10	- 0.20	.12	0.17
	Female gender	**- 1.29**	**- 0.40**	**< .001**	
	Time since diagnosis	- 0.01	- 0.03	.83	
	SDQ emotion	0.01	0.01	.93	
	SDQ hyperactivity/inattention	- 0.02	- 0.03	.82	
	High educational level parents[b]	0.28	0.09	.46	
	Radiotherapy	- 0.09	- 0.03	.82	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	0.23	0.07	.64	
	Supratentorial	0.38	0.11	.46	
Total score	Age	0.21	0.08	.48	0.30
	Female gender	- 2.61	- 0.16	.15	
	Time since diagnosis	- 0.17	- 0.07	.51	
	SDQ emotion	**1.23**	**0.31**	**.004**	
	SDQ hyperactivity/inattention	**1.07**	**0.31**	**.006**	
	High educational level parents[b]	0.10	0.01	.95	
	Radiotherapy	- 0.92	- 0.05	.60	
	Tumor location supratentorial midline	Reference	Reference	Reference	
	Infratentorial	0.53	0.03	.82	
	Supratentorial	- 0.32	- 0.20	.89	

Abbreviations: DIMS = Disorders of Initiating and Maintaining Sleep; DOES = Disorders Of Excessive Somnolence; SBD = Sleep Breathing Disorders; SD = Standard Deviation; SDSC = Sleep Disturbance Scale for Children; SHY = Sleep Hyperhidrosis; SWTD = Sleep-Wake Transition Disorders

[a] Significant results (P < .008) are presented in bold.

[b] Low or intermediate - primary education, general secondary education and secondary vocational education; high - higher vocational education and university.

Potential risk factors for sleep problems

Behavioral problems according to SDQ subscales (emotional problems: P < .001, beta = 0.39; hyperactivity/inattention: P < .01, beta = 0.34) were significantly associated with higher scores on DIMS. Behavioral problems were also significantly related to higher scores on the total score (emotional problems: P = .004, beta = 0.31; hyperactivity / inattention: P = .006, beta = 0.31). Female gender was significantly associated with lower scores on SHY (P < .001, beta = - 0.40), indicating that females had fewer sleep problems on this subscale than males. Age, time since diagnosis, the educational level of parents, radiotherapy, and tumor location were not significantly associated with any of the subscales or the total score of the SDSC. Results are shown in Table 3.

Relationship between sleep problems and behavioral executive functioning

Total sleep problems, as reflected by the SDSC total score, corrected for medical and sociodemographic variables, were significantly associated with both BRIEF parent indices (metacognition index: P = .005, beta = 0.32; behavioral index: P .001, beta = 0.34) and the BRIEF parent total score (P .001, beta = 0.38) with medium ES. According to the teacher-reported BRIEF, sleep was not significantly associated with behavioral executive functioning. Results are shown in Table 4.

Table 4 Association models of sleep and behavioral executive functioning

Dependent variable	Independent variables[a]	B	Beta	P-value
BRIEF parent (n=82)				
Metacognition index	**SDSC total score**	**0.32**	**0.32**	**.005**
	Age	-0.30	-0.12	.32
	Female gender	-1.26	-0.08	.50
	Time since diagnosis	0.22	0.10	.42
	High educational level parents[b]	2.51	0.16	.16
	Radiotherapy	1.57	0.10	.38
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	2.50	0.16	.29
	Supratentorial	3.83	0.23	.12
Behavioral index	**SDSC total score**	**0.46**	**0.34**	**.001**
	Age	0.74	0.21	.06
	Female gender	-5.30	-0.24	.03
	Time since diagnosis	-0.02	-0.01	.95
	High educational level parents[b]	-2.53	-0.11	.26
	Radiotherapy	-1.49	-0.06	.51
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	1.55	0.07	.60
	Supratentorial	5.57	0.24	.08
Total score	**SDSC total score**	**0.40**	**0.38**	**.001**
	Age	0.07	0.03	.82
	Female gender	-2.82	-0.17	.14
	Time since diagnosis	0.14	0.06	.59
	High educational level parents[b]	0.47	0.03	.79
	Radiotherapy	0.68	0.04	.70
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	2.40	0.14	.31
	Supratentorial	4.81	0.28	.05
BRIEF teacher (n=73)				
Metacognition index	SDSC total score	-0.19	-0.10	.37
	Age	-1.71	-0.40	.002
	Female gender	3.73	0.14	.25
	Time since diagnosis	0.38	0.10	.42
	High educational level parents[b]	-2.47	-0.09	.43
	Radiotherapy	6.44	0.22	.05
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	4.83	0.17	.24
	Supratentorial	-0.90	-0.03	.83

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Behavioral index	SDSC total score	-0.28	-0.16	.18
	Age	-0.89	-0.23	.08
	Female gender	3.39	0.14	.28
	Time since diagnosis	0.18	0.05	.69
	High educational level parents[b]	-3.53	-0.14	.24
	Radiotherapy	2.50	0.10	.42
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	3.10	0.13	.43
	Supratentorial	-2.70	-0.11	.51
Total score	SDSC total score	-0.22	-0.12	.28
	Age	-1.34	-0.34	.007
	Female gender	4.52	0.18	.14
	Time since diagnosis	0.35	0.10	.43
	High educational level parents[b]	-3.38	-0.13	.25
	Radiotherapy	5.05	0.19	.10
	Tumor location supratentorial midline	Reference	Reference	Reference
	Infratentorial	5.28	0.21	.16
	Supratentorial	-0.65	-0.03	.87

Abbreviations: BRIEF = Behavior Rating Inventory of Executive Functioning; SDSC = Sleep Disturbance Scale for Children

[a] Significant results (P < .017) are presented in bold.

[b] Low or intermediate - primary education, general secondary education and secondary vocational education; high - higher vocational education and university.

Discussion

The aim of this study was to determine the rate of occurrence of sleep problems, potential risk factors for sleep problems, and the relation between sleep problems and behavioral executive functioning in pediatric survivors of a brain tumor. We answered these questions through analysis of parent-reported sleep (SDSC) in a large cohort of survivors with parent-reported neurocognitive complaints, and additional analysis with parent and teacher-reported behavioral executive functioning (BRIEF). The BRIEF was chosen because of its ecological validity.[31]

We found a high occurrence of clinically relevant sleep problems in pediatric brain tumor survivors with parent-reported neurocognitive complaints. These sleep problems manifest mainly in initiating and maintaining sleep and excessive somnolence. Previous studies have also shown problems with excessive somnolence and initiating and maintaining sleep, as well as an increased prevalence of insomnia, compared to healthy children and children with other malignancies.[13,14,51,52] Damage of hypothalamic structures due to tumor location or treatment can cause damage to hypocretin and melatonin producing cells, which can subsequently lead to increased somnolence and irregular sleep patterns.[11] Contrary to previous research, there was no increased occurrence of SBD in our population. However, drawing solid conclusions about SBD in our population is somewhat hampered because this disorder was measured in a three-

item scale with moderate internal consistency. Apart from this, measuring SBD with questionnaires is difficult anyway.[53] SBD are often associated with obesity and damage to the brainstem and thalamic nuclei.[11,13,49] The relatively low number of tumors located at the supratentorial midline (20%) could explain the normal occurrence of SBD in our study population. Unfortunately, there was no information available on weight status.

The results indicate that emotional problems and hyperactivity / inattention might be risk factors for sleep problems, though the direction of the relation between sleep problems and emotional problems cannot be confirmed given the cross-sectional design of the study. This finding is in line with results previously been found in healthy children and other populations such as children with ADHD.[3,6-9,54] Similar results were reported by Cohen et al. in groups of children with neurological disorders, they concluded that sleep problems are likely more related to behavioral and environmental factors rather than the neurological disorder itself.[55] There are pathophysiological mechanisms that can explain the increased occurrence of sleep problems in children with a brain tumor. Medical variables such as tumor location and radiotherapy were not statistically significant in predicting sleep problems in our study sample.

As expected, our results show a significant relation between sleep and behavioral executive functioning as scored by the parents. This in line with other studies - parents who reported more sleep problems for their child also reported worse behavioral executive functioning.[25-30,39] However, we did not find a significant association between sleep problems and teacher-rated behavioral executive functioning. There are several potential reasons for this discrepancy. First of all, parents and teachers see the child in different contexts, as can be illustrated by the lack of correlation between the BRIEF parent and teacher scores previously found in our sample.[39] Teachers reported better behavioral executive functioning in brain tumor survivors than the parents did,[39] which may relate to different demands at school versus at home. Teachers have a solid reference for functioning in healthy children at school, whereas parents have a comprehensive view of a child's life including his/her premorbid functioning. Second, associations between two parent-reported outcomes may be more likely than between parent-proxy and teacher-proxy outcomes. Taveras et al. did however find a relation between both parent and teacher-reported BRIEF scores with parent-reported sleep duration, a more objective measure of sleep.[56] Patient self reports and objective measures of sleep such as polysomnography or actigraphy would therefore be informative in the future. Finally, parental psychosocial functioning may influence their perception of their child's sleep and behavioral executive functioning, as has previously been reported for sleep and quality of life in other populations - greater distress and more difficulty sleeping reported by parents was associated with worse parent-proxy scores for their child.[57,58]

Considering the fact that effective interventions for improvement of neurocognitive functioning in survivors of a brain tumor are largely lacking,[32] it is important to look for alternative ways to improve neurocognitive functioning in this vulnerable population. The results of this study point at psychosocial / behavioral factors as potential risk factors for sleep problems, indicating that behavioral sleep interventions could be one such alternative way. A behavioral sleep intervention consisting of information on normal sleep, sleep hygiene, and management strategies for sleep behavior in children with ADHD has been shown to improve both sleep and working memory in an RCT.[59] Cognitive behavior therapy (CBT) encompassing the core components sleep restriction, stimulus control, and cognitive restructuring has been shown to be effective for insomnia in patients with cancer, including brain tumor survivors,[60,61] and could improve initiation and maintenance of sleep. By improving sleep, CBT has also demonstrated to improve psychopathology, including symptoms of ADHD.[62] Interventions for excessive somnolence are dependent on the cause.[63] Behavioral sleep interventions are favorable when somnolence is brought on by insufficient or inadequate sleep, disorders of arousal, or delayed sleep phase syndrome, whereas pharmacological and other additional therapies may be indicated in other causal mechanisms of somnolence.[63]

There are a few limitations to this study. First of all, the study population was selected based on parent-reported neurocognitive complaints and participants more often received chemotherapy and were longer from diagnosis than nonparticipants were. This means results could possibly be less generalizable to a lower-risk population. Second, the sample was diverse regarding the medical variables and thus the power was small to detect the medical correlates of sleep. Third, the primary outcomes are parent reported. The influence of this is unclear, since parents often underestimate the sleep problems reported by their children,[64-66] but parental psychosocial problems can lead to overestimation of child problems too.[57,58] Future studies should include self reports and objective sleep assessments in addition to proxy-reports. Fourth, though Italian SDSC norm values are available, ideally Dutch norm values should have been used. Finally, our results are based on a cross-sectional design, thus, causal relations cannot be proven. To further investigate the potential risk factors identified here, a longitudinal design is necessary.

In conclusion, sleep problems are very common in pediatric brain tumor survivors, with parent-reported neurocognitive problems. Psychosocial factors such as emotional problems and hyperactivity / inattention are potential risk factors for these sleep problems. In turn, sleep problems are associated with worse behavioral executive functioning, at least as reported by parents. The results of this study illustrate that

behavioral executive functioning could potentially be improved by optimizing sleep. Future studies should focus on increasing understanding of this association and longitudinal designs are necessary to prove causal relations. It would be ideal to use multiple measures for behavioral executive functioning and sleep, since self and proxy-reports and actigraphy give different insights and can complement each other. Further development, testing and adaptation of suitable interventions are needed to improve sleep in populations more vulnerable to the executive consequences of disturbed sleep.

References

1. Carter KA, Hathaway NE and Lettieri CF. Common sleep disorders in children. American family physician. 2014; 89(5): 368-377.
2. American Psychiatry Association. What Are Sleep Disorders? https://www.psychiatry.org/patients-families/sleep-disorders/what-are-sleep-disorders. Accessed July 4th 2019.
3. Quach J, Hiscock H and Wake M. Sleep problems and mental health in primary school new entrants: cross-sectional community-based study. Journal of paediatrics and child health. 2012; 48(12): 1076-1081.
4. Paiva T, Gaspar T and Matos MG. Sleep deprivation in adolescents: correlations with health complaints and health-related quality of life. Sleep medicine. 2015; 16(4): 521-527.
5. Chaput JP, Gray CE, Poitras VJ, et al. Systematic review of the relationships between sleep duration and health indicators in school-aged children and youth. Applied physiology, nutrition, and metabolism. 2016; 41(6): S266-282.
6. Brown WJ, Wilkerson AK, Boyd SJ, Dewey D, Mesa F and Bunnell BE. A review of sleep disturbance in children and adolescents with anxiety. Journal of sleep research. 2018; 27(3): e12635.
7. Wang B, Isensee C, Becker A, et al. Developmental Trajectories of Sleep Problems from Childhood to Adolescence Both Predict and Are Predicted by Emotional and Behavioral Problems. Frontiers in psychology. 2016; 7: 1874.
8. Quach JL, Nguyen CD, Williams KE and Sciberras E. Bidirectional Associations Between Child Sleep Problems and Internalizing and Externalizing Difficulties From Preschool to Early Adolescence. JAMA pediatrics. 2018; 172(2): e174363.
9. Shochat T, Cohen-Zion M and Tzischinsky O. Functional consequences of inadequate sleep in adolescents: a systematic review. Sleep medicine reviews. 2014; 18(1): 75-87.
10. Borbely AA and Achermann P. Sleep homeostasis and models of sleep regulation. Journal of biological rhythms. 1999; 14(6): 557-568.
11. Gapstur R, Gross CR and Ness K. Factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors: a review. Oncology nursing forum. 2009; 36(6): 723-731.
12. Macartney G, VanDenKerkhof E, Harrison MB and Stacey D. Symptom experience and quality of life in pediatric brain tumor survivors: a cross-sectional study. Journal of pain and symptom management. 2014; 48(5): 957-967.
13. Brimeyer C, Adams L, Zhu L, et al. Sleep complaints in survivors of pediatric brain tumors. Supportive care in cancer. 2016; 24(1): 23-31.
14. Verberne LM, Maurice-Stam H, Grootenhuis MA, Van Santen HM and Schouten-Van Meeteren AY. Sleep disorders in children after treatment for a CNS tumour. Journal of sleep research. 2012; 21(4): 461-469.
15. Kahalley LS, Conklin HM, Tyc VL, et al. ADHD and secondary ADHD criteria fail to identify many at-risk survivors of pediatric ALL and brain tumor. Pediatric blood and cancer. 2011; 57(1): 110-118.
16. Tsai MH and Huang YS. Attention-deficit/hyperactivity disorder and sleep disorders in children. The Medical clinics of North America. 2010; 94(3): 615-632.
17. Kotagal S and Chopra A. Pediatric sleep-wake disorders. Neurologic clinics. 2012; 30(4): 1193-1212.
18. Watanabe S, Azami Y, Ozawa M, et al. Intellectual development after treatment in children with acute leukemia and brain tumor. Pediatrics international. 2011; 53(5): 694-700.
19. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. Medical and pediatric oncology. 2003; 40(1): 26-34.
20. de Ruiter MA, van Mourik R, Schouten-van Meeteren AY, Grootenhuis MA and Oosterlaan J. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. Developmental medicine and child neurology. 2013; 55(5): 408-417.
21. Winter AL, Conklin HM, Tyc VL, et al. Executive function late effects in survivors of pediatric brain tumors and acute lymphoblastic leukemia. Journal of clinical and experimental neuropsychology. 2014; 36(8): 818-830.
22. Turner CD, Rey-Casserly C, Liptak CC and Chordas C. Late effects of therapy for pediatric brain tumor survivors. Journal of child neurology. 2009; 24(11): 1455-1463.

23. Bruni O, Ferini-Strambi L, Russo PM, et al. Sleep disturbances and teacher ratings of school achievement and temperament in children. Sleep medicine. 2006; 7(1): 43-48.
24. Hysing M, Harvey AG, Linton SJ, Askeland KG and Sivertsen B. Sleep and academic performance in later adolescence: results from a large population-based study. Journal of sleep research. 2016; 25(3): 318-324.
25. Ward TM, Archbold K, Lentz M, Ringold S, Wallace CA and Landis CA. Sleep disturbance, daytime sleepiness, and neurocognitive performance in children with juvenile idiopathic arthritis. Sleep. 2010; 33(2): 252-259.
26. Astill RG, van der Heijden KB, van Ijzendoorn MH and van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychological bulletin. 2012; 138(6): 1109-1138.
27. Camfferman D, Kennedy JD, Gold M, Simpson C and Lushington K. Sleep and neurocognitive functioning in children with eczema. International journal of psychophysiology. 2013; 89(2): 265-272.
28. Caruso NC, Radovanovic B, Kennedy JD, et al. Sleep, executive functioning and behaviour in children and adolescents with type 1 diabetes. Sleep medicine. 2014; 15(12): 1490-1499.
29. Anderson B, Storfer-Isser A, Taylor HG, Rosen CL and Redline S. Associations of executive function with sleepiness and sleep duration in adolescents. Pediatrics. 2009; 123(4): e701-707.
30. Konen T, Dirk J and Schmiedek F. Cognitive benefits of last night's sleep: daily variations in children's sleep behavior are related to working memory fluctuations. Journal of child psychology and psychiatry, and allied disciplines. 2015; 56(2): 171-182.
31. Gioia GA and Isquith PK. Ecological assessment of executive function in traumatic brain injury. Developmental neuropsychology. 2004; 25(1-2): 135-158.
32. de Ruiter MA, Oosterlaan J, Schouten-van Meeteren AY, et al. Neurofeedback ineffective in paediatric brain tumour survivors: Results of a double-blind randomised placebo-controlled trial. European journal of cancer. 2016; 64: 62-73.
33. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014; 146(5): 1387-1394.
34. Oosterlaan J, Scheres A, Antrop I, Roeyers H and Sergeant J. Vragenlijst voor Gedragsproblemen bij kinderen: Nederlandse bewerking van de Disruptive Behavior Disorders Rating Scale [Dutch translation of the Disruptive Behavior Disorders Rating Scale]. Lisse, the Netherlands: Swets & Zeitlinger; 2000.
35. Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC): Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. Journal of sleep research. 1996; 5(4): 251-261.
36. Marriner AM, Pestell C, Bayliss DM, McCann M and Bucks RS. Confirmatory factor analysis of the Sleep Disturbance Scale for Children (SDSC) in a clinical sample of children and adolescents. Journal of sleep research. 2017; 26(5): 587-594.
37. DelRosso LM, Martin K, Bruni O and Ferri R. Sleep disorders in children with incidental pineal cyst on MRI: a pilot study. Sleep medicine. 2018; 48: 127-130.
38. Licis AK, Vallorani A, Gao F, et al. Prevalence of Sleep Disturbances in Children With Neurofibromatosis Type 1. Journal of child neurology. 2013; 28(11): 1400-1405.
39. de Vries M, de Ruiter MA, Oostrom KJ, et al. The association between the behavior rating inventory of executive functioning and cognitive testing in children diagnosed with a brain tumor. Child neuropsychology. 2017: 1-15.
40. Smidts DP and Huizinga M. BRIEF executieve functies gedragsvragenlijst: Handleiding [Dutch manual BRIEF]. Amsterdam, the Netherlands: Hogrefe Uitgevers; 2009.
41. Arman AR, Ay P, Fis NP, et al. Association of sleep duration with socio-economic status and behavioural problems among schoolchildren. Acta paediatrica. 2011; 100(3): 420-424.
42. Olds T, Blunden S, Petkov J and Forchino F. The relationships between sex, age, geography and time in bed in adolescents: a meta-analysis of data from 23 countries. Sleep medicine reviews. 2010; 14(6): 371-378.
43. Moore M, Kirchner HL, Drotar D, Johnson N, Rosen C and Redline S. Correlates of adolescent sleep time and variability in sleep time: the role of individual and health related characteristics. Sleep medicine. 2011; 12(3): 239-245.

44. Pagel JF, Forister N and Kwiatkowki C. Adolescent sleep disturbance and school performance: the confounding variable of socioeconomics. Journal of clinical sleep medicine. 2007; 3(1): 19-23.
45. Goodman R. The Strengths and Difficulties Questionnaire: a research note. Journal of child psychology and psychiatry, and allied disciplines. 1997; 38(5): 581-586.
46. van Widenfelt BM, Goedhart AW, Treffers PD and Goodman R. Dutch version of the Strengths and Difficulties Questionnaire (SDQ). European child & adolescent psychiatry. 2003; 12(6): 281-289.
47. Cohen J. A power primer. Psychological bulletin. 1992; 112(1): 155-159.
48. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
49. Mandrell BN, Wise M, Schoumacher RA, et al. Excessive daytime sleepiness and sleep-disordered breathing disturbances in survivors of childhood central nervous system tumors. Pediatric blood and cancer. 2012; 58(5): 746-751.
50. Rosen GM, Bendel AE, Neglia JP, Moertel CL and Mahowald M. Sleep in children with neoplasms of the central nervous system: case review of 14 children. Pediatrics. 2003; 112(1):e46-54.
51. Rosen G and Brand SR. Sleep in children with cancer: case review of 70 children evaluated in a comprehensive pediatric sleep center. Supportive care in cancer. 2011; 19(7): 985-994.
52. Zhou ES, Manley PE, Marcus KJ and Recklitis CJ. Medical and Psychosocial Correlates of Insomnia Symptoms in Adult Survivors of Pediatric Brain Tumors. Journal of pediatric psychology. 2016; 41(6): 623-630.
53. Jonas DE, Amick HR, Feltner C, et al. Screening for Obstructive Sleep Apnea in Adults: An Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017.
54. Mulraney M, Giallo R, Lycett K, Mensah F and Sciberras E. The bidirectional relationship between sleep problems and internalizing and externalizing problems in children with ADHD: a prospective cohort study. Sleep medicine. 2016; 17: 45-51.
55. Cohen R, Halevy A and Shuper A. Children's sleep disturbance scale in differentiating neurological disorders. Pediatric neurology. 2013; 49(6): 465-468.
56. Taveras EM, Rifas-Shiman SL, Bub KL, Gillman MW and Oken E. Prospective Study of Insufficient Sleep and Neurobehavioral Functioning Among School-Age Children. Academic pediatrics. 2017; 17(6): 625-632.
57. Panepinto JA, Hoffmann RG and Pajewski NM. The effect of parental mental health on proxy reports of health-related quality of life in children with sickle cell disease. Pediatric blood and cancer. 2010; 55(4): 714-721.
58. Ronnlund H, Elovainio M, Virtanen I, Matomaki J and Lapinleimu H. Poor Parental Sleep and the Reported Sleep Quality of Their Children. Pediatrics. 2016; 137(4).
59. Hiscock H, Sciberras E, Mensah F, et al. Impact of a behavioural sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental mental health: randomised controlled trial. BMJ (Clinical research ed). 2015; 350: h68.
60. Zhou ES, Vrooman LM, Manley PE, Crabtree VM and Recklitis CJ. Adapted Delivery of Cognitive-Behavioral Treatment for Insomnia in Adolescent and Young Adult Cancer Survivors: A Pilot Study. Behavioral sleep medicine. 2017; 15(4): 288-301.
61. Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep medicine reviews. 2016; 27: 20-28.
62. de Bruin EJ, Bogels SM, Oort FJ and Meijer AM. Improvements of adolescent psychopathology after insomnia treatment: results from a randomized controlled trial over 1 year. Journal of child psychology and psychiatry, and allied disciplines. 2018; 59(5): 509-522.
63. Kaleyias J, Manley P and Kothare SV. Sleep disorders in children with cancer. Seminars in pediatric neurology. 2012; 19(1): 25-34.
64. Fatima Y, Doi SA, O'Callaghan M, Williams G, Najman JM and Mamun AA. Parent and adolescent reports in assessing adolescent sleep problems: results from a large population study. Acta paediatrica. 2016; 105(9): e433-439.
65. Short MA, Gradisar M, Gill J and Camfferman D. Identifying adolescent sleep problems. PloS one. 2013; 8(9): e75301.
66. Owens JA, Spirito A, McGuinn M and Nobile C. Sleep habits and sleep disturbance in elementary school-aged children. Journal of developmental and behavioral pediatrics. 2000; 21(1): 27-36.