Impact of a pediatric brain tumor: Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention

de Ruiter, M.A.

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Impact of a Pediatric Brain Tumor
Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention

Door Marieke A. Montgomery-de Ruiter

Op vrijdag 9 december om 10.00u in de Agnietenkapel, Oudezijds Voorburgwal 229-231 te Amsterdam

Aansluitend bent u van harte welkom op de receptie in Frenzi, Zwanenburgwal 232 te Amsterdam (5 minuten lopen)

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Impact of a pediatric brain tumor

Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention
COLOFON

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Impact of a pediatric brain tumor
Research into neurocognitive late effects and psychosocial consequences
and the evaluation of a potential intervention

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aan de Universiteit van Amsterdam
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prof. dr. ir. K.I.J. Maex
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in het openbaar te verdedigen in de Agnietenkapel
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Faculteit der Geneeskunde
Voor mijn ouders
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General Introduction
Chapter 1
CANCER DURING CHILDHOOD

In the Netherlands, approximately 550 children are diagnosed with cancer each year. Over the last decades, impressive advances have been made in medicine and one of the most striking advances has been in the treatment of pediatric cancer. Treatment often consists of a combination of surgery, chemotherapy, and/or, radiotherapy. In the first half of the previous century, children who were diagnosed with cancer usually died within weeks. In 1947, for the first time, doctors achieved partial remission in a four-year-old girl who was diagnosed with leukemia. This marks the first of many medical milestones improving early detection and better treatment, which have led the survival rates of pediatric cancer patients to rise from less than 10% in the 1940’s and 1950’s to almost 80% nowadays.

Nevertheless, despite the medical advances, pediatric cancer is still the most common cause of death by a disease in children.

PEDIATRIC BRAIN TUMORS

Brain tumors are the second most common type of cancer in children concerning almost 18% of new pediatric cancer diagnoses, after leukemia with 27% of the cases. In the Netherlands every year approximately 100 children are diagnosed with a brain tumor. There are many different types of brain tumors in childhood and the survival rates vary widely per tumor type. Mostly an infaust prognosis is for diffuse intrinsic pontine gliomas (DIPG), brainstem gliomas that are inoperable due to the location. The best survival is for pilocytic astrocytomas, a form of low-grade glioma (LGG), for which the survival rate is up to 95%. Increased survival comes at a cost. The tumor and its treatment inevitably damage healthy brain tissue. The treatment modalities are targeted to remove or destroy the tumor cells, but often healthy brain tissue and cells are unintentionally also affected. The brain damage from systemic treatment, e.g. chemotherapy and/or radiotherapy, typically white matter loss, can lead to a wide variety of late effects in pediatric brain tumor survivors (PBTS), among which neurocognitive late effects.

NEUROCOGNITIVE CONSEQUENCES OF A PEDIATRIC BRAIN TUMOR

Compared with survivors of other types of cancer, survivors of a brain tumor in childhood bear the greatest risk of neurocognitive impairment. Many PBTS suffer from a wide range of neurocognitive deficits, for example impaired intelligence, slower speed, and memory and attention deficits. Attention and intelligence have often been studied in PBTS. A
major consequence of impairments in attention or intelligence is the decline in ability to acquire new skills and information, which leads to an increasing gap in the development between patients and their unaffected peers. For this reason, metaanalytically studying the magnitude of impairments in neurocognitive functioning, especially attention and intelligence, in PBTS is an important topic.

Although neurocognitive functioning after brain tumor treatment has received intensive study, the available knowledge can be increased. In the past, studies have often focused on a limited array of neurocognitive functions, such as attention or speed, or have focused on a restricted subgroup of PBTS, such as patients with cerebellar tumors. Also, traditionally studies used paper and pencil tasks to measure neurocognitive functioning. Paper and pencil-based measures often unintentionally target multiple neurocognitive functions, while computerized tasks facilitate isolation of particular neurocognitive functions. Therefore Ullrich and Embry advocate the use of computerized measures, to study the neurocognitive functions in PBTS.

PREDICTORS OF NEUROCOGNITIVE CONSEQUENCES

In addition to studying the nature and magnitude of neurocognitive problems in PBTS, it is important to understand the risk factors that are associated with and/or predict these deficits, as that may help in the development of ways to prevent damage or alleviate the consequences. The neurocognitive deficits may also have an impact on educational results, vocational success and may compromise social competence and health related quality of life (HRQOL). In previous studies, multiple child characteristics and medical factors have been investigated as possible predictors of late neurocognitive outcomes. It has been reported that age, gender, and treatment factors are associated with neurocognitive outcomes. Especially cranial irradiation is a major risk factor that has been reported to lead to worse neurocognitive late effects. A younger brain appears to be more vulnerable to the adverse effects of the tumor and the treatment, thus children who are diagnosed earlier in life have on average poorer neurocognitive outcomes than children who are diagnosed later. Furthermore, female patients tend to be more vulnerable than their male counterparts. In addition, presence of a pre-operative hydrocephalus, particularly when it requires a shunt, has been associated with worse neurocognitive outcome.

Brain damage, especially white matter damage as a result of the tumor and the treatment, might be an underlying cause of the neurocognitive late effects. A model has been proposed, in which damage to the white matter causes processing speed deficits. These processing speed deficits in turn cascade into deficits in other neurocognitive functions,
intelligence, and academic achievement.\textsuperscript{17,21} Indeed, processing speed has found to be correlated with white matter integrity in PBTS.\textsuperscript{5,22} Also, in a study by Smith et al, processing speed mediated the association between white matter integrity and reading skills.\textsuperscript{23} The same research group reported a correlation between intellectual outcomes and white matter integrity.\textsuperscript{20} Especially the young brain is vulnerable to white matter damage after treatment for a brain tumor, as the white matter in young children is still immature. Damage to neural progenitor cells, for example, caused by cranial radiation therapy, may challenge healthy age-appropriate white matter growth.\textsuperscript{24} The development of interventions to prevent or alleviate the neurocognitive consequences and could greatly impact the lives of PBTS.

**PSYCHOSOCIAL CONSEQUENCES OF A PEDIATRIC BRAIN TUMOR**

Psychosocial functioning is understudied in PBTS, as compared to other types of cancer. This is largely due to the fact that children with a brain tumor are often excluded from studies on childhood cancer survivors, due to small numbers of patients and the heterogeneity of tumors, treatment, and outcomes.\textsuperscript{25} The neurocognitive consequences in PBTS may depress their psychosocial functioning, i.e. their HRQOL, social competence, self-esteem, and fatigue.

HRQOL comprises multiple aspects of subjective well being and functioning. In the past decades, several studies on HRQOL in PBTS have been conducted.\textsuperscript{26} Although, these studies have reported contradictory findings, with HRQOL either comparable to the general population,\textsuperscript{27} or worse HRQOL.\textsuperscript{28} For example, one study demonstrated PBTS being bullied, having problems with peers, and suffering from stressful and depressive feelings.\textsuperscript{28} A comprehensive review on social-competence found that PBTS reported deficits in this area.\textsuperscript{29} Also, according to another study, PBTS reported lower self-confidence and self-esteem compared to leukemia survivors.\textsuperscript{30} The brain tumor and the treatment frequently causes sleep deficits and decreased sleep quality in PBTS, which leads to fatigue which negatively influences daily functioning.\textsuperscript{31} Fatigue in PBTS may decrease psychosocial functioning.\textsuperscript{32,33} PBTS and their parents or teachers may differ in their view of psychosocial functioning of the PBTS, as it has been reported that proxy-report for chronically ill children often differs from self-report.\textsuperscript{34} Additional insight from different reference persons surrounding PBTS, such as parent-report and teacher-report on top of self-report, would reveal relevant information on the functioning of PBTS from different point of views and in different environments.

Overall, PBTS with neurocognitive deficits seem to be at increased risk for decreased psychosocial functioning.\textsuperscript{35} Therefore it is important to study psychosocial functioning in PBTS with neurocognitive complaints.
Chapter 1

SCREENING FOR NEUROCOGNITIVE LATE EFFECTS IN PBTS

It is important to screen PBTS for neurocognitive problems regularly, in order to enable timely referral to the appropriate professional when indicated. For this reason, neurocognitive functioning of PBTS should be assessed systematically, e.g. as suggested by Wash and colleagues. However, extensive assessments are time consuming and costly. Preferably, PBTS would be screened regularly with a brief questionnaire and only further assessed in case of screener indication.

Computerized tests and questionnaires that are designed to measure the same neurocognitive domain (e.g. attention) do differ. Computerized tests are highly structured and have the ability of measuring a specific function objectively, by using built-in control conditions that manipulate the level of difficulty for the domain of interest, while keeping other functions consistent. This leads to high experimental control and internal validity. On the other hand, questionnaires measure subjective functioning and may provide better ecological validity by assessing complex behavioral problems faced in daily life. It would be expected, however, that a computerized test and a questionnaire targeting the same neurocognitive domain show a relation.

PBTS have been reported to have impaired executive functioning. The Behavior Rating Inventory of Executive Function (BRIEF, Dutch version is a questionnaire that measures behavioral executive functioning. In PBTS it has been found that one of the BRIEF scales, the working memory scale, correlates to working memory tasks, implying that the BRIEF can potentially be employed as a screener for deficits after a brain tumor.

It would be interesting to study whether a questionnaire, the BRIEF, is correlated to tasks measuring different neurocognitive domains PBTS often show deficits, such as attention, cognitive flexibility, memory, and inhibition. Furthermore, we are interested to investigate the differences and relation between different respondents; by comparing the BRIEF parent-report to the BRIEF teacher-report. As mentioned above, different reporters see PBTS in different environments, which may lead to different views. Lastly we will explore the clinical utility of the BRIEF as a screening tool.

INTERVENTIONS FOR NEUROCOGNITIVE LATE EFFECTS IN PBTS

With the robust knowledge of the neurocognitive late effects of the tumor and the treatment in PBTS, interventions to improve the neurocognitive functioning in PBTS are warranted. However, to date there is a paucity of effective interventions. A few neurocognitive training programs have been developed and investigated, although the samples were small and the effectiveness modest. Butler and colleagues developed
a cognitive remediation program using techniques from brain injury rehabilitation, special education and clinical psychology. They performed a randomized controlled trial including 161 childhood cancer survivors with central nervous system involvement, aged 6-17 years. Caregivers reported improved attention and academic achievement, although the effect sizes were modest and were not found on neurocognitive functioning, which acted as primary outcome in the study. The researchers argued that the modest effects are comparable to other rehabilitation interventions for children with brain injuries.

In another study, Van ‘t Hooft et al. investigated the effects of a cognitive training program on neurocognitive function in patients with acquired brain injury, aged 9-16 years, including 14 brain tumor survivors. The training program consisted of memory and attention exercises, in combination with cognitive behavioral training. The training showed positive effects on memory and attention functioning until six months after the training, but not on processing speed.

A third study into an intervention for neurocognitive functioning of PBTS was conducted by Conklin et al. These researchers published a randomized controlled trial with PBTS and leukemia survivors (N=68, aged 8-16 years) on the effects of a computerized working memory training, CogMed. The results showed improvements directly after the intervention as compared to pre-intervention in visual working memory, but not in verbal working memory. Pharmacological interventions such as methylphenidate, have also been reported to be effective for neurocognitive deficits in PBTS. A drawback of pharmacotherapy, though, is the possibility of side effects, e.g. sleep disturbance, weight loss, anxiety, and sadness. Also, this medication does not lead to a sustained effect unless the patient continues the pharmacotherapy.

NEUROFEEDBACK

The limited current available intervention options for neurocognitive late effects in PBTS call for the search of alternatives. Neurofeedback (NF) training is a relatively new form of therapy, which has never been investigated in PBTS. NF training is an intervention based on the principles of operant conditioning. Direct feedback of the current brain activity is offered to the patient, in order to teach the patient to regulate his or her brain activity. Reinforcement may comprise seeing a movie or hearing music. The desired brain wave is determined by a quantified electro encephalogram (EEG), which is conducted prior to the training. The efficacy of NF training in patients with attention deficit hyperactivity disorder (ADHD) has been studied extensively and promising results have been reported in uncontrolled and controlled studies. The effects of NF training were found to be smaller in randomized controlled trials than in uncontrolled trials. At the start of our study, no
double blind randomized controlled study had been published yet. However, in recent years, three double-blind and one single-blind RCTs have been published on NF training in children with ADHD. These studies found improvements over time on ADHD symptoms in the NF-group; however, similar improvements were found in the placebo feedback (PF) group, potentially reflecting non-specific treatment effects.

Brain tumor survivors differ from ADHD patients, as they have structural brain damage caused by the tumor, hydrocephalus, surgery, radiotherapy and/or chemotherapy. An indication that NF training might be an effective intervention for PBTS derives from the results of studies into the effects of NF training in patients with traumatic brain injury. A review by Thornton and colleagues describes several studies with traumatic brain injury patients, reporting improved attention, cognitive flexibility, cognitive performance, and problem solving after NF training, but no control group was included in the studies reviewed. In our hospital, Aukema and colleagues conducted a pilot study into the feasibility of NF training on 9 nine brain tumor survivors and found that NF training was feasible in PBTS. All participants completed the training and would recommend it to others. Patients reported less fatigue after the training. Also processing speed improved in six out of nine patients. The results of the studies on NF training in children with ADHD and children with acquired brain injury that were published at the time our study started, as well as the results of the pilot study, identified the need for a randomized controlled trial (RCT) into the effects of NF training in PBTS.

AIMS OF THE THESIS

The focus of the present thesis is on the neurocognitive and psychosocial functioning of PBTS and investigating the efficacy of NF training to improve their functioning. Specifically, the aims of the current thesis were:

- To provide a systematic review of studies into intellectual and attention functioning of PBTS.
- To outline the neurocognitive functions that might be affected after treatment for a pediatric brain tumor, while potential predictors for neurocognitive functioning were also investigated.
- To assess the psychosocial functioning of the PBTS.
- To investigate the correlation between proxy-report questionnaires (parent and teacher) and tasks measuring neurocognitive functioning in PBTS.
- To investigate the effects of NF training on neurocognitive and psychosocial functioning in PBTS using a double-blind randomized placebo-controlled trial.
SAMPLE AND DESIGN

This thesis describes neurocognitive and psychosocial functioning of PBTS with subjective neurocognitive complaints, as well as the results of the first double-blind randomized placebo-controlled trial investigating the efficacy of NF training in PBTS (clinicaltrials.gov NCT00961922).

For this purpose, 249 PBTS were invited to participate. Participants were included if they were aged 8 to 18 years, treated for a brain tumor in the Netherlands >2 years prior to enrolment, as neurocognitive deficits often appear or increase over time. Lastly we included PBTS who suffered from neurocognitive complaints, in order to study the nature of deficits in these PBTS. Siblings of participants in the age range 8-18 were invited to participate as a control group to study the nature of the deficits.

OUTLINE OF THE THESIS

Firstly, we conducted a meta-analysis (Chapter 2) to establish the magnitude of the neurocognitive problems in PBTS. We searched for studies on intelligence and attention functioning of PBTS, as these are areas that PBTS have often been reported to have problems. Furthermore, exploratory analyses investigated the possible impact of medical risk factors on general intelligence.

The problems that are reportedly experienced by PBTS require an intervention to improve neurocognitive functioning. In Chapter 3 we describe the design of the PRISMA study, a double-blind randomized placebo-controlled trial to investigate the efficacy of NF training in PBTS with neurocognitive complaints. In Chapter 4 the neurocognitive functioning of the participating PBTS at enrollment in the study is compared to the functioning of a sibling control group. In Chapter 5 the baseline psychosocial functioning of the participants of PRISMA is presented, as compared to normative data. Chapter 6 describes the relationship between tasks and questionnaire measures of executive functions in PBTS. Finally, the results of the randomized controlled trial are presented in Chapter 7. The neurocognitive and psychosocial functioning of PBTS in the NF group was compared to the functioning of the PF group. The last chapter of this thesis, Chapter 8, is the summary and general discussion of the results of the studies described in this thesis.
REFERENCES


General introduction


General introduction


Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis

Marieke A. de Ruiter
Rosa van Mourik
Antoinette Y.N. Schouten-van Meeteren
Martha A. Grootenhuis
Jaap Oosterlaan

Developmental Medicine & Child Neurology 2013, 55(5), 408-417
ABSTRACT

Aims: This meta-analysis provides a systematic review of studies into intellectual and attentional functioning of paediatric brain tumour survivors (PBTS) as assessed by two widely used measures: the Wechsler Intelligence Scale for Children (3rd edition; WISC-III) and the Conners’ Continuous Performance Test (CPT).

Methods: Studies were located that reported on performance of PBTS (age range 6–16y). Meta-analytic effect sizes were calculated for Full-scale IQ, Performance IQ, and Verbal IQ as measured by the WISC-III, and mean hit reaction time, errors of omission, and errors of commission as measured by the CPT. Exploratory analyses investigated the possible impacts of treatment mode, tumour location, age at diagnosis, and time since diagnosis on intelligence.

Results: Twenty-nine studies were included: 22 reported on the WISC-III in 710 PBTS and seven on CPT results in 372 PBTS. PBTS performed below average ($p_s<0.001$) on Full-scale IQ (Cohen’s $d=-0.79$), Performance IQ ($d=-0.90$), and Verbal IQ ($d=-0.54$). PBTS committed more errors of omission than the norm ($d=0.82$, $p<0.001$); no differences were found for mean hit reaction time and errors of commission. Cranial radiotherapy, chemotherapy, and longer time since diagnosis were associated with lower WISC-III scores ($p_s<0.05$).

Conclusions: PBTS have seriously impaired intellectual functioning and attentiveness. Being treated with cranial radiotherapy and/or chemotherapy as well as longer time since diagnosis leads to worse intellectual functioning.
INTRODUCTION

In the USA the incidence of cancer in children aged 0 to 14 years is almost three per 100 000.1 Approximately 17 to 22.5% of children with cancer have a brain tumour.1,2 Advances in medicine have led to an increasing number of children surviving cancer. The 5-year survival rate of children diagnosed with a brain tumour under the age of 15 increased from 57% for patients diagnosed from 1975 to 1977 to 74% for patients diagnosed from 1996 to 2004.3

With more children becoming long-term survivors, the need has grown to understand fully the nature and magnitude of the late effects of the tumour and treatment. Compared with survivors of other malignancies, survivors of brain tumours in childhood bear the greatest risk of neurocognitive impairment.4 Numerous studies have shown that 40 to 100% of paediatric brain tumour survivors (PBTS) show some form of neurocognitive deficit.5 Frequently reported impairments in PBTS are declining levels of general intelligence and attention deficits. Deficits in these areas can have a deleterious effect on academic achievement and psychosocial functioning.6–8

Besides the burden of the tumour itself, the treatment can contribute to neurocognitive impairments. Radiotherapy is especially considered to have an impact on neurocognitive functioning.9,10 Chemotherapy, however, has also been found to be associated with poor outcomes in PBTS.11 In addition to the treatment, tumour location can affect the neurocognitive outcome of PBTS, with infratentorial tumours being associated with worse outcomes than supratentorial tumours.12 Furthermore, age at diagnosis is known to have an impact on neurocognitive outcome.13 The young brain is especially vulnerable to the adverse effects of treatment because of the rapid cell proliferation, dendritic and axonal outgrowth, as well as myelination, which take place during infancy, childhood, and adolescence. Therefore, radiotherapy is postponed or omitted in most protocols if the child is under the age of 3 years.11 In addition, time since treatment is an important determinant of neurocognitive deficits, as the deficits often increase over time, owing to a slower rate of acquiring new skills and knowledge compared with healthy peers.13,14

The current paper reports the results of a quantitative meta-analysis, investigating the magnitude and consistency of neurocognitive deficits in PBTS. Analysis of the literature determined general intelligence and attention as two frequently studied areas of neurocognitive functioning. General intelligence provides insight into the generic cognitive functioning of the patient and is measured most often using the Wechsler Intelligence Scale for Children (3rd edition; WISC-III).15 Attention is required to some extent for nearly all components of neurocognitive functioning and is therefore a crucial area to study thoroughly. The Conners’ Continuous Performance Test (CPT, CPT II) is the most widely used measure for attention.16,17 Besides intelligence and attention, processing speed and working memory
are often studied in PBTS. These areas are important in understanding the neurocognitive functioning of a patient; they are, however, beyond the scope of this meta-analysis, which focuses on the two key areas: intelligence and attention. The CPT comprises a measure for processing speed; therefore, this area is reported as well. Additionally, exploratory analyses investigated the possible impact of cranial radiotherapy, chemotherapy, tumour location, age at diagnosis, and time since diagnosis on general intelligence.

METHOD

Selection of studies
Studies were searched using the PubMed, Web of Science, and Embase computerized databases. Relevant studies were located by combining the search terms: neurocogniti*, neuropsych*, cogniti*, child*, pediatric*, tumor, tumour, cancer, neoplasm*, central nervous system, and brain.

All retrieved studies were reviewed to include studies meeting the following criteria: (1) the participants included children treated for a brain tumour by neurosurgery, radiotherapy, and/or chemotherapy; (2) intelligence was assessed using the full WISC-III (as abbreviated versions might yield unreliable data) and/or attention was assessed using the CPT; (3) mean age of PBTS at assessment was between 6 years and 16 years, corresponding to the age range covered by the WISC-III; (4) the study was published in a peer-reviewed English language journal; and (5) the study was published before November 2011. The last search was performed on 25 November 2011. The reference lists of included studies were explored to locate additional potentially relevant studies for inclusion in the meta-analysis. No research protocol of the present meta-analysis exists.

Dependent variables
The WISC-III is the most widely used intelligence test for children aged 6 to 16 years. Dependent measures include Full-scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ), on which normative samples obtain a mean score of 100 with a standard deviation (SD) of 15. VIQ is a measure of the ability to use and understand language. PIQ assesses perceptual reasoning. FSIQ is calculated by averaging VIQ and PIQ. Higher scores indicate better intellectual functioning. WISC-IV studies were not included because the WISC-IV does not allow calculation of VIQ and PIQ scores, and only few PBTS studies reported WISC-IV scores.18,19

The CPT is a widely used test to assess attention. In the CPT, a sequence of different letters is shown, one at a time, and the participant is instructed to press the space bar as quickly as possible without committing errors when any letter other than ‘X’ appears on the screen.
Each letter is displayed for 250 ms, with different time intervals between each letter. Main dependent variables are (1) mean hit reaction time (MHRT), measuring processing speed, (2) errors of omission, measuring inattentiveness, and (3) errors of commission, measuring impulsivity. Scores are reported in T scores, with a mean of 50 and an SD of 10. For all CPT variables, higher scores indicate worse performance.

Quality assessment
Two authors (MAAdR and RvM) independently assessed the quality of the included studies using the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale assesses quality in terms of the selection of children (four criteria), comparability of study groups if applicable (one criterion), and outcome assessment (three criteria). Differences in assessment between both authors were resolved by consensus. Some criteria were not applicable to all studies; therefore we used the percentage of the applicable criteria each study met as a score.

Statistical analyses
The computer programs Comprehensive Meta-Analysis 2.2 and SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) were used for statistical analyses. Techniques by Hozo et al. were used to convert medians into means and SDs if necessary. Where studies compared two or more subgroups of PBTS, the data were aggregated into one mean and SD per study. For each of the dependent measures, effect sizes were calculated for each study separately. Effect sizes were calculated in terms of Cohen’s d, with sizes of 0.20, 0.50, and 0.80 translating into small, medium, and large effects respectively. Only one study used a comparison group of healthy participants; all other studies used normative data to interpret data derived from PBTS. For comparability, normative data were used to calculate effect sizes for all studies. For each dependent variable, an overall effect size was calculated by weighting all the effect sizes according to the sample sizes. To test whether the variability in effect sizes exceeded what could be expected from sampling error alone, Q and I² tests of heterogeneity were conducted. That is, when homogeneously distributed, an identical underlying effect size is representative for all studies and so-called fixed effects analysis can be used for estimating the assumed common effect. If the effect sizes are heterogeneously distributed, a random effects analysis estimates the mean of distribution of effects across all studies, which yields wider confidence intervals for the combined effect size.

A major concern in conducting a meta-analysis is the presence of publication bias, meaning that studies reporting non-significant results are less likely to be published, leading to erroneous inflation of meta-analytic effect sizes. The possibility of publication bias was reduced by including unpublished data. Furthermore, the possibility of publication bias was studied using two methods. First, we calculated Rosenthal’s fail-safe N, which calculates the necessary number of studies to nullify the overall effect, for each significant combined
effect size. Second, the correlation between sample sizes (the number of PBTS) and effect sizes was calculated for each dependent variable. A significant negative correlation between sample sizes and effect sizes would indicate a tendency that significant results in small samples are easier to publish than non-significant results in small samples.

We studied the possible moderating effects of the following variables on the study specific effect sizes for the dependent variables of the WISC-III: (1) cranial radiotherapy as measured by the percentage of patients treated with cranial radiotherapy (% cRT); (2) chemotherapy as measured by the percentage of patients treated with chemotherapy (% chemo); (3) tumour location as measured by the percentage of patients treated for infratentorial brain tumour (% infra); (4) age at diagnosis (age at dx); and (5) time since diagnosis (time since dx). The effects were analysed using Comprehensive Meta-Analysis by meta-regression analyses, assessing the relationship between the moderating variables and the effect sizes on the dependent variables. For each moderating variable we calculated the proportion of variance accounted for, with 1%, 9%, and 25% being interpreted as small, moderate, and large effects respectively. These analyses were not conducted on the CPT, because of the limited number of studies available. Alpha was set at 0.05 in all analyses.

RESULTS

Figure 1 shows the selection of studies in a flowchart. Twenty-nine studies met inclusion criteria. Twenty-two studies reported scores on the WISC-III for a total of 710 PBTS. Seven studies reported CPT results for a total of 372 PBTS. When two or more studies reported on the same participants, we included the most recently published study to prevent erroneously inflated homogeneity of meta-analytic results. Grill et al. and Kieffer-Renaux et al. report partly on the same participants. The most recent publication by Grill et al. reports on PIQ and VIQ, but does not report on FSIQ. The earlier publication of Kieffer-Renaux et al., however, does report on FSIQ. Therefore, the study by Grill et al. was included in the meta-analysis of PIQ and VIQ, whereas the study by Kieffer-Renaux et al. was included in the meta-analysis of FSIQ.

For five of the 22 WISC-III studies we aggregated data on two or more PBTS subgroups into one mean and SD per study: (1) Patel et al. compared PBTS according to their tumour location; (2) Callu et al. compared patients with low-grade gliomas and malignant cerebellar tumours; (3) Lacaze et al. studied three samples of patients with optic pathway tumours who received three different treatments; (4) Kieffer-Renaux et al. compared patients with medulloblastoma who received two different doses of radiotherapy; and (5) Mulhern et al. compared patients with medulloblastoma with those having low-grade glioma.
Figure 1. Flow chart of study selection n, number of studies; PBTS, paediatric brain tumour survivors; WISC, Wechsler Intelligence Scale for Children; CPT, Conners’ Continuous Performance Test.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants and diagnosis</th>
<th>Treatment</th>
<th>Location</th>
<th>Time/age</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazin et al.49</td>
<td>13 LGG, 7 MB</td>
<td>35% cRT</td>
<td>35% Chemo</td>
<td>100%</td>
<td>8.3</td>
</tr>
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### Neurocognitive Consequences of a Brain Tumor

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<td>% Chemo</td>
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Ages are in years. *Calculated by subtracting age at assessment and age at diagnosis.* bStereotactic radiotherapy. BTNS, brain tumour not specified; % cRT, percentage of patients treated with cranial radiation therapy; % Chemo, percentage of patients treated with chemotherapy; % Infra, percentage of patients with an infratentorial tumour; dx, diagnosis; NOS, Newcastle-Ottawa Scale, in percentages of applicable criteria that were met; WISC-III, Wechsler Intelligence Scale for Children (3rd edition). LGG, low-grade glioma; MB, medulloblastoma; BT, mixed diagnosis group; NA, not available; HGG, high-grade glioma; GNS, glioma not specified; PF, posterior fossa tumour; EP, ependymoma; GCT, germ cell tumour; CPT, Conners’ Continuous Performance Test.
Table I displays details of the studies incorporated in this meta-analysis. Some studies reported insufficient details to allow calculation of effect sizes. In these cases, authors were contacted to provide the missing data.\textsuperscript{32–34,50,51} For some studies, data were unavailable on one or more of the dependent variables, leading to unequal numbers of studies for these dependent variables.

Figures 2 and 3 display the studies’ effect sizes as well as the overall effect sizes for each of the dependent variables and the accompanying 95% confidence intervals. Effect sizes of all dependent variables were heterogeneously distributed and a random effect analysis was used in all analyses. There was no significant association between the study quality ratings and effect sizes (all $p > 0.08$) for any of the dependent variables.

**Wechsler Intelligence Scale for Children-III**

PBTS had lower FSIQ scores than their peers, as indicated by a combined random effect size of $d=-0.79$ ($p<0.001$), translating into a large effect. Of the 21 studies that reported on FSIQ, 14 reported scores significantly ($p<0.05$) below the average FSIQ of 100,\textsuperscript{9,12,26,34,36–41,45–48} whereas none of the studies reported scores significantly higher than average.

PIQ scores were significantly lower in PBTS than in the normative sample, as indicated by a combined random effect size of $d=-0.90$ ($p<0.001$), again translating into a large effect. Fifteen of the 19 studies found PIQ scores of PBTS significantly ($p<0.05$) below average,\textsuperscript{9,12,24,26,34,36–40,43,44,47–49} whereas in none of the studies were scores significantly higher than average found.

VIQ scores of PBTS were significantly below average. The combined random effect size was $d=-0.54$ ($p<0.001$), which represents a medium effect size. Eleven of the 19 studies reported scores that were significantly ($p<0.05$) below the mean.\textsuperscript{9,12,23,34,36–38,40,44,47,48} Eight studies reported VIQ scores that did not differ significantly from the mean of the normative sample.\textsuperscript{24–26,29,39,42,43} The combined effect size for PIQ was significantly higher than the combined effect size for VIQ ($d=-0.29$, $p<0.001$), indicating greater impairments in PIQ than in VIQ.

There was no evidence for publication bias for any of the WISC-III measures, as we found high fail-safe N values and non-significant (ns) positive correlations between sample size and effect size (FSIQ: fail-safe N=871, $r=0.36$, ns; PIQ: fail-safe N=1030, $r=0.16$, ns; and VIQ: fail-safe N=406, $r=0.25$, ns).
### Variable Study $d$ p-Value

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**Figure 2.** Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) study results. CI, confidence interval; FSIQ, Full-scale IQ; PIQ, Performance IQ; VIQ, Verbal IQ.
### Figure 3. Conners’ Continuous Performance Test (CPT) study results.

Higher scores indicate worse performance for all three dependent variables. CI, confidence interval; EC, errors of commission; EO, errors of omission; MHRT, mean hit reaction time.

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<td>0.97</td>
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<td></td>
<td>Mabbott et al. 2008</td>
<td>-0.19</td>
<td>0.28</td>
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<td></td>
<td>Conklin et al. 2007</td>
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<td></td>
<td>Stargatt et al. 2007</td>
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<td></td>
<td>Reeves et al. 2006</td>
<td>-0.50</td>
<td>0.03</td>
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<td></td>
<td>Mulhern et al. 2004</td>
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<td>0.78</td>
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Conners’ Continuous Performance Test

The studies were ambiguous about the scores of PBTS on MHRT of the CPT. Three of seven studies found significantly slower MHRT,\textsuperscript{51,53,54} whereas two studies found responses of the PBTS to be significantly faster than average.\textsuperscript{32,33} Two other studies found PBTS scores in the average range.\textsuperscript{50,52} Across studies a non-significant combined random effect size of $d=0.15$ was found for MHRT.

The number of errors of omission on the CPT committed by PBTS was higher than the normative sample, as indicated by a combined random effect size of $d=0.82$ ($p<0.001$), which is considered to be a large effect. All but one study found significantly higher errors of omission rates in PBTS than the normative sample.\textsuperscript{32,33,51–53} Fail-safe $N$ was 64 and there was a positive non-significant correlation between sample sizes and effect sizes ($r=0.85$), together indicating that there was no evidence for publication bias.

PBTS did not differ from the normative sample on the number of errors of commission, as indicated by a non-significant combined random effect size of $d=0.03$. Five of seven studies found no performance differences between PBTS and the normative sample;\textsuperscript{32,33,50,51,54} one study reported PBTS to make fewer errors of commission than the normative sample,\textsuperscript{52} and another study found that more errors were made by the PBTS than the normative sample.\textsuperscript{53}
Exploratory analyses

Table II reports the results for the meta-regression analysis for the five moderating variables. Cranial radiotherapy was a strong predictor of lower intellectual functioning, accounting for 26%, 32%, and 19% of the variance in FSIQ, PIQ, and VIQ respectively, with cranial radiotherapy leading to lower scores as opposed to no cranial radiotherapy. Chemotherapy accounted for 22% of the variance in FSIQ and 29% of the variance in PIQ scores, with chemotherapy leading to lower scores as opposed to no chemotherapy. There was no association between chemotherapy and VIQ. Furthermore, we found no predictive value of tumour location or age at diagnosis for intelligence scores. Longer time since diagnosis, however, was highly predictive of lower scores on all WISC-III scales, accounting for large proportions of the variance (FSIQ 41%; PIQ 44%; VIQ 25%). As expected, there was a strong association between cranial radiotherapy and chemotherapy ($r=0.54$, $p<0.05$), and between age at diagnosis and time since diagnosis ($r=-0.66$, $p<0.05$), not allowing us to distinguish between the effects of these moderating variables.

Table II. Meta-regression analyses, Wechsler Intelligence Scale for Children (3rd edition) studies

<table>
<thead>
<tr>
<th></th>
<th>FSIQ</th>
<th>PIQ</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>β</td>
<td>R2</td>
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<td>Treatment module</td>
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<td></td>
<td></td>
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<tr>
<td>cRT</td>
<td>21</td>
<td>-0.51</td>
<td>0.26</td>
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<tr>
<td>Chemo</td>
<td>18</td>
<td>-0.47</td>
<td>0.22</td>
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<tr>
<td>Tumour location</td>
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<tr>
<td>Infra</td>
<td>19</td>
<td>-0.12</td>
<td>0.01</td>
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<tr>
<td>Age at diagnosis</td>
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<tr>
<td>Time since diagnosis</td>
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<td>-0.64</td>
<td>0.41</td>
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</table>

FSIQ, Full-scale IQ; PIQ, Performance IQ; VIQ, Verbal IQ; n, number of studies; β, standardized Beta coefficient; R2, R squared; cRT, cranial radiation therapy; Chemo, chemotherapy; Infra, infratentorial tumour.

DISCUSSION

This meta-analysis summarized neurocognitive functioning of 710 (WISC-III) and 372 (CPT, CPT II) PBTS. We found substantial impairments in intellectual functioning and attentional abilities. PBTS scored on average $-0.54SD$ to $-0.90SD$ lower on the WISC-III scales than the normative sample, with PIQ scores being even more depressed than VIQ scores. The number of PBTS in this meta-analysis that were at grade level and succeeding academically is unknown. However, a large body of research has demonstrated that intellectual functioning, as assessed with intelligence tests, is a powerful predictor of academic achievement and
vocational success. In PBTS this association was substantiated by Reddick et al., who found a positive relation between intelligence scores of PBTS, as measured with the Wechsler intelligence scales, and academic achievement, as measured with the abbreviated Wechsler Individual Achievement Test. Moreover de Boer et al. report academic failure and lower intelligence to be risk factors for decreased employment rates in PBTS, with PBTS being nearly five times more likely to be unemployed than healthy peers.

This meta-analysis found performance intelligence to be more vulnerable to the detrimental effects of a brain tumour and its associated treatment than verbal intelligence, with the observed PIQ scores in this meta-analysis being on average ~0.29SD lower than the VIQ scores. Similar findings have been reported in other populations at risk for brain damage, including children born very preterm and those with traumatic brain injury. The discrepancy between PIQ and VIQ findings in PBTS might be related to the high rate of cerebellar tumours in this group, as half of the paediatric brain tumours are located within the posterior fossa. PIQ subtests are of a multi-component nature and draw more heavily on motor functions, visuomotor integration, visual attention, abstract reasoning, and working memory than the VIQ subtests. Information about how many PBTS were excluded from the analyses because of a persistent motor or sensory disability was lacking. However, it is well known that many of these neurocognitive functions depend heavily on cerebellar functioning. Therefore damage to the cerebellum is expected to be related to depressed PIQ scores. Secondly, lower PIQ than VIQ scores may be related to a general slowing in information processing resulting from white matter damage. Compared with VIQ subtests, many PIQ subtests draw heavily on processing speed owing to their timed character. Although grey matter development peaks during childhood, white matter continues to develop gradually until early adulthood. The maturation of white matter is therefore challenged in PBTS because cancer therapy damages the healthy cells of the central nervous system. Glial progenitor cells are especially vulnerable to the effects of chemotherapy and radiotherapy. These cells are responsible for the formation of oligodendrocytes and astrocytes, both myelinating cells that are crucial for white matter integrity. White matter integrity plays a major role in information processing speed with decreased white matter integrity, resulting in slower processing speed.

In the present meta-analysis, severe attentional problems in PBTS were revealed, as indicated by the high mean number of errors of omission committed by PBTS on the CPT compared with the normative sample. In addition to the errors of omission of the CPT, attention problems in PBTS have been reported using other measures of attention. PBTS perform below the norm on the Freedom of Distractibility Index, the attentional factor of the WISC-III. Also, measuring attention using the Gordon Diagnostic System, PBTS scores on focused attention have been reported to be almost 1SD below the mean of the normative sample.
and more than 1SD below the mean on selective attention.\textsuperscript{66} Other researchers have used the Conners’ Rating Scale for Parents and Teachers to identify attention deficits in PBTS; they found more than half of the patients obtained scores above the 75th centile, indicating attentional difficulties.\textsuperscript{67} Attentional abilities develop early in life and form the basis for other emerging and proliferating neurocognitive functions.\textsuperscript{59} As a result, attentional abilities are an important prerequisite for scholastic development and are strongly associated with academic achievement.\textsuperscript{59} Reddick et al.\textsuperscript{57} found worse attentional functioning in PBTS, measured with the CPT, to be associated with lower academic achievement scores, as measured with the abbreviated Wechsler Individual Achievement Test.

Interestingly, this meta-analysis found no evidence for slow processing speed in PBTS as measured with MHRT on the CPT. Individual studies revealed conflicting findings, with some researchers reporting worse performance of PBTS than the normative sample and others reporting no difference or even better performance by PBTS. Our failure to find evidence for slowed information processing as measured by the MHRT on the CPT does not fit with the frequently observed impairments in white matter integrity in PBTS. Such impairments are expected to result in slower processing speed.\textsuperscript{65} Perhaps MHRT is a limited measure for processing speed. It is possible that slowed information processing becomes evident only in tasks that place demands on the integration of multiple stimulus modalities and involve more complex mental operations, which would engage widespread neural networks in the brain. Speed on such complex tasks, for example the performance subtests of the WISC-III, draw more heavily on white matter integrity than simple stimulus response tasks such as the CPT. Indeed, several researchers have reported decreased scores of PBTS on the processing measures obtained with more complex tasks such as the speed index of the Wechsler Scale and the Trail Making Task.\textsuperscript{12,29,38}

Inhibitory control seems to be spared in PBTS, as the number of errors of commission on the CPT was in the average range. This result converges with results of earlier studies into inhibitory control, which failed to find evidence for inhibitory problems.\textsuperscript{58,69} The absence of an effect on inhibitory control may be explained in terms of tumour location. Inhibition of responses is primarily mediated by the prefrontal cortex, and paediatric brain tumours in the frontal lobe are rare.\textsuperscript{59,70} On the other hand, there are a multitude of connections between the cerebellum and the frontal lobes, which can be damaged by local radiotherapy, so causing inhibitory problems.\textsuperscript{61} Also, frontal lobes are irradiated in craniospinal radiotherapy, for example for medulloblastomas. Indeed Aukema et al.\textsuperscript{29} found vulnerability of the white matter in the frontal lobes in survivors of medulloblastoma, which was associated with slower processing speed. The fact that we did not find inhibitory control problems might also be caused by the relatively slow development of the prefrontal cortex at the ages the patients were tested.\textsuperscript{59}
As described above, cancer treatment inevitably causes cell damage, challenging the normal maturation and myelination of the neural pathways in the young brain, and consequently challenging the development of cognitive, motor, behavioural, and emotional functioning. In our exploratory analyses we found that cranial radiotherapy and chemotherapy are indeed strong predictors of worse intellectual functioning. In our analyses it was impossible to make the distinction between different doses and volumes of radiotherapy, but it is known from the literature that higher doses and larger volumes are associated with worse neurocognitive outcomes. The combination of radiotherapy and chemotherapy in adults is believed to play an important role in neurocognitive deficits, owing to the induced damage to neural progenitor cells for hippocampal neurogenesis and the maintenance of subcortical white matter integrity. Moreover, we found that longer time since diagnosis is highly associated with worse intellectual outcomes. This finding is probably explained in terms of the neurocognitive problems such as reduced attentiveness, slower processing speed, and memory problems exhibited by PBTS that challenge the learning process, causing an increasing gap between PBTS and their peers in intellectual functioning. No effect was found for tumour location on intellectual functioning. Although the adverse effects of the tumour and its treatment are considered detrimental for the developing brain, interestingly no relationship was found between mean age at diagnosis and WISC-III scores of PBTS. Longer follow-ups might reveal effects of age at diagnosis.

This meta-analysis has some limitations that need to be taken into account. A limited number of studies were available for this meta-analysis. Also, the available studies did not allow a distinction to be made between the different brain tumour diagnoses, tumour locations, and treatment intensities. This may have contributed to heterogeneity in the study findings. For the quality analysis, we used the most relevant quality rating that we found. Nevertheless, not all criteria were applicable to the included studies, which potentially decreased the reliability of the quality ratings. Furthermore, it has been reported in the literature that there is an effect of sex in outcome, to the disadvantage of female children. However, owing to lack of variability in proportions of male and female children in the included studies, it was not possible to include sex in the analyses. It would have been interesting to compare scores of patients on the WISC-III and the CPT; unfortunately none of the included studies reported on both a full WISC-III and the CPT. In addition, with one single exception, the included studies used an uncontrolled study design or compared PBTS with other patient groups. Also, working memory and other important cognitive areas have not been addressed in this meta-analysis, despite their interdependence with intelligence, attention, and processing speed. Even though the WISC-III and the CPT are well-validated tests and normative data are available, the use of a healthy comparison group, matched on demographic background characteristics, would have been preferable.
CONCLUSIONS

This meta-analysis highlights the negative neurocognitive sequelae of paediatric brain tumours and their treatment in terms of intellectual functioning and attentiveness. Moreover, longer time since diagnosis was found to be associated with worse intellectual functioning. Poor intellectual functioning and inattentiveness might underlie the negative outcomes of PBTS in terms of academic achievement, vocational success, and general adaptive functioning. The field is in urgent need of developing effective screening and treatments for these negative neurocognitive sequelae of PBTS.
REFERENCES


Neurocognitive consequences of a brain tumor

Neurofeedback to improve neurocognitive functioning of children treated for a brain tumor: design of a randomized controlled double-blind trial

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ABSTRACT

Background: Neurotoxicity caused by treatment for a brain tumor is a major cause of neurocognitive decline in survivors. Studies have shown that neurofeedback may enhance neurocognitive functioning. This paper describes the protocol of the PRISMA study, a randomized controlled trial to investigate the efficacy of neurofeedback to improve neurocognitive functioning in children treated for a brain tumor.

Methods/design: Efficacy of neurofeedback will be compared to placebo training in a randomized controlled double-blind trial. A total of 70 brain tumor survivors in the age range of 8 to 18 years will be recruited. Inclusion also requires caregiver-reported neurocognitive problems and being off treatment for more than two years. A group of 35 healthy siblings will be included as the control group. On the basis of a qEEG patients will be assigned to one of three treatment protocols. Thereafter patients will be randomized to receive either neurofeedback training (n=35) or placebo training (n=35). Neurocognitive tests, and questionnaires administered to the patient, caregivers, and teacher, will be used to evaluate pre- and post-intervention functioning, as well as at 6-month follow-up. Siblings will be administered the same tests and questionnaires once.

Discussion: If neurofeedback proves to be effective for pediatric brain tumor survivors, this can be a valuable addition to the scarce interventions available to improve neurocognitive and psychosocial functioning.

Trial registration: ClinicalTrials.gov NCT00961922
BACKGROUND

As a result of improved treatment, the survival rate of children diagnosed with a brain tumor has increased considerably. As a consequence, neurocognitive long-term effects of the tumor and the treatment are reported more often, including deficits in attention, processing speed, and memory. Radiotherapy, chemotherapy, tumor location, and longer time since diagnosis are related to worse neurocognitive functioning. A major consequence of these impairments is the decline in ability to acquire new skills and information, which leads to an increasing gap in the development between patients and their peers. This, in turn, has its impact on educational results, vocational success and may compromise social competence and quality of life.

Butler and Mulhern have emphasized that interventions should be developed to improve neurocognitive functioning and subsequently improve future perspectives of these children. Interventions that are considered relevant for survivors with cancer-related brain injury are cognitive remediation and pharmacotherapy. A cognitive remediation program, using techniques from three disciplines: brain injury rehabilitation, special education and clinical psychology, has been developed and tested by Butler and colleagues. Participants in the randomized controlled trial were 161 survivors of a childhood cancer, whose malignancy and/or treatment involved the central nervous system. The results showed improvements in caregiver reported attention and academic achievement, although the effect sizes were modest. Van 't Hooft et al. have investigated the effects of a cognitive training program on neurocognitive function with a randomized controlled trial, enrolling 38 patients with acquired brain injury, including 14 brain tumor survivors. The training program consisted of memory and attention exercises, in combination with cognitive behavioral training. The children in the treatment group showed sustained positive effects on memory and attention functioning until six months after the training, but not on processing speed.

Regarding pharmacotherapy, it has been suggested that survivors of childhood cancer may benefit from stimulant medication as used in the treatment of attention deficit hyperactivity disorder (ADHD). Attention deficits in survivors of brain tumors are likely to improve by methylphenidate. Mulhern and colleagues found improvements of attention in 37 long term survivors of a malignant brain tumor after methylphenidate. In a randomized placebo-controlled double-blinded trial including 32 survivors of a brain tumor (n=25) or acute lymphoblastic leukemia (n=7), Thompson et al. found that methylphenidate led to improved sustained attention. A drawback of pharmacotherapy is the possibility of side effects, e.g. sleep disturbance, weight loss, anxiety, and sadness. Also, this medication does not lead to a sustained effect unless the patient continues the pharmacotherapy.

The limited current available options warrant the search for alternatives. Neurofeedback is a relatively new form of therapy, which has never been investigated in pediatric brain tumor
survivors. Neurofeedback is a behavioral intervention that is based on the principles of operant conditioning. During the therapy the patient is presented with real-time feedback on his or her brainwaves, as measured by one or more electrodes on the scalp. The patient is reinforced when the brain produces a certain desired wave. Reinforcement may comprise seeing a movie or hearing music. The desired brain wave is determined by a quantified electro encephalogram (qEEG), which is conducted prior to the training.

The effects of neurofeedback have been discovered serendipitously by Sterman, when cats having received feedback of 12–15 Hz on the motor cortex showed to be less susceptible to epileptic seizures.14 There is a large body of scientific research documenting the effectiveness of neurofeedback for the treatment of diverse pathological conditions as summarized in comprehensive reviews, including ADHD, traumatic brain injury and schizophrenia.15–19 Strehl et al. showed that children with ADHD were able to learn to regulate their brain activity by neurofeedback.20 After training, significant improvements in behavior, attention, and IQ scores were found. All changes proved to be stable at six months follow-up after the end of training. Hodgson et al. conclude in their meta-analysis on nonpharmacological interventions for ADHD that neurofeedback resulted in significant improvements of DSM-IV symptoms of ADHD, neurocognitive functioning and behavior.18 In a comparative study researchers found that the positive effects of neurofeedback for children with ADHD were superior to a computerized attention training at six months follow up.21 However, to date there is a lack of published studies that employ a randomized placebo-controlled double-blind design when investigating neurofeedback.22

Brain tumor survivors differ from ADHD patients, as they have structural brain damage caused by the tumor, surgery, radiotherapy and/or chemotherapy. An indication that neurofeedback might be effective in pediatric brain tumor survivors may be derived from the results of studies into the effects of neurofeedback in patients with traumatic brain injury. A review of Thornton and colleagues describes a total of 44 studies (12 RCT, 16 comparative, 16 correlation) with traumatic brain injury patients reporting improved attention, cognitive flexibility, cognitive performance, and problem solving after neurofeedback, providing strong initial support for the idea that neurofeedback could be used in patients with structural brain damage. Subsequently, Aukema and colleagues conducted a pilot study into the feasibility of neurofeedback on 9 brain tumor survivors in our hospital.24 This study demonstrated that it was feasible to use neurofeedback with brain tumor survivors. All participants completed the training and were positive about the training they received, as they would recommend it to others. Patients reported decreased subjective fatigue after the training. Also the test results showed that processing speed improved in 6 out of 9 patients. These findings warranted the set up of a larger study into the effectiveness of neurofeedback for pediatric brain tumor survivors.
The current paper describes the protocol of the PRISMA study (pediatric research on improving speed, memory, and attention); a randomized controlled double-blind trial, approved by the medical ethical committee of the Academic Medical Centre in Amsterdam. The primary aim of the PRISMA study is to investigate the efficacy of neurofeedback for improving neurocognitive functioning after treatment for a pediatric brain tumor. Secondary, we hypothesize that subsequent to the expected neurocognitive changes achieved with neurofeedback, children will experience improved psychosocial functioning. Neurocognitive functioning will be investigated by tests administered to the patient. Psychosocial functioning will be measured using patient-reported as well as caregiver and teacher reported questionnaires. Assessments will take place pre and post training, as well as six months post training, in order to examine the long-term effects of the training. Comparing the effects of neurofeedback to placebo feedback will assess efficacy of neurofeedback. Pre training results obtained with the brain tumor survivors will be compared to a control group of healthy siblings, to assess the level of dysfunction on the measures used in this study.

METHODS

Study design
This study is a randomized placebo-controlled double-blind trial, to investigate whether neurofeedback improves neurocognitive functioning in children who have received treatment for a brain tumor (trial number clinicaltrials.gov NCT00961922). After enrollment, patients will be randomized into two groups: (1a) the experimental group, receiving neurofeedback, and (1b) the placebo group, receiving placebo training. In addition, (2) a control group of healthy siblings is included; this group will not receive any training. If effectiveness of neurofeedback is demonstrated after completion of the study, patients in the placebo group will be given the opportunity to receive neurofeedback.

Participants
Eligible for inclusion are patients in the Netherlands, aged 8 to 18 years, who finished treatment for a brain tumor at least two years prior to enrolment and who suffer from problems in neurocognitive functioning. Problems in neurocognitive functioning include attention problems, problems with information processing speed and/or memory problems as assessed by caregiver report. Exclusion criteria are premorbid diagnosis of ADHD or ADD, a mental or physical condition that prohibits neurocognitive assessment and insufficient mastery of the Dutch language. Siblings, aged between 8 and 18 years, form the control group.
Chapter 3

Intervention

The neurofeedback training is performed at home or school using a Dell notebook (Inspiron N5030, 15.6 inch screen), with BioExplorer software, version 1.5 installed, and a portable Brainquiry PET neurofeedback device. Reinforcement is provided by a self-selected movie that will be presented on the screen if the brain produces the desired activity, as detected by an electrode placed at Cz (see Figure 1). Each patient receives two sessions weekly for 15 weeks, 30 sessions in total. Each session takes 39 minutes to administer, divided in ten blocks of three-minutes training, alternated with one-minute breaks. In the breaks the patient will be instructed to sit quietly with the eyes closed.

The neurofeedback sessions are hosted by extensively trained research assistants who have successfully completed a full day schooling session on administration of the neurofeedback training in accordance with detailed standard operating procedures. During the first neurofeedback session, the research assistant will be accompanied by one of the researchers to ensure adherence to the standard operating procedures. After each session, the research assistant is required to fill out a checklist providing information about the training that includes items on start and finish time of the training, duration of the session, selected movie, alertness of the patient, and any deviations from the standard procedures. Checklists are e-mailed to the researchers on a weekly basis.

![Figure 1. EEG locations. Patients in PRISMA are trained on location Cz. Location Cz is the location exactly halfway between the nasion (the bridge of the nose) and the inion (the most prominent point on the lower rear of the skull) and halfway between the two ears.](image-url)
Neurofeedback treatment modules
The neurofeedback treatment modules were developed in the software program BioExplorer. To increase comparability, we decided to develop three standard treatment modules based on the qEEGs from the pilot study, rather than designing an individualized treatment module for each participant. The three treatment modules are (1) beta 1 up training, (2) sensory motor rhythm (SMR) up/beta 1 down training, and (3) beta 1 down training. The qEEG of the patient determines the most suitable of the three neurofeedback treatment modules. The mean Z-score for the power in the beta 1 frequency band (15–20 Hz) for the electrodes on locations Fcz, Cz, C3, C4 and Cpz are calculated (see Figure 1). For SMR no Z-scores are provided in the brain resource report. SMR power is calculated and p-values are obtained over the average of 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4). The beta 1 up training is given if the beta 1 power is within the normal range (within 1 standard deviation from the mean) or lowered (more than 1 standard deviation below the mean). The SMR up/beta 1 down training is chosen if the beta 1 power is elevated (more than 1 standard deviation above the mean) and SMR (12–15 Hz) is within the normal range (p>0.05) or lowered (p<0.05). The beta 1 down training is chosen if the patient has beta spindles, ascertained by an EEG specialist via observation, or if both beta 1 is elevated (more than 1 standard deviation above the mean) and SMR power is elevated (p<0.05). Three identical placebo treatment modules were matched to the three neurofeedback treatment modules; beta 1 up placebo, SMR up/beta 1 down placebo and beta 1 down placebo. In the placebo treatment modules, the provided reward of a movie is not based on the desired brain waves from the patient, but on the ‘random signal generator’ that is incorporated in the BioExplorer software.

Randomization
The three neurofeedback treatment modules and three placebo treatment modules have been designed to have the exact same appearance on the screen of the notebook, in order to be indistinguishable during training. The six treatment modules have randomly been
assigned a number (treatment module 1–6). J.O., one of the members of the research team, holds the key to the codes; the other members are blinded. Another member of the research team analyzes the qEEG and informs J.O. which of the three neurofeedback treatment modules is indicated according to the protocol (see Figure 2). J.O. is then responsible for randomizing the patient into the actual neurofeedback or the placebo training using a randomization table generated by SPSS. For stratification purposes, randomization takes place after selection of the most appropriate neurofeedback treatment module. After randomization, J.O. notifies M.d.R. of the assigned treatment module (treatment module 1–6) and M.d.R. sends the assigned treatment module via email to the designated research assistant providing the neurofeedback training. Due to his not-blind status, J.O. is not involved in training any patients or the processing of the data.

**Figure 2.** Flow chart of the PRISMA study.
PROCEDURE

Recruitment
Five out of seven Dutch University hospitals accepted the invitation to join the study. Participating hospitals are the Emma children’s hospital/Academic Medical Centre in Amsterdam, VU medical centre in Amsterdam, university medical centre Utrecht in Utrecht, St. Radboud university medical centre in Nijmegen and university medical centre Maastricht in Maastricht. A letter via their oncologist or psychologist informs patients and their caregivers about the study. Interested caregivers will be provided with a screening questionnaire concerning their child’s neurocognitive functioning (including items on attention functioning, memory and speed) and exclusion criteria (e.g. premorbid diagnosis of ADHD or ADD) to verify eligibility of the patient. If eligible for inclusion, the patient is invited for the pre training assessment. If applicable, a sibling will also be invited for assessment to participate in the control group. On the day of the pre training assessment, the informed consent form is signed by caregivers, the patient, and if applicable, the sibling.

Assessment
Assessments are conducted at one of the three cooperating EEG centers in the Netherlands; Pels institute in Amsterdam, Brainfact in Amsterdam, and EEG resource institute in Nijmegen. Patients are assessed on three occasions: pre training (T0), directly post training (T1), and six months post training (T2); see Figure 2. Assessments include neurocognitive testing, questionnaires filled out by patient, caregiver, and teacher, and a qEEG, see Table 1. Assessment of the siblings occurs only once, and is identical to the assessments used in patients with the exception of questionnaires filled out by parents and teachers.

qEEG
An EEG is recorded from the patients at three time points. A Quick-cap with NuAmp 10–20 electrodes international system from neuroscan is used, with 28 channels;\textsuperscript{40} Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2. During the first three minutes an eyes-open resting EEG is registered, in the consecutive three minutes an eyes-closed resting EEG. After the resting EEG, event related potentials are measured during an odd ball and a go–no go task. The Brain Resource International Database (BRID),\textsuperscript{41,42} comprising EEG power spectra of over 4,000 healthy controls, provides normative data to quantify the EEG (qEEG) and obtain Z-scores for the participants in the current study.

Neurocognitive tests
To objectify the primary hypothesis of the study, that neurofeedback will improve neurocognitive functioning, different neurocognitive domains are assessed. The tests are
conducted by one of the researchers or extensively trained research assistants and take approximately two and a half hours. Based on literature describing late effects in brain tumor patients, the following neurocognitive domains were targeted for assessment:\(^{43}\) attention, processing speed, memory, intellectual functioning, inhibition, and visuomotor integration. Well-validated computerized and pencil-and-paper tests were selected to provide a comprehensive assessment of neurocognitive functioning before the training and the efficacy of neurofeedback (see Table 1).

**Questionnaires**

Our secondary hypothesis regards the impact of neuropsychological performance on psychosocial functioning.\(^{25,44}\) Based on studies reports, the following domains are assessed using questionnaires: social/emotional functioning, self-esteem, and health related quality of life. Because of the reported decrease in fatigue after training in the pilot study, we also included questionnaires assessing fatigue and sleep disturbance.\(^{24}\) In addition, two questionnaires on attention and executive functioning were added to assess caregiver and teacher rated neurocognitive functioning. Widely used, reliable, and validated questionnaires were selected in order to assess the domains of interest, as well as the effect of neurofeedback on these domains (see Table 1). Questionnaires were administered to either patient, caregivers or teacher, if applicable. The online questionnaires take approximately 30 minutes to fill out. In addition, as an interim measurement, caregivers fill in the attention questionnaire (SWAN)\(^{38}\) one extra time, after the first 10 sessions of the patient.

**Power calculation**

Power calculations used the neurocognitive measures as primary outcome measures. The calculations were done in the statistical program nQuery Advisor.\(^{45}\) We expect that the neurofeedback will have a medium (d=0.5) to large effect (d=0.8) on neurocognitive functioning as measured at T1 and compared to T0, based on improvements found in children with ADHD who were trained with neurofeedback and on the improvements found in learning-impaired childhood cancer survivors treated with methylphenidate.\(^{12,15}\) Given an effect size of 0.6 with alpha set at 0.05 (one-sided) and a power of 0.80, a minimum of 35 patients is required in both the neurofeedback group and the placebo group.
Table 1. Outcomes, measures and to whom it is administered

<table>
<thead>
<tr>
<th>Neurocognitive assessment</th>
<th>Measurement</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Attention Network task (ANT)</td>
<td>Patient/sibling (8-18)</td>
<td>Patient (8-18)</td>
<td>Patient (8-18)</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Baseline Speed ANT</td>
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<td></td>
<td>Digit Span (age appropriate Wechsler scale)</td>
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<td>Patient (8-18)</td>
<td>Patient (8-18)</td>
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<td>-</td>
<td>Patient (8-16)</td>
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<tr>
<td></td>
<td>Abbreviated WAIS-III*</td>
<td>Patient/sibling (17-18)</td>
<td>-</td>
<td>Patient (17-18)</td>
</tr>
<tr>
<td>Inhibition</td>
<td>Stop Signal task</td>
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<td>Visuomotor integration</td>
<td>Tracking and Pursuit task</td>
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<td>Patient (8-18)</td>
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<td></td>
<td></td>
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<td>Questionnaires</td>
<td></td>
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<td></td>
</tr>
<tr>
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<tr>
<td></td>
<td>SDQ teacher version 32</td>
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<td>Teacher (8-18)</td>
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<tr>
<td>Self esteem</td>
<td>Dutch version SPPC 31</td>
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<td>Patient (8-11)</td>
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<td>Fatigue</td>
<td>CIS 36</td>
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<td>SDSC 37</td>
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<td>Teacher (8-18)</td>
<td>Teacher (8-18)</td>
<td>Teacher (8-18)</td>
</tr>
</tbody>
</table>

Note. Intellectual functioning is assessed at T0 and T2 but not at T1. Siblings are assessed at T0 only.

* The following subtasks were administered: Arithmetic, Similarities, Block Design, and Picture Completion.

SDQ = Strengths and Difficulties Questionnaires; SPPC/SPPA = Self Perception Profile for Children/Adolescents; CIS = Checklist Individual Strength; Sleep Disturbance Scale for Children; SWAN = Strengths and Weaknesses of ADHD-symptoms and Normal-behavior; BRIEF = Behavior Rating Inventory of Executive Functioning; WISC-III = Wechsler Intelligence Scale for Children – Third version; WAIS-III = Wechsler Adult Intelligence Scale – Third version.
Statistical analyses

Intention-to-treat analyses will be conducted. Because of possible withdrawal before treatment starts, dropouts during the study, failure to fill out questionnaires, or research procedure violations, missing data will occur. Imputation of missing values will be carried out as much as possible to make intention-to-treat analyses feasible. Missing data will be imputed using Imputation and Variance Estimation Software.46 Prior to the training (T0) we will assess differences between patients and siblings on neurocognitive and psychosocial functioning, using mixed modelling. Subsequently, we will conduct multivariate analysis of variance (MANOVA) to determine the effect of neurofeedback post-treatment (T1) on the primary and secondary outcomes, comparing the patients in the neurofeedback group to the patients in the placebo group. To control for possible differences in neurocognitive functioning prior to the training, T0 data will be included in the model as covariate. Finally, we will use repeated measures analysis for group (neurofeedback and placebo) x time (T0, T1, and six months follow-up, T2) to investigate the changes over time. To examine the possible effects of patient characteristics on the efficacy of the neurofeedback, the following variables will be assessed as covariates in the MANOVA and repeated measures analyses: age at assessment, age at diagnosis, diagnosis, time since diagnosis, and treatment modalities. All analyses will be conducted using SPSS. A P-value <0.05 will be considered significant.

DISCUSSION

This article describes the design of the PRISMA study, a randomized controlled trial investigating the efficacy of neurofeedback in pediatric brain tumor survivors with neurocognitive problems. Although neurocognitive problems in pediatric oncology survivors are reported in numerous studies, empirically validated interventions addressing these deficits are scarce. There is growing evidence for neurofeedback as a valuable treatment in different brain disorders.15,21 Our study is the first to investigate the efficacy of neurofeedback in pediatric brain tumor survivors using a randomized placebo-controlled double-blind trial, comparing neurofeedback to placebo training. By setting an automatically adjusted threshold of feedback as opposed to a manually adjusted threshold, we enabled blinding the trainers; trainers were not required to monitor the brain activity of the patient during the sessions. Furthermore, we ensure the standardization of the neurofeedback treatment by employing carefully instructed research assistants providing the neurofeedback treatment. At the same time we increased the feasibility for the patients, by administering the training at the patients’ home or school. In addition, the effects of neurofeedback on neurocognitive and psychosocial functioning are thoroughly investigated by using well-validated paradigms.
and psychometrically sound questionnaires administered to patient, caregiver and teacher. Lastly, we have included a control group of healthy siblings, to compare performance of the brain tumor survivors to children without a history of a brain tumor.

The design of PRISMA has some methodological pitfalls to take into account. Because of time factors and the population, this study might be at risk for losing patients during the treatment phase and during follow-up. With five year survival rates of approximately 65%, some patients may relapse[47], or they may discontinue their participation in the study. We increase comparability by employing three different training modules; however, the training might be less effective than an individualized training. The groups receiving each of the three treatment modules are small. Also, the group of brain tumor patients is heterogeneous, e.g. in terms of tumor diagnosis, tumor location, age at diagnosis, treatment, time since diagnosis, and time since end of treatment. It is well documented that these variables play an important role in neurocognitive outcomes. These heterogeneities may be reflected in our results.

In conclusion, if neurofeedback proves to be effective in improving neurocognitive deficits after treatment for a brain tumor, this would be a valuable addition to the currently available effective interventions for this vulnerable group of pediatric brain tumor survivors.
Chapter 3

REFERENCES

Neurofeedback in PBTS: Design RCT


Timed performance weaknesses on computerized tasks in pediatric brain tumor survivors: a comparison with sibling controls

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ABSTRACT

Background: With more children surviving a brain tumor, insight into the late effects of the disease and treatment is of high importance. This study focused on profiling the neurocognitive functions that might be affected after treatment for a pediatric brain tumor, using a broad battery of computerized tests. Predictors that may influence neurocognitive functioning were also investigated.

Methods: A total of 82 pediatric brain tumor survivors (PBTSs) aged 8–18 years (M = 13.85, SD = 3.15, 49% males) with parent-reported neurocognitive complaints were compared to a control group of 43 siblings (age M = 14.27, SD = 2.44, 40% males) using linear mixed models. Neurocognitive performance was assessed using measures of attention, processing speed, memory, executive functioning, visuomotor integration (VMI), and intelligence. Tumor type, treatment, tumor location, hydrocephalus, gender, age at diagnosis, and time since diagnosis were entered into regression analyzes as predictors for neurocognitive functioning.

Results: The PBTSs showed slower processing speeds and lower intelligence (range effect sizes .71–.82, p < .001), as well as deficits in executive attention, short-term memory, executive functioning, and VMI (range effect sizes .40–.57, p < .05). Older age at assessment was associated with better neurocognitive functioning (B = .450, p < .001) and younger age at diagnosis was associated with lower intelligence (B = .328, p < .05). Medical risk factors, e.g., hydrocephalus, did not show an association with neurocognitive functioning.

Conclusions: Late effects in PBTSs include a broad range of neurocognitive deficits. The results suggest that even PBTSs that were traditionally viewed as low risk for neurocognitive problems (e.g., surgery only, no hydrocephalus) may suffer from decreased neurocognitive functioning.
INTRODUCTION

A brain tumor is the second most frequently occurring type of childhood malignancy. During the last decades, the treatment of childhood brain tumors has improved considerably, leading to substantially lower mortality rates. Increased survival has, however, not come without cost. Many pediatric brain tumor survivors (PBTSs) experience neurocognitive late effects. The tumor and its treatment inevitably damage healthy brain tissue, leading to a wide range of neurocognitive deficits. Neurocognitive deficits have deteriorating effects on the psychosocial development and academic achievement of PBTSs.

Although neurocognitive functioning after brain tumor treatment has been subject of many studies, the focus is often on a limited array of neurocognitive functions. Studies that do include a more comprehensive assessment of neurocognitive functions have mostly focused on a restricted subgroup of PBTSs, e.g., posterior fossa tumor patients, preventing the results from being generalized to the PBTS population, although this may aid a better understanding of the impact on specific subgroups. Other studies used paper and pencil tasks to measure neurocognitive functioning. Paper-and-pencil-based measures often unintentionally target multiple neurocognitive functions within one instrument, such as visuomotor abilities, while computerized tasks facilitate the isolation of individual neurocognitive functions. This may be done by either systematically manipulating the load on the function of interest while holding all other function demands constant (e.g., the demand on motor functioning in a visuomotor integration [VMI] task is kept constant, while the demand on VMI is increased by manipulating speed and structure; see De Kieviet et al., 2013) or by the use of built-in control conditions allowing control over performance on functions that are not of interest (e.g., with regard to an inhibition task, the demand on processing speed and motor response are controlled for in order to isolate response inhibition; see De Zeeuw et al., 2008). Furthermore, computerized tasks are highly standardized and thereby increase accuracy in administration and scoring, allow a more accurate response-time recording, and reduce examiner burden with regard to assessment and scoring. Computerized tasks also facilitate the development of alternative versions and distribution of the tasks with software. To the best of our knowledge, this study is among the first to focus on a broad range of neurocognitive deficits using mainly computerized measures in PBTSs with varied etiological and treatment backgrounds.

In addition to studying the occurrence and magnitude of neurocognitive deficits after a pediatric brain tumor, defining predictors of these deficits is of great clinical relevance. Our recent quantitative meta-analysis found that young age at diagnosis, radiotherapy, chemotherapy, and longer time since diagnosis were associated with worse neurocognitive outcomes in terms of intelligence and attention. In addition, female gender and complications such as hydrocephalus have been found to be associated with worse neurocognitive functioning.
In the present study, we employed computerized tests to improve understanding of the profile of neurocognitive deficits displayed by PBTSs. The performance of PBTSs with subjective neurocognitive complaints was compared to that of sibling controls. Because neurocognitive functions are known to be highly influenced by genetic factors, sibling controls are preferred as a comparison group over, for example, classmates. The use of sibling controls also controls for socioeconomic background. Groups were compared on a broad range of neurocognitive functions including attention, processing speed, memory, inhibition, VMI, and intelligence. All tasks, except for the intelligence measures, were designed to measure one single neurocognitive function, thereby controlling for other possible functions using tasks with built-in control conditions or tasks that parametrically manipulate the difficulty level of the neurocognitive function of interest. We hypothesized that PBTSs would perform worse than sibling controls on all measures of neurocognitive functioning. This study also addressed the predictive value of gender, tumor type, tumor location, treatment, hydrocephalus, age at diagnosis, and time since diagnosis for neurocognitive outcome, hypothesizing that male gender, low-grade tumor, infratentorial tumor, treatment with surgery only, no hydrocephalus, older age at diagnosis and shorter time since diagnosis would lead to better functioning.

METHOD

Participants
Eligible for inclusion were children treated for a brain tumor in the Netherlands, aged 8–18 years, who finished treatment at least 2 years prior to enrollment and who suffered from neurocognitive complaints as reported by parents. Children with a premorbid diagnosis of attention deficit/hyperactivity disorder (AD/HD) were excluded. Furthermore, exclusion criteria were a mental or physical condition that restricts possibilities for neurocognitive assessment (e.g., blindness) or insufficient mastery of the Dutch language. Siblings, aged 8–18 years, formed the control group. Only siblings mentally and physically able to participate in the assessment and who had a sufficient mastery of the Dutch language were included. Data included in this manuscript were obtained in compliance with the regulations of the Academic Medical Center Amsterdam and the Helsinki Declaration.

Procedure
Data collection took place between January 2010 and August 2012 as part of the PRISMA study, a randomized placebo-controlled double-blind trial to investigate the effects of neurofeedback on neurocognitive functioning of PBTSs. The present paper reports data on neurocognitive functioning at study entry. The study protocol was approved by the
Medical Ethical Committee of the Academic Medical Center Amsterdam and registered at ClinicalTrials.gov (NCT00961922).

Five out of seven Dutch university hospitals accepted the invitation to join the study: Emma Children's Hospital/Academic Medical Center Amsterdam, the VU Medical Center Amsterdam, the University Medical Center Utrecht, the Radboud University Medical Center Nijmegen, and the Maastricht University Medical Center. A letter informed children and their parents about the study. Interested parents were provided with an online screening questionnaire concerning inclusion and exclusion criteria. Children eligible for inclusion were invited for baseline assessment. If available, siblings were invited to participate as controls in the study. Informed consent was signed by parents and participating children. Testing took place in a quiet room by trained examiners using standardized instructions. The total testing time was approximately two and a half hours. Tests were administered in a fixed order for both groups. Frequent breaks were taken to avoid fatigue.

NEUROCOGNITIVE OUTCOME MEASURES

Attention

The Attention Network Task (ANT) is a computerized task designed to measure the functioning of three independent neural networks that enable alerting, orienting, and executive attention. Reliability and validity has been established. In this study, we used a child-friendly adaptation of the ANT.

In the ANT, children are required to push as quickly and accurately as possible one of two buttons corresponding to the location of a target stimulus presented at either the left- or right-hand side of a computer screen. There are four trial types: (1) neutral trials, in which a neutral cue appears in the center of the screen preceding the target stimulus; (2) alerting trials, in which no cue is provided before the onset of the target stimulus; (3) orienting trials, in which a central cue points to the location of the subsequently presented target stimulus; and (4) executive trials, in which the central cue points to the location opposite the subsequently presented target stimulus (causing slower reaction times due to the necessary shift in attention). The task consists of 312 trials, randomly presenting the four trial types. The efficiency of the alerting, orienting, and executive attention networks was assessed by contrasting the mean reaction times of the correct responses for each of the three corresponding trials (alerting, orienting, and executive) with the mean reaction time of the correct responses on the neutral trials.

In addition, the intraindividual coefficient of variation across all trials was used as a measure of maintenance of attention. The intraindividual coefficient of variation is defined as the standard deviation of reaction times on correct responses divided by the mean reaction time of correct responses.
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**Processing speed**
Processing speed was measured by the mean reaction time on correct responses on the neutral ANT trials.\(^{21}\)

**Memory: Visual short-term memory**
A computerized version of a visual sequencing task was used to measure visual short-term memory. Psychometric properties have been reported in several studies.\(^{21,22}\) During a trial, a sequence of yellow circles appears one by one in a 4×4 grid. The participant is required to repeat the sequence by tapping the correct locations on a touch screen. The difficulty level is manipulated by increasing the number of circles to be repeated (2–9 circles), with each difficulty level comprising two trials. If a participant makes an error on both trials of a difficulty level, the task is terminated. The total number of correct trials was used as the outcome variable.

**Memory: Auditory short-term memory**
Auditory short-term memory was measured by the forward items of the Digit Span task of the age-appropriate Wechsler scale (the Wechsler Intelligence Scale for Children –Third Edition [WISC-III] or the Wechsler Adult Intelligence Scale – Third Edition [WAIS-III]\(^{23,24}\)). In this task, participants are required to repeat verbally presented sequences of digits, increasing in length (2–9 digits). The task is terminated after an error on both items of a difficulty level. The number of correct forward items (i.e., the raw score associated with Digit Span forward) on the Digit Span task was used as the outcome variable.

**Executive functioning: Working memory**
The backward items on the Digit Span task of the age-appropriate Wechsler scale were used as a measure of working memory.\(^{23,24}\) During the backward items, the participants are asked to repeat verbally presented sequences of digits, increasing in length (2–9 digits), in the reverse order, requiring simultaneous storage and processing of information.\(^{25}\) The task is terminated after an error on both items of a difficulty level. The total number of correct items (i.e., the raw score associated with Digit Span backward) was used as the outcome variable, with the number of correct forward items as covariate.

**Executive functioning: Response inhibition**
The Stop Signal task was used to assess response inhibition. Reliability and validity have been established in several studies.\(^{26,27}\) The task presents participants with two kinds of trials: go trials and stop trials. The participant is required to press as quickly and accurately as possible one of two buttons corresponding to the location of a target stimulus presented on either the left- or right-hand side of a computer screen. On stop trials, the stimulus is
followed by a stop signal—a cross, superimposed on the stimulus—requiring participants to inhibit the response. The time between stimulus and stop signal (stop signal delay) is varied to accomplish on average 50% successful inhibition on stop trials. The stop signal reaction time (SSRT), measuring the speed of the inhibitory response, was calculated by subtracting the mean stop signal delay from the mean reaction time on the correct go trials, and served as the outcome variable.

VMI
A computerized tracking and pursuit task was used to measure VMI, which had been adapted and extended for use with children. The psychometric properties are detailed in de Sonneville (1999). The task comprises a structured part and an unstructured part. In both parts, participants are required to follow the trail of a moving caterpillar with a computer pencil in their preferred hand. During the structured part, the caterpillar moves in a fixed circular way around the screen. In the unstructured part of the task, the caterpillar moves in random directions around the screen. Both parts consist of six trials of 30 seconds each, with increasing speed levels (40–140 mm/s). For each trial, accuracy was calculated as the mean distance (in mm) between the position of the pencil and the caterpillar. The accuracy scores on the structured and unstructured part of the six different speed levels were used as measures of VMI.

Intelligence
Full Scale Intelligence Quotient (FSIQ) was estimated using a four-subtask short form of the age-appropriate WISC-III or WAIS-III containing the subtests Arithmetic, Similarities, Block Design, and Picture Completion (see Sattler, 1992). Satisfactory reliability (Cronbach’s alphas >.80) and validity (rs with full test >.77) have been reported for this short form for both the WISC-III and the WAIS-III.

Medical and demographic data
For participating PBTSs, information from the medical records was provided by the oncologist and included tumor type and grade (high-grade/low-grade tumor, based on histopathology), type of treatment (surgery only versus chemotherapy and/or radiotherapy with or without surgery), tumor location (supratentorial/infratentorial, based on MRI) and history of hydrocephalus (based on MRI), age at diagnosis, and time since diagnosis. Information on demographics was provided by the parents (gender, parental country of origin, and the highest level of parental education assessing socioeconomic status). Medical and demographic data were also collected for a subsample of non-participants (45 of 71 non-participants) to study selective dropout. For non-participants, the “age at assessment” was defined as the difference between birth date and the average assessment date of participating PBTSs.
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**Statistical analyses**

All analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Differences between PTBSs and controls on age at assessment and demographical data were tested with an independent-samples t-test and chi-square test, respectively. Differences between participating and non-participating PTBSs on demographical and medical data were tested with an independent-samples t-test (age at assessment, age at diagnosis, time since diagnosis), a chi-square test (gender, tumor type, tumor location, treatment, hydrocephalus), or a binomial test (diagnosis). Linear mixed models were used to evaluate differences in neurocognitive functioning between survivors and controls, controlling for age. These analyses accounted for the dependency of the data of PTBSs and controls from the same families and in the case of repeated measurements (ANT and VMI task), also for the dependency of the data within subjects. In all models, neurocognitive function was predicted by group (survivors versus controls) and age as fixed factors with a random intercept for “family”. Additionally, in the model of the data derived from the ANT assessing the efficiency of the alerting, orienting, and executive attention networks, trial type was included as a within-subject factor. Group and the two-way interaction group × trial type were included as fixed factors. This two-way interaction was used to test differences in the efficiency of the three attention networks between PTBSs and controls, contrasting the performance on neutral trials to the performance on the alerting, orienting, and executive trials. Likewise, in the model of the VMI task, structure and speed were added as within-subject factors. Group, structure, speed, the two-way interaction structure × speed, and all interactions with group were included as fixed factors. These interactions were used to test the differential effects of structure and speed between PTBSs and controls.

Effect sizes were calculated in terms of Cohen’s d by dividing the difference in mean score between PTBSs and controls by the pooled standard deviation with values of .20, .50, and .80 considered as small, medium, and large effects, respectively. Regression analyses were used to study the predictors of neurocognitive functioning. To limit the number of outcomes (criterion variables), a “summary factor of neurocognitive functioning” was constructed. We grouped all neurocognitive measures into one aggregated score using principal component analysis (PCA). PCA with oblique rotation was performed on those neurocognitive outcomes on which patients and controls differed significantly, except intelligence (see below). For the VMI task, only the highest speed level of the unstructured part was included (this variable was regarded as most representative of the data collected with this task). The resulting one factor harbored the variance common to all neurocognitive measures. These factor scores were used to analyze risk factors for poor neurocognitive functioning. As age plays an important role in performance on neurocognitive tasks, age at assessment was entered in the first step in the regression model, followed by all other predictor variables: tumor type (high-grade versus low-grade tumor), type of treatment...
(surgery only versus chemotherapy and/or radiotherapy with/without surgery), tumor location (supratentorial versus infratentorial), history of a hydrocephalus, gender, age at diagnosis, and time since diagnosis. Due to the fact that intelligence scores are age corrected, a separate regression analysis was performed with estimated FSIQ as the outcome, in which age at assessment was not entered. A p-value < .05 was considered significant.

RESULTS

Participants
The final sample in the present study included 82 PBTSs and 43 controls (for a flowchart of inclusion, see Figure 1). Of the survivors, 20 received special education (24%) and 39 have been held back a class in the past (48%). Data on age at assessment, demographic characteristics, and disease characteristics are displayed in Table 1. PBTSs and controls did not differ in age at assessment, gender, country of origin of parents, or highest level of parental education (p > .324).

Participating and non-participating PBTSs did not differ in age at assessment (p > .062), gender (p > .062), or tumor location (p > .116), but they did differ with regard to the distribution of tumor types (p < .01) as well as the grade of tumor, with relatively more high-grade tumors in the participants than in the non-participants (p < .05). The participants were on average younger at diagnosis (p < .05), and time since diagnosis was longer (p < .05) than in the case of the non-participants. More participating PBTSs had undergone radiotherapy (p < .05) and chemotherapy (p < .05) than non-participating PBTSs.

Figure 1. Flowchart of inclusion.
Note. AD/HD = attention deficit/hyperactivity disorder; PBTSs = Pediatric brain tumor survivors.
Table 1. Demographics and medical information of Pediatric Brain Tumor Survivors (PBTSs) and sibling controls.

<table>
<thead>
<tr>
<th>Table 1. Demographics and medical information of Pediatric Brain Tumor Survivors (PBTSs) and sibling controls.</th>
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<td>Controls N = 43</td>
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<td>Chemotherapy 35 43 n/a</td>
</tr>
<tr>
<td>Surgeryb 72 88 n/a</td>
</tr>
<tr>
<td>Otherc 2 2</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Supratentorial 46 56 n/a</td>
</tr>
<tr>
<td>Infratentorial 36 44 n/a</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Yes 39 48 n/a</td>
</tr>
<tr>
<td>No 43 52 n/a</td>
</tr>
<tr>
<td>Note. aHighest level of education of father or mother is reported, where Low or Intermediate = primary education, general secondary education, and secondary vocational education and High = Higher vocational education and university; b37 patients were treated with surgery only; cBiopsy only, n = 1; cerebrospinal fluid pressure relief only, n = 1. M = Mean; n/a = Not applicable; PBTSs = Pediatric brain tumor survivors; PNET = Primitive neuroectodermal tumor; SD = Standard deviation. PBTSs and controls did not differ in terms of age at assessment, gender, country of origin of parents, and highest level of parental education.</td>
</tr>
</tbody>
</table>
Neurocognitive outcomes
The results of the neurocognitive measures are displayed in Table 2 and Figure 2.

Attention
No group differences were found for alerting (d = .07, p = .799) and orienting attention (d = .43, p = .104), but PBTSs showed a less efficient executive attention network than the controls, as reflected in a greater difference between mean reaction times on correct neutral and executive trials (d = .47, p < .01). PBTSs showed poorer maintenance of their attention than controls, as reflected by the higher intraindividual coefficient of variation (d = .40, p < .05).

Processing speed
Information processing speed was slower in PBTSs compared to controls, as measured by the mean reaction time of correct responses on the neutral trials of the ANT (d = .74, p < .001).

Memory: Visual short-term memory
PBTSs had a lower number of correct items on the visual sequencing task than the controls (d = .56, p < .01), reflecting worse visual short-term memory performance.

Memory: Auditory short-term memory
PBTSs completed fewer forward items correctly on the Digit Span task (d = .57, p < .01), indicative of poorer auditory short-term memory.

Executive functioning: Working memory
The total number of correct backward items on the Digit Span task, controlling for the correct number of forward items, was lower in the PBTSs than in the control group (d = .41, p < .05), indicating poorer working memory.

Executive functioning: Response inhibition
SSRT scores were higher in PBTSs than the controls (d = .40, p < .05), reflecting slower inhibitory processes.
Table 2. Neurocognitive outcomes of the Pediatric Brain Tumor Survivors (PBTSs) compared to sibling controls.

<table>
<thead>
<tr>
<th>Measure</th>
<th>PBTS</th>
<th>Sibling controls</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 82</td>
<td>N = 43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT alerting attention</td>
<td>53.91</td>
<td>31.45</td>
<td>55.99</td>
</tr>
<tr>
<td>ANT orienting attention</td>
<td>40.58</td>
<td>34.61</td>
<td>27.30</td>
</tr>
<tr>
<td>ANT executive attention</td>
<td>41.67</td>
<td>56.55</td>
<td>18.74</td>
</tr>
<tr>
<td>ANT intraindividual coefficient</td>
<td>.23</td>
<td>.07</td>
<td>.20</td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT mean reaction time</td>
<td>442.84</td>
<td>167.00</td>
<td>340.46</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual short-term memory</td>
<td>13.59</td>
<td>4.39</td>
<td>15.84</td>
</tr>
<tr>
<td>Auditory short-term memory</td>
<td>7.83</td>
<td>2.06</td>
<td>8.95</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>5.26</td>
<td>2.22</td>
<td>6.14</td>
</tr>
<tr>
<td>Stop task response inhibition*</td>
<td>261.61</td>
<td>69.89</td>
<td>235.65</td>
</tr>
<tr>
<td><strong>Intelligence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated FSIQ</td>
<td>89.71</td>
<td>18.67</td>
<td>103.49</td>
</tr>
</tbody>
</table>

Note. *p < .05; n = 78 for PBTSs and n = 39 for sibling controls. ANT = Attention Network Task; FSIQ = Full Scale IQ; M = Mean; PBTSs = Pediatric brain tumor survivors; SD = Standard deviation. For all outcomes, except for intelligence, raw scores are reported and age was entered as a covariate in the analyses. For intelligence, age-standardized scores are given. Effect sizes “d” were calculated using the pooled SD of both groups. The results for the VMI task are displayed in Figure 2 and described in the text.

Figure 2. Results for the VMI task for pediatric brain tumor survivors and sibling controls for both the structured and unstructured parts.
VMI
There was a significant main effect of group, with PBTSs overall being less accurate in following the caterpillar than controls, F(1,46) = 17.307, p < .001, indicative of poorer VMI. Accuracy decreased with higher speed in both sibling controls and PBTSs, F(5,1256) = 2305, p < .001, but the decrease in accuracy with higher speed levels was stronger in PBTSs than in sibling controls, according to the significant two-way interaction effect of group × speed, F(5,1256) = 7.176, p < .001. VMI performance was worse in the unstructured condition than in the structured condition, F(1,1260) = 4095, p < .001, and the decrease in accuracy with higher speed levels was the strongest in the unstructured condition, as shown by the significant two-way interaction effect of speed × structure, F(5,1256) = 298, p < .001. However, these effects of structure and speed × structure were not different for PBTSs and controls, as indicated by the non-significant two-way (group × structure, F(1,1265) = 1.981, p > .05) and three-way (group × structure × speed, F(5,1256) = 0.616, p > .05) interaction effects.

Intelligence
PBTSs had lower estimated FSIQs compared to controls (d = .82, p < .001).

Predictors of neurocognitive outcome
All outcomes on which PBTSs and controls appeared to differ, except intelligence, were entered in a principal components analysis. For the VMI task, the highest speed level of the unstructured part was included. The principal components analysis yielded one factor that explained 49% of the variance of all outcome variables entered. The factor loadings for each variable on the factor are provided in Table 3. The loadings are all .60 or higher and the average loading is .70. According to MacCallum, Widaman, Zhang, and Hong (1999) and MacCallum, Widaman, Preacher, and Hong (2001) this justifies performing the principal component analysis, given our sample size.32,33 We interpret the resulting factor as primarily reflecting neurocognitive processing speed, since all tasks except for the span tasks had a timing factor. Also, almost all the variables entered into the PCA strongly correlated with the ANT mean reaction time, with correlations ranging from r = .53 (working memory) to r = .69 (ANT intraindividual coefficient). Together, these findings strengthen the idea that the scores on our factor mainly represent neurocognitive processing speed. A higher score on the factor represents better neurocognitive functioning. The Kaiser–Meyer–Olkin (KMO) was calculated as .78, showing that our available data fulfill criteria for PCA. In fact, the ratio of the squared correlation between the variables and the squared partial correlation between the variables of .78 can be described as good.34
Table 3. Factor loadings per variable of the Principal Component Analysis (PCA).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Factor loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANT executive attention</td>
<td>.71</td>
</tr>
<tr>
<td>ANT intraindividual coefficient</td>
<td>.65</td>
</tr>
<tr>
<td>ANT mean reaction time</td>
<td>.87</td>
</tr>
<tr>
<td>Visual short-term memory</td>
<td>-.74</td>
</tr>
<tr>
<td>Auditory short-term memory</td>
<td>-.72</td>
</tr>
<tr>
<td>Working memory</td>
<td>-.60</td>
</tr>
<tr>
<td>Stop task response inhibition</td>
<td>.70</td>
</tr>
<tr>
<td>Visuomotor integration (VMI)</td>
<td>.61</td>
</tr>
<tr>
<td><strong>Eigenvalue</strong></td>
<td>3.95</td>
</tr>
<tr>
<td><strong>% variance</strong></td>
<td>49%</td>
</tr>
</tbody>
</table>

Note. ANT = Attention network task. All outcomes on which PBTSs and controls appeared to differ, except intelligence, were entered in the PCA. For VMI, the highest speed level of the unstructured part was included. N = 74 applies to the entire table/PCA.

Table 4. Regression analysis of medical and child factors on neurocognitive functioning of Pediatric Brain Tumor Survivors (PBTSs).

<table>
<thead>
<tr>
<th>Neurocognitive summary factor (n = 74)</th>
<th>Estimated FSIQ (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
</tr>
<tr>
<td>Age assessment (years)</td>
<td>0.499</td>
</tr>
<tr>
<td>F</td>
<td>23.932</td>
</tr>
<tr>
<td>r2</td>
<td>0.249</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
</tr>
<tr>
<td>Age assessment (years)</td>
<td>0.450</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>-0.061</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.030</td>
</tr>
<tr>
<td>Location tumor</td>
<td>0.014</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.081</td>
</tr>
<tr>
<td>Gender</td>
<td>0.110</td>
</tr>
<tr>
<td>Age diagnosis (years)</td>
<td>0.144</td>
</tr>
<tr>
<td>F change</td>
<td>0.675</td>
</tr>
<tr>
<td>r2 change</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Note: B = Standardized regression coefficient; FSIQ = Full scale IQ; Gender = males (1) versus females (2); Hydrocephalus = No (history of) hydrocephalus (1) versus (history of) hydrocephalus (2); Location of tumor = Infratentorial (1) versus supratentorial (2); Neurocognitive summary factor = Factor derived from the PCA; Treatment = Surgery, biopsy or cerebrospinal fluid pressure relief only (1) versus radiotherapy and/or chemotherapy with or without surgery (2); Tumor grade = Low-grade tumor (1) versus high-grade tumor (2). Time since diagnosis was excluded from the analysis due to multicollinearity.
Timed performance weaknesses in PBTS

Table 4 displays the results of the regression analysis predicting the neurocognitive summary factor as well as estimated FSIQ. Age at assessment was significantly associated with the neurocognitive summary factor, with older children performing better than younger children ($p < .001$). No other predictors significantly contributed to the neurocognitive summary factor. For estimated FSIQ, it was found that age at diagnosis positively predicts estimated FSIQ, indicating that children who are older at diagnosis have a higher estimated FSIQ ($p < .05$). None of the other risk factors included in the model contributed significantly to estimated FSIQ.

**DISCUSSION**

This study investigated a broad range of neurocognitive functions in PBTSs with subjective neurocognitive complaints as compared to sibling controls. The results demonstrate that PBTSs have problems of medium ($d = -.40$) to large ($d = -.82$) size across the whole range of examined neurocognitive functions, including executive attention, maintenance of attention, processing speed, visual and auditory short-term memory, working memory, inhibition, VMI, and estimated FSIQ. Furthermore, older PBTSs performed better on the tasks than younger PBTSs did. Also, PBTSs who were younger when they were diagnosed had lower estimated IQ scores than PBTSs who were older at diagnosis.

In line with research on childhood cancer survivors and (subsamples of) PBTSs we found worse attention performance compared to controls.35–37 Our study is novel in the use of the ANT, which adds to the existing literature by studying the functionality of three independent attention networks: alerting, orienting, and executive attention. We found that PBTSs show more difficulty resolving contradictory information than controls, as reflected by a less efficient executive attention network. Furthermore, maintenance of attention in our PBTS sample was worse compared to the controls. As maintaining attention and ignoring irrelevant cues are crucial skills for acquiring new information, this finding might be related to the decrease in school functioning seen over time in PBTSs who received cranial irradiation.38

Regarding memory and working memory, previous study results consistently showed visual memory and working memory deficits; however, previous work was inconsistent regarding auditory memory, with findings varying from normal memory to a strongly diminished memory function.39–43 According to the most influential model of working memory proposed by Baddeley,44 working memory comprises three subsystems: the visuospatial sketchpad maintaining visual information, the phonological loop maintaining auditory information, and the central executive controlling and allowing the manipulation of the information contained in the visuospatial sketchpad and phonological loop. In PBTSs, hippocampal volume could be an underlying factor in these deficits, as it has been reported that hippocampal volumes...
are positively associated with auditory attention in the context of a verbal memory task in PBTSs, especially in patients treated with radiotherapy. In our study, PBTSs demonstrated more difficulty in keeping both visual and auditory information in their short-term memory as compared to controls, suggesting an underlying problem in the visuospatial sketchpad and phonological loop, respectively. We also found evidence for deficits in the central executive, since PBTSs performed worse than controls on the Digit Span backward condition (requiring the manipulation of verbal information, assessing functioning of the central executive), even after controlling for performance on the forward condition (assessing phonological loop functioning). Together, our findings suggest impairments in all aspects of working memory, a neurocognitive function that has been found highly predictive of IQ and academic performance.

PBTSs showed worse response inhibition skills than the controls, contrary to what we found in a meta-analysis. Response inhibition is an important skill for social functioning, with impaired inhibition being associated with social problems. Results in VMI when measured with a pen and paper task (Beery Developmental Test of Visual-Motor Integration) have been ambiguous. As stated in the introduction, computerized tasks allow the workload for a specific function to be increased while maintaining other conditions as equal. If an increasing difficulty level leads to greater performance decrements in PBTSs then this would pinpoint a deficit in VMI not confounded by other functions necessary to conduct the task. With the computerized VMI task, we were able to demonstrate that the performance of PBTSs decreased to a greater extent with an increase in VMI workload in terms of speed than the performance of controls, illustrating a poorer ability to rapidly integrate visual information in order to guide a motor response. Compared to the structured condition, the unstructured condition resulted in poorer task performance, indicating that performance became worse when participants were required to trace a target following an unpredictable course as compared to a target following a predictable course. However this effect was not different for PBTSs and controls, suggesting that predictability of the visuomotor response does not explain poor visuomotor performance in PBTSs, but that these problems rather result from deficits in VMI speed. Impairments in VMI speed may cause difficulty in writing ability under conditions of time pressure, which often exists in the school context. Poor writing skills may affect schoolwork and is associated with poor school performance and low self-esteem. Previously, studies have reported that medical factors such as hydrocephalus, young age at diagnosis, or cranial irradiation had a negative effect on neurocognitive functioning in medulloblastoma and ependymoma survivors. In our sample of PBTSs with neurocognitive complaints, none of the medical risk factors were predictive of neurocognitive functioning. Our finding suggests that even children who do not carry the commonly reported risk factors for poor neurocognitive outcomes, such as hydrocephalus, young
age at diagnosis, or cranial irradiation, may still be at risk in terms of their neurocognitive functioning. We were surprised to find this, as often in the literature an association is found between medical risk factors and neurocognitive functioning. It would have been interesting to analyze risk factors for poor neurocognitive functioning using each of the neurocognitive measures separately. However, given the sample size and the number of tests, it was not possible to correct for multiple testing. Alternatively, to reduce the chance of type I error, we grouped all neurocognitive measures into one aggregated score using PCA. The resulting one factor harbored the variance common to all neurocognitive measures. PCA also allows a reduction of error variance, since scores on a factor derived from PCA have higher reliability compared to the variables contributing to this factor. It must be noted that the participants were younger at diagnosis, had a longer time since diagnosis and had more often had chemotherapy and radiotherapy than the non-participants, which possibly caused the group of participants to have relatively worse neurocognitive functioning than the non-participants. This may have increased homogeneity and therefore contributed to the lack of association we found between the risk factors and neurocognitive functioning.

We did not find evidence for a possible moderating effect of age on treatment, as we found a small and non-significant correlation between both age and age at diagnosis and radiation therapy. It must be noted that in the Netherlands, children diagnosed with a brain tumor at very young age (<3 years) are not treated with radiotherapy. Our study was limited to PBTSs with subjective neurocognitive complaints, which may have limited the range of scores on our neurocognitive function measures. However, this interpretation seems unlikely given the spread observed in our neurocognitive function measures. Although numerous studies have reported correlations between risk factors and neurocognitive functioning, we are not the first study to report no significant correlation with neurocognitive functioning; e.g., Ris et al. and Butler et al. did not find a relationship between gender and neurocognitive outcome, Grill et al. found no significant association between tumor location and intelligence in posterior fossa survivors, and Riva et al. and Mulhern, Fairclough, and Ochs did not find a significant association between cognitive outcomes and treatment intensity (chemotherapy and cranial irradiation, respectively).

In line with previous research, we found that PBTSs have slower reaction times than controls. Moreover, the profile of neurocognitive functions shows that tasks which are timed or draw more heavily on information processing speed, such as reaction time and estimated FSIQ, all seem to be more affected than untimed tasks, such as performance on memory tasks. This finding is in accordance with the fact that estimated FSIQ was found to be significantly correlated with processing speed ($r = -.45, p < .001$). White matter damage might play a crucial role in information processing speed. Palmer and Wolfe et al. suggest a model in which neurological damage, and in particular damage to the white matter resulting from the tumor and the treatment of the tumor, is the underlying cause of processing.
speed deficits. These processing speed deficits in turn cascade into deficits in other neurocognitive functions, intelligence, and academic achievement. Indeed, several studies have found slower processing speed to be associated with damaged white matter tracts in PTs. Also, it has been reported that processing speed mediates the association between white matter integrity and reading skills. Another study by the same research group reported intellectual outcomes as being associated with white matter integrity. White matter is vulnerable to the negative effects of treatment for a brain tumor, especially in young children, whose white matter is still immature. Damage to neural progenitor cells, for example, caused by cranial radiation therapy, may challenge healthy age-appropriate white matter growth. In our sample, 42% of the PTs underwent irradiation as treatment. However, in additional exploratory analyses we did not find any differences on any of the neurocognitive domains studied between the irradiated and the non-irradiated group, or between groups receiving different radiation doses and locations: (1) no irradiation; (2) local irradiation only, excluding supratentorial ≥50 gray; (3) craniospinal irradiation ≥23 gray and <36; (4) craniospinal irradiation ≥36 gray; and (5) local irradiation supratentorial ≥50 gray. Further study is clearly warranted.

The neurocognitive deficits we have found in our sample of PTs are in line with the problems these children experience in daily life. In our sample, 48% have repeated a class and 24% of the PTs received special education. This underscores the importance of support for the PTs with neurocognitive problems. Teachers and parents need to be informed of possible late effects and taught how to assist PTs suffering from poor neurocognitive functioning, for example by giving these children more time to complete tasks. Furthermore, future studies should use more fine-grained measures of medical predictors, rather than dichotomous measures. It would also be interesting to test whether white matter integrity, as assessed using diffusion tensor imaging, mediates the association between medical risk factors and neurocognitive functioning, as has been found in reading skills. Lastly, there is a clear call for the development of (non-medical) interventions targeting neurocognitive late effects. Some interesting studies are currently being carried out, including a study using working memory training (CogMed) and neurofeedback training (PRISMA study).

This study has some limitations that should be taken into account. Firstly, the results cannot be generalized beyond PTs with neurocognitive complaints, as study inclusion was based on the presence of parent-reported neurocognitive problems in the PTs and participants were also invited for participation in a treatment study (ClinicalTrials.gov, NCT00961922). Secondly, the heterogeneous group of PTs harbors mutually interacting risk factors, which make it difficult to investigate the influence of earlier described predictors of neurocognitive outcome. Another limitation is that only PTs who were willing to participate in the PRISMA study were included. This inclusion process may have led to an underestimation of the impairments, as some children declined participation due to severe neuropsychological
impairments. On the other hand, this may have led to an overestimation of neurocognitive impairments, as children without complaints did not participate. Also, the non-participants were on average older at diagnosis, had a shorter time since diagnosis, and were less often treated with chemotherapy and radiotherapy. These differences suggest that a more severely impaired group of PBTSs participated in our study, which may have led to an overestimation of the neurocognitive problems faced by the general population of PBTSs.

There are also advantages inherent to the current study’s design: it targeted a broad range of neurocognitive functions using measures with built-in control conditions designed to isolate each neurocognitive function, computerized tests were used to enhance the reliability of measurement, and the inclusion of siblings as control group allowed for controlling genetic factors and socioeconomic background.

To summarize, PBTSs with neurocognitive complaints exhibit a broad range of neurocognitive late effects. The results suggest that even PBTSs that have traditionally been viewed as at low risk of developing neurocognitive problems (e.g., surgery only, no hydrocephalus) may suffer from decreased neurocognitive functioning.
REFERENCES

Timed performance weaknesses in PBTS


Timed performance weaknesses in PBTS


Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints

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ABSTRACT

Aim: With more children surviving a brain tumor, neurocognitive consequences of the tumor and its treatment become apparent, which could affect psychosocial functioning. The present study therefore aimed to assess psychosocial functioning of pediatric brain tumor survivors (PBTS) in detail.

Methods: Psychosocial functioning of PBTS (8–18 years) with parent-reported neurocognitive complaints was compared to normative data on health-related quality of life (HRQOL), self-esteem, psychosocial adjustment, and executive functioning (one-sample t tests) and to a sibling control group on fatigue (independent-samples t test). Self-, parent-, and teacher-report questionnaires were included, where appropriate, providing complementary information.

Results: Eighty-two PBTS (mean age 13.4 years, SD 3.2, 49 % males) and 43 healthy siblings (mean age 14.3, SD 2.4, 40 % males) were included. As compared to the normative population, PBTS themselves reported decreased physical, psychological, and generic HRQOL (d = 0.39–0.62, p < 0.008). Compared to siblings, increased fatigue-related concentration problems (d = 0.57, p < 0.01) were reported, although self-reported self-esteem and psychosocial adjustment seemed not to be affected. Parents of PBTS reported more psychosocial (d = 0.81, p < 0.000) and executive problems (d = 0.35–0.43, p < 0.016) in their child than parents of children in the normative population. Teachers indicated more psychosocial adjustment problems for female PBTS aged 8–11 years than for the female normative population (d = 0.69, p < 0.025), but they reported no more executive problems.

Conclusions: PBTS with parent-reported neurocognitive complaints showed increased psychosocial problems, as reported by PBTS, parents, and teachers. Systematic screening of psychosocial functioning is necessary so that tailored support from professionals can be offered to PBTS with neurocognitive complaints.
INTRODUCTION

Due to developments in the medical field, survival rates in children with a brain tumor have increased drastically to over 74%. These successes have led to a growing number of pediatric brain tumor survivors (PBTS). Tumor- and treatment-induced brain injury exerts negative effects on neurocognitive functions, such as attention, processing speed, and memory. As a result, 40–100% of PBTS suffer from neurocognitive decline. The decline in neurocognitive functioning appears to increase when the children grow older, resulting in an increasing gap between the PBTS and their peers. Consequently, children treated for a brain tumor may experience lower academic achievements, resulting in lower vocational success, and decreased psychosocial functioning compared to their healthy peers later in life.

To date, studies on psychosocial functioning of PBTS are relatively scarce as compared to other types of cancer, especially because children with a brain tumor have often been excluded from studies, due to their atypical outcomes, i.e., they seem to suffer from more serious problems on a variety of domains (e.g., neurocognitive, social, and adjustment problems) than other pediatric cancer survivors. The studies with PBTS found in the literature focused on health-related quality of life (HRQOL), social competence, self-esteem, and fatigue. Attention for HRQOL, a multidimensional construct covering perceived physical, emotional, mental, social, and behavioral components of well-being and functioning, in PBTS has started to emerge in the past decades. However, no studies to our knowledge have focused on PBTS with neurocognitive complaints. The results of the studies on HRQOL in PBTS in general were contradictory, with HRQOL comparable to the general population, or worse HRQOL in several domains. PBTS reported being bullied, encountering problems with peers, and suffering from stressful and depressive feelings. The researchers mention late effects of the cancer treatment as a possible cause of the decreased HRQOL scores. Decreased neurocognitive functioning was found to be associated with worse HRQOL in PBTS 1 year after treatment.

The literature on self-esteem in PBTS is scarce; however, social competence, an aspect of self-esteem which may predict psychosocial functioning, has been investigated in PBTS. In a comprehensive review on social competence, it was concluded that PBTS experienced deficits in this area. In a cross-sectional study, PBTS reported lower social competence than healthy peers and patients with a pediatric brain tumor during treatment, indicative of a decline of social competence of PBTS over time. Furthermore, PBTS experienced more problems with self-confidence and self-esteem compared to leukemia survivors. Fatigue is a common adverse effect of cancer treatment. In addition, due to the nature of their disease, PBTS frequently experience sleep problems and decreased sleep quality, leading to fatigue and negatively influencing daily functioning. Fatigue in childhood cancer survivors and PBTS is associated with worse psychosocial functioning.
Chapter 5

The influence of executive deficits on psychosocial functioning has been acknowledged. Executive functions, an umbrella term for mental skills concerning planning, behavioral control, and self-regulation, such as attention control, cognitive flexibility, and goal setting are critical skills to function properly in society. Executive functions are often reported to be affected in PBTS. Since psychosocial functioning is important but understudied in PBTS as compared to other types of cancer, we aimed to investigate various domains of psychosocial functioning of PBTS who suffer from parent-reported neurocognitive complaints: HRQOL, self-esteem, psychosocial adjustment, executive functioning, and fatigue. Based on the previous, we can conclude that it is especially important to study psychosocial functioning of PBTS who suffer from neurocognitive problems, as the literature indicated that patients with neurocognitive problems are vulnerable to psychosocial problems. We take multiple informants (self-, parent-, and teacher report) into account, providing complementary information on how PBTS function, both at home and at school, investigating psychosocial functioning of PBTS who suffer from parent-reported neurocognitive complaints. We hypothesize that PBTS experience decreased HRQOL, self-esteem, psychosocial adjustment, executive functioning, and increased fatigue as reported by PBTS themselves, their parents, and/or teachers.

METHODS

Procedures and participants
Data collection took place between January 2010 and August 2012, as part of the PRISMA study, a randomized placebo-controlled double-blind trial to investigate whether neurofeedback can improve neurocognitive functioning in PBTS. Eligible for inclusion were children treated for a brain tumor in the Netherlands, aged 8–18 years, who finished treatment >2 years prior to enrollment and who suffered from neurocognitive complaints as reported by a parent on a screening questionnaire, assessing attention, speed, information processing and memory as well as exclusion criteria. Children with a premorbid diagnosis of attention deficit/hyperactivity disorder, a mental or physical condition prohibiting neurocognitive assessment, or insufficient mastery of the Dutch language were excluded from the study.

PBTS (n = 249) who were treated in one of the participating Dutch hospitals (Emma Children’s Hospital/Academic Medical Center Amsterdam, VU University Medical Center Amsterdam, University Medical Center Utrecht, St. Radboud University Medical Center, Nijmegen, and University Medical Center Maastricht) and their parents received a letter via their pediatric oncologist or psychologist informing them about the PRISMA study. Additionally, three patients from other hospitals made contact via email about participation, after they learned about the study.
Of the PBTS, 89 (35 %) did not meet inclusion criteria and 71 (29 %) declined participation (‘non-participants’) (see Fig.1 for reasons). Parents of PBTS willing to participate (n = 92, 37 %) were provided with an online screening questionnaire concerning their child’s neurocognitive functioning, in order to verify eligibility. Ten PBTS (4 %) were excluded after online screening.

89 (35% of total) excluded
6 no brain tumor, wrongly invited
48 no complaints according to parents
11 no treatment or not >2 years post treatment
9 insufficient physical/mental abilities
15 untraceable

71 (28% of total) non participants
71 refused participation

10 (4% of total) excluded
9 no parent reported
attention/memory/speed problems
1 premorbid adhd diagnosis

249 PBTS were sent
an invitation letter
3 PBTS approached us
for participation
92 (37% of total) screened
with online questionnaire
for eligibility
43 healthy sibling controls
included
82 (33% of total) PBTS
included

Figure 1. Flowchart of inclusion.
Note. Self-reported questionnaires were completed by 81 PBTS and 40 sibling controls. Parent data were available for all 82 PBTS, and teacher data were available for 73 of the included PBTS.

If the included PBTS had a sibling in the age range from 8 to 18 years, he or she was invited via telephone to participate in the control group for the fatigue outcome measure. Siblings were not considered to be optimal as a control group for the other psychosocial outcomes since the cancer diagnosis of the sibling could affect the scores on psychosocial functioning.30,31 Informed consent was obtained from the included 82 PBTS (33 %) and 43 siblings. Subsequently, PBTS, parents, siblings, and the case where parents and PBTS gave permission (n = 76), teachers of PBTS, were sent the questionnaires via email. For parent-report questionnaires, the primary caregiver was asked to fill out the questionnaire. For the teacher-report questionnaires, the parent was asked to indicate which teacher was most suitable to fill out questionnaires about the functioning of the child.

The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center Amsterdam and was registered at ClinicalTrials.gov (NCT00961922).

Demographic and medical characteristics
Parents of participating PBTS supplied information on gender and demographics (the parental country of origin and the highest level of parental education). Medical characteristics were taken from the medical records and included tumor histopathology and grade, type...
of treatment (surgery only vs. chemotherapy and/or radiotherapy with/without surgery),
tumor location (supratentorial vs. infratentorial) and prior hydrocephalus, age at diagnosis,
and time since diagnosis.
Medical and demographic data were also collected for a subsample of non-participants
(45 out of 71 non-participants) to study selection bias at inclusion. As the non-participants
deprecated participation, they were not assessed. To compare the age of participants and
non-participants, ‘age at assessment’ for non-participants was calculated as the difference
between the birth date and the average assessment date of participating PBTS.

Outcome measures
It is well-known that proxy report (parent/teacher) on the functioning of chronically ill
children often yields discrepancies with self-report, although results of studies have been
contradictory. For this reason, we included a combination of self-report, parent-report,
and teacher-report questionnaires.

Self-report
HRQOL - The Kidscreen-27 was administered to evaluate HRQOL in children by means of
27 items, scored on a 5-point Likert scale, divided over 5 dimensions: physical well-being,
psychological well-being, autonomy and parents, peers and social support, and school
environment. In addition, a Generic score was calculated by summing the ten items
that comprise the Kidscreen-10, a shorter version of the Kidscreen, derived from the
Kidscreen-27. Raw scores for each dimension were transformed into T values with a mean
of 50 and a standard deviation of 10 in a European sample.
T values of a Dutch normative sample are available. Higher scores indicated better HRQOL.
The Kidscreen-27 and Kidscreen-10 have good levels of validity and reliability (Cronbach’s
alpha normative samples >0.70; Cronbach’s alpha PBTS 0.71–0.88). The Dutch normative
sample did not differ in age and gender distribution from the PBTS group (p > 0.10).

Self-esteem - We used the self-perception profile for children (SPPC, age 8–12) and
adolescents (SPPA, age 12–18) to investigate self-esteem. The SPPC consists of 36 items,
divided into six scales: scholastic competence, social acceptance, athletic competence,
physical appearance, behavioral conduct, and global self-worth. The adolescent version
(SPPA) contains 35 items and comprises one additional scale: close friendship. Each item
was presented on a 4-point Likert scale, with higher scores indicating stronger self-esteem.
The SPPC and SPPA have acceptable to good validity and reliability (Cronbach’s alpha Dutch
manual >0.70; Cronbach’s alpha PBTS 0.62–0.91). The manual provided mean scores for
males and females separately. For comparison with the total group of PBTS, scores of males
and females in the normative population were combined after weighting by the gender
distribution in the PBTS group. Age was not taken into account, as the SPPC and SPPA have separate norms based on age.

**Psychosocial adjustment** - The Strengths and Difficulties Questionnaire (SDQ) was used to assess psychosocial adjustment.\(^3\)\(^8\),\(^3\)\(^9\) The items were scored on a 3-point Likert scale. A total problem score was calculated by adding the scores of 20 items, with a higher score indicating more problems. The SDQ total problem score has good validity and reliability (Cronbach’s alpha Dutch controls = 0.70; Cronbach’s alpha PBTS = 0.77).\(^3\)\(^9\) Dutch norms were available for children aged 11–16 years; therefore, analyses on the SDQ were restricted to PBTS aged 11–16 years. The gender distribution did not differ between the Dutch normative group and the PBTS, but mean age of the normative population was lower than of the PBTS. However, since total problem score is not affected by age, age was not taken into account in the analysis.

**Fatigue** - Fatigue was measured with the checklist individual strength (CIS).\(^4\)\(^0\) The CIS is a questionnaire that measures fatigue-related problems and consists of 20 items, scored on a 7-point Likert scale. The four subscales were subjective fatigue, concentration, motivation, and physical activity. A total score was calculated by summing up all items. Higher scores indicated more fatigue-related problems. The CIS has good reliability, with Cronbach’s alpha of the sibling controls and the PBTS 0.72–0.94. The data collected in the sibling control group were used for comparison with the PBTS. The sibling control group and the PBTS did not differ significantly (\(p > 0.10\)) in gender and age.

**Parent report**

**Psychosocial adjustment** - The SDQ was used to measure the parental perspective of PBTS’ psychosocial adjustment (see ‘Self-report’ for the description of the questionnaire). Reliability of the total problem score is good (Cronbach’s alpha Dutch controls = 0.70; Cronbach’s alpha PBTS = 0.77).\(^3\)\(^9\) PBTS were compared to a Dutch normative sample of children aged 8–16. The Dutch normative sample did not differ in age and gender from the PBTS (\(p > 0.10\)).

**Executive functioning** - Parents rated their child’s behavioral executive functioning using the behavior rating inventory of executive function (BRIEF).\(^4\)\(^1\) The BRIEF contains 75 items, scored on a 3-point Likert scale. The scores were summarized in eight scales (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. The raw scores of the scales and indices were transformed into age- and gender-specific standardized T scores, as provided in the manual, with a mean of 50 and a standard
deviation of 10. Higher scores indicated more problems. Validity and reliability range from good to excellent, with Cronbach’s alphas reported in the manual between 0.78 and 0.96 and Cronbach’s alphas of the PBTS between 0.66 and 0.94.\(^\text{42}\)

**Teacher report**

*Psychosocial adjustment* - The SDQ was used to measure the teacher perspective of psychosocial adjustment of the PBTS (see ‘Self-report’ for the description of the questionnaire). The reliability of the total problem score of the teacher report is reported to be good (Cronbach’s alpha Dutch controls = 0.88; Cronbach’s alpha PBTS = 0.77).\(^\text{39}\) A Dutch normative population of children aged 8–11 was available; therefore, the answers from teachers of PBTS within that age range were analyzed. The total problem score was analyzed separately for females and males, because the PBTS sample had more females than the normative population. The mean age of the Dutch normative population did not differ from the mean age of the PBTS aged 8–11.

*Executive functioning* - The BRIEF teacher-report version measures executive functioning of PBTS in the school situation (see ‘Parent-report’ for the description of the BRIEF). Validity and reliability are good to excellent, with Cronbach’s alphas ranging from 0.88 to 0.98 as reported in the manual and between 0.82 and 0.97 of the PBTS.\(^\text{42}\)

**Statistical analyses**

All analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). To be able to detect possible confounders, one-sample *t* tests (age) and binomial tests (gender) were performed to test differences between PBTS and the normative population. Independent-samples *t* tests (age) and Chi-square tests (gender, country of birth, education) were used to test differences between PBTS and sibling controls. A *p* value of <0.10 was considered statistically significant for these analyses.

Differences between the participating PBTS and the subsample of 45 non-participating PBTS were tested with one-sample *t* tests (age at assessment, age at diagnosis, time since diagnosis), binomial tests (gender, tumor grade, tumor location, treatment, and hydrocephalus), or Chi-square test (tumor type).

One-sample *t* tests were used to evaluate differences between PBTS and the normative population regarding self-reported HRQOL, self-esteem, and regarding psychosocial adjustment, and proxy-reported psychosocial adjustment and executive functioning. Self-reported fatigue was analyzed with independent-samples *t* test (PBTS vs. sibling controls).

Effect sizes were calculated in terms of Cohen’s *d*, with 0.20, 0.50, and 0.80, reflecting small, medium, and large effect sizes, respectively.\(^\text{43}\) To adjust for multiple testing, Bonferroni correction was applied to the significance levels, as follows: HRQOL and self-esteem
8–11 years 0.05/6 = 0.008; self-esteem 12–18 years 0.05/7 = 0.007; fatigue 0.05/5 = 0.01; indices/total executive functioning 0.05/3 = 0.016; scales executive functioning 0.05/8 = 0.006. Differences with p values <0.05 in combination with effect size >0.35 were considered to be trends.

RESULTS

Participants
The inclusion flowchart is depicted in Fig. 1. One enrolled PBTS, three enrolled siblings, and three teachers of enrolled PBTS did not complete the questionnaires. Self-report data were therefore available for 81 PBTS, 40 siblings, and teacher-report data for 73 PBTS. Characteristics of the participating PBTS, the sibling control group and the non-participating PBTS are depicted in Table 1. Regarding the demographics, 20 of the participating PBTS received special education (24%) and 39 have been held back a class (48%). The participating and non-participating PBTS were comparable in age at assessment, gender, and education (p > 0.062). Participants and non-participants did not differ in tumor location, but they did differ with regard to the distribution of tumor grade, with more high-grade tumors in the participants than in the non-participants (p < 0.05). The participants were younger at diagnosis (p < 0.05) and had a longer interval past diagnosis than the non-participants (p < 0.05). More participating than non-participating PBTS underwent radiotherapy (p < 0.05) and chemotherapy (p = 0.001). The participating PBTS and the sibling control group were comparable in age, gender, parental country of origin, and the highest level of parental education (p > 0.324).

Outcomes
In Tables 2 and 3, the results of the self-report and proxy-report questionnaires’ analyses are displayed, respectively. Figure 2 is a graphical summary of the results (effect sizes) from Tables 2 and 3, showing the profile of psychosocial functioning in PBTS. For self-esteem, average effect sizes are depicted, weighted by the number of PBTS who completed the SPPC and SPPA.
**Table 1.** Demographics and medical information of participating pediatric brain tumor survivors, sibling controls, and non-participating pediatric brain tumor survivors

<table>
<thead>
<tr>
<th></th>
<th>PBTS participants</th>
<th>Controls</th>
<th>PBTS non-participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 82</td>
<td>n = 43</td>
<td>n = 45</td>
</tr>
<tr>
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<td></td>
<td></td>
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<tr>
<td>Age at assessment</td>
<td>13.85 3.15</td>
<td>14.27 2.44</td>
<td>14.28 3.04</td>
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<tr>
<td>Age diagnosis</td>
<td>6.87 3.77</td>
<td>–</td>
<td>8.23 3.95</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>6.98 3.57</td>
<td>–</td>
<td>6.05 3.31</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>40 49</td>
<td>17 26</td>
<td>58</td>
</tr>
<tr>
<td>Country of origin mother</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>71 87</td>
<td>37 14</td>
<td>n/a n/a</td>
</tr>
<tr>
<td>Other</td>
<td>11 13</td>
<td>9 14</td>
<td>n/a n/a</td>
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<tr>
<td>Country of origin father</td>
<td></td>
<td></td>
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<tr>
<td>Netherlands</td>
<td>73 89</td>
<td>40 93</td>
<td>n/a n/a</td>
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<tr>
<td>Other</td>
<td>9 11</td>
<td>3 7</td>
<td>n/a n/a</td>
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<td>Highest education parent(^a)</td>
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<td></td>
<td></td>
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<tr>
<td>Low or Intermediate</td>
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<td>23 54</td>
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<tr>
<td>High</td>
<td>43 52</td>
<td>20 46</td>
<td>n/a n/a</td>
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<tr>
<td><strong>Education</strong></td>
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<tr>
<td>Regular education</td>
<td>62 80</td>
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<td>28 62</td>
</tr>
<tr>
<td>Special education</td>
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<td>n/a</td>
<td>11 24</td>
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<td>Unknown</td>
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<td>n/a</td>
<td>6 13</td>
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<td><strong>Tumor type and grade</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>34 42</td>
<td>–</td>
<td>13 29</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>12 15</td>
<td>–</td>
<td>6 13</td>
</tr>
<tr>
<td>Supratentorial PNET</td>
<td>8 10</td>
<td>–</td>
<td>2 4</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>5 6</td>
<td>–</td>
<td>2 4</td>
</tr>
<tr>
<td>Astrocytoma gr III</td>
<td>5 6</td>
<td>–</td>
<td>1 2</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>4 5</td>
<td>–</td>
<td>2 4</td>
</tr>
<tr>
<td>Low grade</td>
<td>48 59</td>
<td>–</td>
<td>32 71</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>35 43</td>
<td>–</td>
<td>26 58</td>
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<tr>
<td>Craniopharyngioma</td>
<td>7 9</td>
<td>–</td>
<td>5 11</td>
</tr>
<tr>
<td>Plexus papilloma</td>
<td>6 7</td>
<td>–</td>
<td>1 2</td>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Radiotherapy</td>
<td>34 42</td>
<td>–</td>
<td>14 31</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>35 43</td>
<td>–</td>
<td>12 27</td>
</tr>
<tr>
<td>Surgery(^b)</td>
<td>72 88</td>
<td>–</td>
<td>41 91</td>
</tr>
<tr>
<td>Other</td>
<td>2 2</td>
<td>–</td>
<td>1 2</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>1 1</td>
<td>–</td>
<td>1 2</td>
</tr>
<tr>
<td>CSF pressure relief only</td>
<td>1 1</td>
<td>–</td>
<td>0 0</td>
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Psychosocial effects of pediatric brain tumors

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Location</td>
<td></td>
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<tr>
<td>Supratentorial</td>
<td>46</td>
<td>56</td>
<td>–</td>
<td>–</td>
<td>22</td>
<td>49</td>
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<td>Infratentorial</td>
<td>36</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>23</td>
<td>51</td>
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<tr>
<td>Yes</td>
<td>39</td>
<td>48</td>
<td>–</td>
<td>–</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>52</td>
<td>–</td>
<td>–</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

The information was available for 45 of 71 non-participating PBTS. The siblings did not differ significantly from the participating PBTS on any of the variables. The non-participating PBTS differed from the participants on age at diagnosis, time since diagnosis, tumor type, tumor grade, radiotherapy and chemotherapy.

PBTS pediatric brain tumor survivors, M mean, SD standard deviation, n/a not available

* p < .05; ** p < .001

aHighest education of father or mother is reported: Low or Intermediate = Primary education, general secondary education and secondary vocational education; High = Higher vocational education and university

b37 patients were treated with surgery only
### Table 2. Psychosocial functioning of the pediatric brain tumor survivors compared to the controls; self-report

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>PBTS</th>
<th>Controls</th>
<th>Group differences</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>HRQOL—KIDSCREEN-27/Kidscreen-10</td>
<td>81</td>
<td>46.69</td>
<td>9.69</td>
<td>52.88</td>
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<tr>
<td>Physical well-being</td>
<td>81</td>
<td>49.09</td>
<td>9.09</td>
<td>52.79</td>
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<tr>
<td>Psychological well-being</td>
<td>81</td>
<td>51.99</td>
<td>8.21</td>
<td>53.95</td>
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<tr>
<td>Autonomy and parents</td>
<td>81</td>
<td>49.11</td>
<td>10.94</td>
<td>52.36</td>
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<tr>
<td>Peers and social support</td>
<td>78</td>
<td>51.08</td>
<td>8.70</td>
<td>53.06</td>
</tr>
<tr>
<td>School environment</td>
<td>78</td>
<td>49.55</td>
<td>8.32</td>
<td>54.10</td>
</tr>
<tr>
<td>Generic (Kidscreen-10)</td>
<td>81</td>
<td>14.79</td>
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<tr>
<td>Self-esteem—SPPC (8–12)</td>
<td>24</td>
<td>18.33</td>
<td>3.91</td>
<td>17.55</td>
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<tr>
<td>Scholastic competence</td>
<td>24</td>
<td>16.08</td>
<td>4.24</td>
<td>17.88</td>
</tr>
<tr>
<td>Social acceptance</td>
<td>24</td>
<td>20.67</td>
<td>3.50</td>
<td>19.24</td>
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<tr>
<td>Behavioral conduct</td>
<td>24</td>
<td>20.29</td>
<td>3.58</td>
<td>17.72</td>
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<tr>
<td>Global self-worth</td>
<td>24</td>
<td>20.63</td>
<td>3.32</td>
<td>19.55</td>
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<tr>
<td>Self-esteem—SPPA (12–18)</td>
<td>57</td>
<td>13.23</td>
<td>2.93</td>
<td>13.88</td>
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<tr>
<td>Scholastic competence</td>
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<td>15.14</td>
<td>2.97</td>
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<tr>
<td>Social acceptance</td>
<td>57</td>
<td>12.37</td>
<td>4.26</td>
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<td>Athletic competence</td>
<td>57</td>
<td>13.67</td>
<td>3.50</td>
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<td>Physical appearance</td>
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<td>15.49</td>
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<td>14.24</td>
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<tr>
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<td>16.47</td>
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<tr>
<td>Global self-worth</td>
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<td>15.28</td>
<td>3.71</td>
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<tr>
<td>Close friendship</td>
<td>57</td>
<td>15.28</td>
<td>3.71</td>
<td>15.52</td>
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<tr>
<td>Psychosocial adjustment—SDQ (11–16)</td>
<td>48</td>
<td>10.02</td>
<td>5.09</td>
<td>9.90</td>
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<tr>
<td>Total problem score</td>
<td>48</td>
<td>20.53</td>
<td>10.75</td>
<td>10.02</td>
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<tr>
<td>Fatigue—CIS41</td>
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<td>23.57</td>
<td>11.16</td>
<td>20.53</td>
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<tr>
<td>Subjective fatigue</td>
<td>76</td>
<td>19.09</td>
<td>7.78</td>
<td>14.45</td>
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<tr>
<td>Concentration</td>
<td>76</td>
<td>11.29</td>
<td>4.91</td>
<td>9.82</td>
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<tr>
<td>Motivation</td>
<td>76</td>
<td>9.27</td>
<td>5.00</td>
<td>6.97</td>
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<tr>
<td>Physical activity</td>
<td>76</td>
<td>63.23</td>
<td>21.80</td>
<td>57.76</td>
</tr>
</tbody>
</table>

Significant differences after Bonferroni correction are presented in bold. Effect sizes ‘d’ were calculated by dividing the difference in mean score between the PBTS and the normative population or sibling controls by the pooled standard deviation. Lower scores reflect worse HRQOL and Self-Esteem. Higher scores reflect more problems on Psychosocial adjustment and fatigue.

*PBTS* pediatric brain tumor survivors, *HRQOL* health related quality of life, *M* mean, *SD* standard deviation

*Sibling controls. n = 40*
## Table 3. Psychosocial functioning of the pediatric brain tumor survivors compared to the controls; proxy report

<table>
<thead>
<tr>
<th></th>
<th>PBTS</th>
<th>Controls</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Parent report</strong></td>
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<td></td>
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</tr>
<tr>
<td>Psychosocial adjustment—SDQ (8–16)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total problem score</td>
<td>67</td>
<td>11.01</td>
<td>5.16</td>
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<tr>
<td>Behavioral executive functioning—BRIEF</td>
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<td></td>
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<tr>
<td>Behavioral index</td>
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Significant differences after Bonferroni correction are presented in bold. Effect sizes ‘d’ were calculated by dividing the difference in mean score between the PBTS and the normative population by the pooled standard deviation. Higher scores reflect worse psychosocial adjustment and behavioral functioning.

PBTS pediatric brain tumor survivors, M mean, SD standard deviation.
Figure 2.
Profile of psychosocial functioning in pediatric brain tumor survivors in standardized effect sizes as compared to the mean of the control group (0.00). *Significant difference between PBTS and controls after the Bonferroni correction, effect sizes presented in red and bold. Note. Effect sizes 'd' were calculated using the pooled standard deviation. Scores have been adjusted in a way that for all domains, lower scores reflect worse psychosocial functioning. For self-esteem, weighted average effect sizes of the SPPC and SPPA are depicted. For teacher report of psychosocial adjustment (SDQ), scores for males and females are reported separately due to more females in our sample as compared to the control group. HRQOL = health-related quality of life, physical = physical well-being subscale of the Kidscreen-27, psych = psychological well-being subscale of the Kidscreen-27, autonomy = autonomy and parents subscale of the Kidscreen-27, peers = peers and social support subscale of the Kidscreen-27, school = school environment subscale of the Kidscreen-27, generic = generic health-related quality of life subscale of the Kidscreen-10, scholastic = scholastic competence subscale of the SPPC/SPPA, social = social acceptance subscale of the SPPC/SPPA, athletic = athletic competence subscale of the SPPC/SPPA, appearance = physical appearance subscale of the SPPC/SPPA, conduct = behavioral conduct subscale of the SPPC/SPPA, self-worth = global self-worth subscale of the SPPC/SPPA, friendship = close friendship subscale of the SPPA, psy adj = psychosocial adjustment, total score SDQ, fatigue = subjective fatigue subscale of the CIS, concentr = concentration subscale of the CIS, motivation = motivation subscale of the CIS, activity = physical activity subscale of the CIS, behavioral EF = behavioral executive functioning BRIEF, behavioral = behavioral regulation index of the BRIEF, metacog = metacognition index of the BRIEF. (Color figure online)
Self-report

HRQOL - PBTS showed significantly worse HRQOL than the normative sample \((p < 0.008)\) on 2 subscales of the Kidscreen-27: physical well-being and psychological well-being, and on the generic scale (medium-to-large effect sizes). A tendency toward lower HRQOL in PBTS than the norm was found for peers and social support \((p < 0.05; \text{ medium effect size})\).

Self-esteem - PBTS aged 8–11 years obtained significantly higher behavioral conduct scores compared to the normative population \((p < 0.008, \text{ large effect size})\), indicating higher self-esteem regarding their behavior; PBTS aged 12–18 tended toward higher self-esteem on this scale \((p < 0.05, \text{ medium effect size})\). A trend toward lower self-esteem in PBTS aged 8–11 was found for scholastic competence and for athletic competence, and also for athletic competence of PBTS aged 12–18 \((p < 0.05, \text{ medium effect size})\). No differences between the normative population and the PBTS were observed on the other scales.

Psychosocial adjustment - PBTS between 11 and 16 years of age did not experience more psychosocial adjustment problems than the normative population as shown by their total problem score of the SDQ.

Fatigue - PBTS reported more concentration problems than the sibling control group \((p < 0.01, \text{ medium effect size})\). A trend toward decreased physical activity in PBTS compared to the sibling control group was found as well as a trend toward a higher total scale compared to the siblings \((p < 0.05, \text{ medium effect sizes})\), indicating more fatigue-related problems. The PBTS did not differ from the siblings on subjective fatigue and motivation problems.

Parent report

Psychosocial adjustment - The parent-reported total problem score of psychosocial adjustment (SDQ) was higher in the PBTS than in the norm \((p < 0.001, \text{ large effect size})\), indicating more problems in psychosocial adjustment.

Executive functioning - Parents of PBTS considered their children’s behavioral expressions of executive functioning to be significantly worse than parents in the normative population. More specifically, PBTS had lower scores regarding the two indices and the total score \((p < 0.016; \text{ medium effect sizes})\). Subsequent analyses showed worse functioning on the scales’ emotional control, and on initiate and working memory \((p < 0.006; ds 0.47, 0.59, \text{ and } 0.71, \text{ respectively})\). No significant differences were found on the other subscales.
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Teacher report

Psychosocial adjustment - For the female PBTS aged 8–11 years (n = 9), teachers reported significantly higher total problem scores (SDQ) than the norm (p < 0.01, large effect size). No difference was found between the male PBTS (n = 21) and the males in the normative population.

Executive functioning - According to the teacher report, no differences were found between the PBTS and the normative population on the indices and the total score of the BRIEF.

DISCUSSION

This study provides the first multidimensional (self-, parent- and teacher report) view of psychosocial functioning of PBTS with parent-reported neurocognitive complaints. The multidimensional approach is an advantage of the study because of the symptom burden of patients and complexity of their social situation. PBTS showed decreased psychosocial functioning on a number of the tested domains: self-reported HRQOL and fatigue, parent-reported psychosocial adjustment and executive functioning, and teacher-reported psychosocial adjustment for females only. These results are in line with a study by Meeske et al., who reported PBTS to exhibit problems in physical, social, psychosocial, school, cognitive domains, and fatigue. The decreased HRQOL scores of PBTS on psychological well-being may be caused by the neurocognitive complaints from which they suffer. This is supported by the trend we found toward lower self-esteem regarding scholastic competence the PBTS show and by the literature. This should be further studied in future studies. However, despite the neurocognitive complaints, PBTS functioned within normal ranges in several psychosocial domains or showed only trends toward worse functioning: self-reported self-esteem and psychosocial adjustment, and teacher-reported executive functioning and psychosocial adjustment for males.

Physical functioning was specifically compromised in PBTS. Besides worse physical HRQOL, a tendency toward decreased self-reported athletic competence (domain of self-esteem) and decreased physical activity (domain of the fatigue questionnaire) was observed. It is known that PBTS are at increased risk of functional impairments, which is related to physical self-esteem. It is important that professionals working with PBTS are aware of these possible late effects and monitor physical well-being in relation to self-esteem and HRQOL.

Regarding self-esteem, no problems other than the trends toward physical-related and scholastic-related problems were seen. PBTS behavioral conduct scores were even better than the norm. This positive finding has been observed previously, e.g., after a trauma, but has recently also received attention in pediatric oncology literature. It has been attributed, among other factors, to the resilience of the PBTS and posttraumatic growth.
The PBTS in our sample did not report more psychosocial adjustment problems as assessed with the SDQ than their peers, in contrast with parents and teachers who did report psychosocial adjustment problems in PBTS. This finding is not surprising, as in the literature it has been found that both healthy children and childhood cancer survivors typically report different levels of psychosocial problems than their parents and/or teachers. Some studies found child-reported levels of problems to be higher than parent- and/or teacher-reported levels, while other studies found the opposite. Sato et al. concluded that parent and child ratings are influenced by different factors. Among others, parents’ perception was influenced by their level of distress, whereas the child’s perception tended to be dependent on trait anxiety. Others found that childhood cancer survivors may report less psychosocial problems influenced by social desirability, stress-related growth, or a positive coping strategy. In this study, the diagnosis and treatment resulting neurocognitive consequences might have led to increased parental distress, causing parents to report more problems than their children. Another possible reason for the discrepancy between the observed scores of the different informants in our study is the age difference in self-reports versus parent and teacher reports concerning psychosocial adjustment: Due to age-restricted normative data, the results on the self-reported SDQ were based on PBTS aged 11–16 (n = 48), whereas parent- and teacher-reported results were based on PBTS aged 8–16 (n = 67) and 8–12 (n = 30), respectively.

Teachers reported no executive problems in PBTS, whereas parents did, especially regarding emotional control, initiation, and working memory. This discrepancy could be the result of the ‘observation environment.’ Teachers observed the PBTS in a school environment, which is more structured than the home situation. Possibly, the problems parents saw at home did not exist in the same way in structured settings like school. Turner and colleagues describe problems of PBTS to increase as they leave the structured school environment. This implies that PBTS may benefit from a structured environment. Another reason for the difference between the parent and teacher perspective could be that they have a different reference background. Parents know the child’s premorbid functioning, whereas teachers have the behavior of classmates as a reference. A large proportion of the children in our sample were in special education (24%), where many classmates suffered from chronic conditions, which could also affect psychosocial functioning.

This study has some limitations to take into account. The results are not generalizable to the PBTS population as a whole, since PBTS in this study were selected on the basis of parent-reported neurocognitive problems and the willingness to participate in a study of a treatment aimed to improve neurocognitive functioning. This may have led to an overestimation of the psychosocial problems. It is easy to consider this a non-representative sample, but we have to take into account that many children with a brain tumor suffer from neurocognitive problems (40–100%). Therefore, this study sheds light on a vulnerable group of PBTS.
Chapter 5

Awareness for their psychosocial functioning from a complementary perspective is of utmost importance. Another limitation of the study is that normative data were not available for all questionnaires within all age groups. So for some outcomes, especially the SDQ, comparison with the normative population was possible for only small subgroups of PBTS. This limits the reliability and generalizability of the results. For this reason, we would like to urge future studies to aim at collecting norm data for broader age ranges. Nevertheless, this study adds to the existing knowledge as it provides a broad, multidimensional profile of functioning of PBTS with neurocognitive complaints, based on multi-informants.

Better insight into psychosocial functioning in the growing group of PBTS with neurocognitive complaints will help professionals to identify those patients susceptible to developing psychosocial problems. Timely identification is important to prevent problems from escalating. Screening for possible psychosocial late effects should be done in a systematic way, preferably by using the perspective of the patient, parent, and teacher. In daily clinical practice, patient- and/or parent-reported outcomes (PROs) are recommended, because this will increase awareness of and attention for psychosocial functioning during routine checkups. Increased awareness can improve provision of aftercare. Furthermore, providing tailored support to this group of vulnerable children is necessary. Interventions for PBTS with (imminent) psychosocial problems should be aimed at improving HRQOL, coping with fatigue, and providing structure in daily life.
Psychosocial effects of pediatric brain tumors

REFERENCES


Psychosocial effects of pediatric brain tumors


The association between the behavior rating inventory of executive functioning and neurocognitive testing in children diagnosed with a brain tumor

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Marieke A. de Ruiter
Kim J. Oostrom
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Heleen Maurice-Stam
Jaap Oosterlaan
Martha A. Grootenhuis

Submitted for publication
**ABSTRACT**

Aim: Pediatric Brain Tumor Survivors (PBTS) suffer from cognitive late effects, such as worse Executive Functioning (EF), which might worsen over time and influence daily life. It is important to screen for these late effects. While EF-tasks measure cognitive (dys)function, questionnaires (e.g., the Behavior Rating Inventory of Executive Function; BRIEF) assess daily life consequences of cognitive (dys)function. We explored the suitability of the BRIEF as screener for EF-problems in PBTS by assessing the relationship between the BRIEF and EF-tasks. We also investigated the association between the BRIEF-Parent and BRIEF-Teacher, and explored the clinical utility.

Methods: Eighty-two PBTS (8-18 years) were assessed with EF-tasks measuring attention (Attention Network Test; ANT), cognitive flexibility (ANT), inhibition (Stop Signal Task; SST), visual memory (Visual Sequencing Task; VST), and working memory (WM; Digit Span). The BRIEF-Parent and BRIEF-Teacher measured daily EF-problems. We studied the Pearson’s correlations between the BRIEF and EF-tasks, and between BRIEF-Parent and BRIEF-Teacher.

Results: The BRIEF-Parent related poorly to EF-tasks ($rs<.26$, $ps>.01$), but several subscales of the BRIEF-Teacher related significantly to some EF-tasks (WM-scale, Monitor-scale, Behavioral Regulation Index, Total score, and Meta-cognition Index ($rs>.31$, $ps<.01$)). Only the Inhibit-scales of the BRIEF-Parent and BRIEF-Teacher correlated significantly ($r=.33$, $p<.01$). Children with clinically elevated scores on BRIEF-scales that correlated with EF-tasks, performed worse on all EF-tasks than children without clinically elevated BRIEF-scores ($ds$ 0.56–1.23, $ps<.05$).

Conclusions: Although subscale-scores might capture separate functions insufficiently, Total and Index-scores may capture general EF. The BRIEF-Teacher might better screen EF in PBTS than the BRIEF-Parent.
INTRODUCTION

Survival rates of children who have been treated for a brain tumor have increased in the last decades due to improved diagnostic and neurosurgical techniques, radiation therapy and chemotherapy. The 5-year survival rate has risen from 57% (1975-1977) up to 74% (2004-2010). This increasing survival rate comes with a cost; childhood brain tumors and their treatment have long lasting developmental consequences, particularly in the cognitive domain. The brain tumor and its treatment may provoke a cascade of cognitive consequences, with immediate consequences followed by impaired cognitive skills that have yet to emerge, leading to the children to ‘grow into deficit’. To screen for changes in cognitive functioning over time, it is important that PBTS undergo cognitive assessment systematically to obtain information on the nature, severity, and course of cognitive consequences. ‘Screening’ protocols based on international requirements as formulated in Société Internationale d’Oncologie Pédiatrique (SIOP) and the Children’s Oncology Group (COG) include comprehensive cognitive assessment. However, as this is time and resource intensive, this is not always feasible. It might be preferable to conduct brief, repeated assessments, or screen all PBTS regularly with a questionnaire, and extensively examine only those children who report cognitive problems.

Tasks and questionnaires that measure cognitive functioning cannot simply replace each other. EF tasks are designed to measure cognitive (dys)function, whereas questionnaires assess the consequences of the (dys)function in daily life. However, to reliably screen for cognitive (dys)function with a questionnaire, the outcomes of questionnaire should correlate to cognitive tasks for which psychometric properties have been determined. PBTS are known to show deficits in executive functioning (EF). Executive functions are those cognitive functions that are needed to adapt behavior to varying demands of the environment, and are comprised of a multitude of cognitive functions, including working memory (WM), inhibition, and cognitive flexibility. The Dutch Behavior Rating Inventory of Executive Function (BRIEF) is a standardized questionnaire to measure daily life EF. Findings on the correlation between the BRIEF and EF tasks vary widely (0 – 50% significant correlations, \( r = 0 \ldots .48 \)) in both clinical (neurological or psychiatric) and healthy control groups. However, the BRIEF-WM parent-report scale correlates significantly to WM tasks in PBTS. Given that EF demands differ per context, e.g. home versus school, it is particularly interesting to study the relation between the BRIEF-Parent and BRIEF-Teacher. Teachers might be better able to evaluate EF than parents, as EF correlates to academic skills, and teachers have a professional background to evaluate academic skills. Indeed, BRIEF-Teacher scores appear strongly correlated to school functioning, while small to medium-sized associations have been reported between BRIEF-Parent scores and school functioning.
We aimed to study whether the BRIEF-Parent, and/or BRIEF-Teacher are adequate screening instruments for EF problems in PBTS. To do so, we first studied the correlations between the BRIEF (Parent and Teacher) and a battery of EF tasks measuring attention, cognitive flexibility, inhibition, visual-, and verbal memory, on which PBTS show difficulties. Secondly, we examined the correlation and tested group differences between the scores on the BRIEF-Parent and the BRIEF-Teacher. Thirdly we explored the clinical utility of the findings by testing whether children who obtained clinically elevated scores (T score > 65) on either the BRIEF-Parent or BRIEF-Teacher, also scored worse on the EF tasks.

METHODS

Participants
Eighty-two children (8-18 years) diagnosed with a brain tumor participated in the cohort of the PRISMA study. Inclusion criteria for the PRISMA study consisted of having finished treatment at least two years prior, being able (mentally and physically) to undergo cognitive assessment, and parent-reported cognitive problems (a score > 14 on the attention scale of the Disruptive Behavior Disorders Rating Scale [DBDRS], or if parents indicated at least two problems with respect to attention, memory, speed, and information processing). Exclusion criteria were a premorbid attention disorder diagnosis or being non-fluent in Dutch language. See Table 1 for demographic and medical details.

Procedure
The data collection of the current cross-sectional study was part of the baseline assessment of a randomized controlled trial on neurofeedback for PBTS. Data collection took place between 2010 and 2012. The study was approved by the Medical Ethical Committee of the Academic Medical Center (METC 09/137). Children were recruited through 5 Dutch academic hospitals (Emma Children’s Hospital/Academic Medical Center Amsterdam, the Vrije Universiteit Medical Center Amsterdam, the University Medical Center Utrecht, the Radboud University Medical Center Nijmegen, and the Maastricht University Medical Center). After receiving an information letter, parents were asked to fill out online screening questionnaires (see Participants) concerning inclusion and exclusion criteria. Informed consent was signed by the parents and children. Next, parents filled out the BRIEF online and indicated which teacher was most suitable to evaluate the child’s functioning; usually a mentor or otherwise the teacher spending most time with the children. Teachers were contacted by email, and filled out the BRIEF online. Children’s EFs were tested in a quiet room by trained examiners, and tests were administered in a fixed order. The total testing time was approximately 150 minutes, and regular breaks were taken to avoid fatigue.
## Table 1. Participants’ demographic and clinical characteristics

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Chapter 6

MEASURES

**EF questionnaires**
To measure EF problems in daily life the Dutch parent and teacher version of the BRIEF⁶ were administered. The BRIEF (75 items, 3-point Likert scale) includes a Total score and two indices, subdivided into eight subscales. The Behavior Regulation index consists of the subscales Inhibit, Shift, and Emotional control. The Meta-Cognition Index consists of Initiate, WM, Plan/Organize, Organization of Materials, and Monitor. The BRIEF parent and teacher version has good test-retest stability and high internal consistency in the general population (Cronbach’s αs BRIEF-Parent .78-.96; BRIEF-Teacher .88—.98),⁷ as well as in PBTS (Cronbach’s αs BRIEF-Parent .66-.94; BRIEF-Teacher .82-.97).¹³,¹⁴ The BRIEF is validated with the Child Behavior Checklist,¹⁵ the Disruptive Behavior Disorder rating scale,¹² and the Diagnostic Interview Schedule for Children.¹⁶,¹⁷ Moreover, both convergent and divergent validity were adequate and in the expected direction (medium to large correlations with the Child Behavior Checklist¹⁵ and the Disruptive Behavior Disorders Rating Scale).¹⁸ The age-, and gender standardized T-scores on the subscales, Index scores, and Total score were used as outcome measures. Higher scores indicate more problems. A T-score > 65 is considered a clinically elevated score.⁷

**EF tasks**
*Attention and cognitive flexibility*
To measure several components of attention we administered an adapted version of the Attention Network Test ANT.¹⁹ The ANT measures three subdomains of attention: Alerting (maintaining an alert state), Orienting (selecting information from sensory input), and Executive control (resolving conflict among responses).¹⁹ In the current version,²⁰ on each trial a picture of a ship appears on the right or the left side of the computer screen and the child has to respond by pressing the corresponding key. In the different trials, the ship is preceded by different cues. The different trial types measure the before mentioned subdomains of attention; 1) A palm tree appears before the ship appears (neutral cue); 2) No cue, only the ship appears (alerting; the participant has to stay alert without any triggers); 3) A parrot pointing in the direction where the ship will appear precedes the appearance of the ship (orienting cue) and 4) A parrot pointing in the opposite direction of where the ship will appear precedes the appearance of the ship (executive cue). The difference in reaction times between the neutral cue (1) and other cues is used as a measure of the subdomains of attention. The ANT consists of 312 trials. The standard deviation (SD) divided by mean reaction time of the alerting trials (2) is used as a measure of inattention (the intra individual coefficient of variation [IICV]), and the reaction time on the executive trials is used as a measure of cognitive flexibility. The ANT can be considered a valid measure of
the three different subdomains of attention, as the three corresponding distinct subcortical anatomical networks are activated during task performance. Higher scores indicate worse functioning.

**Inhibition**

To measure inhibition an adaptation of the Stop Signal Task was administered. The Stop Signal Task is a cognitive inhibition task (as compared to a motivational inhibition task) with a medium to high temporal stability, and discriminates well between typically developing children and children with an impulse control disorder. A picture of an airplane appears on the computer screen, facing left or right. The child has to press a corresponding key. In 25% of the trials a cross on top of the airplane indicates that the response has to be inhibited. The time between stimulus and stop signal (stop signal delay) is adapted to the child’s performance throughout the task, to accomplish about 50% correct stop trials. The outcome measure is the stop-signal reaction time (SSRT); the time the child needs to inhibit his/her response. De Zeeuw (2008) explains: ‘SSRT was estimated using the race model in which the go process and the inhibitory process are conceived of as competing processes (see De Zeeuw, 2008 for more details). Whether a response will be executed or inhibited in a stop trial depends on which of these processes “wins” the race. In the case in which 50% of stop trials result in successful stopping, the mean stop signal delay is where both the stop and the go processes have equal probability of “winning” the race (i.e., the mean go process duration [mean reaction time] and the sum of the mean stop signal delay plus the duration of the stop process [SSRT] are approximately equal). It follows that SSRT can be calculated using the equation SSRT = mean reaction time - mean stop signal delay.’ A higher score indicates worse inhibition.

**Visual short-term memory**

To measure visual short-term memory the valid and reliable Visual Sequencing Task was administered to the children. In a four by four grid a sequence of dots lights up and has to be repeated on a touch screen. The length of the sequence ranges from two to nine, with four trials per sequence, divided into two difficulty levels; a level of two relatively simple trials and a level of two relatively difficult trials. After an error on both trials of the same difficulty level, the task is terminated. The total number of correctly repeated sequences was the outcome measure, hence, a higher score indicates a better visual memory.

**Verbal (working) memory**

Digit span from the WISC-III or WAIS-III was administered to measure verbal WM. Digit span correlates significantly with other verbal WM tasks. The participant is asked to verbally repeat sequences of digits (2–9 digits, increasing in length), first in the same order,
and next in the reverse order. The task is terminated after two errors on a difficulty level. The total number of correctly repeated sequences (raw score) was used as the outcome measure. Higher scores indicate a better WM.

**Statistical analyses**

To control for possible non-response bias, we compared BRIEF-Parent, BRIEF-Teacher, and EF task scores of children whose data was complete with children whose data was incomplete using T-tests. For the main analyses we firstly tested whether the BRIEF-Parent and BRIEF-Teacher correlated with the ANT-IICV (attention), Stop Signal Task SSRT (inhibition), Visual Sequencing (visual short-term memory), Digit Span (WM), and ANT-Executive (cognitive flexibility). We were particularly interested in the Pearson’s correlations between BRIEF-scales and EF tasks that aim to measure the same construct; 1) the Inhibit scale, and the Stop Signal Task, 2) the Shift scale, and the ANT-Executive, 3) the WM scale, and Visual Sequencing and Digit Span, and 4) the Monitor scale, and the ANT-IICV. Moreover, we were interested in the Pearson’s correlations of the BRIEF-Parent and BRIEF-Teacher Index and Total scores with the EF tasks.

Secondly, we compared the BRIEF-Parent subscale-, Index-, and Total scores with the BRIEF-Teacher subscale-, Index-, and Total scores using Pearson’s correlations. In addition, a repeated measures ANOVA was performed to study the difference between parent and teacher reports while correcting the analyses for dependency of the parent and teacher reports.

Considering the large number of comparisons, we set the alpha at $p \leq .01$ to control for Type I errors.

Finally, we explored the clinical utility of the findings with independent sample t-tests. We tested whether children who showed any clinically elevated score (T score > 65) on the Index or Total scales of either the BRIEF-Parent or the BRIEF-Teacher, also scored higher on the EF tasks than children without any clinically elevated score. Moreover, we studied EF task performance of children with versus children without T scores > 65 on those BRIEF scales that correlated significantly with the EF tasks. For these explorative analyses we did not correct for multiple testing.

**RESULTS**

**Response**

BRIEF teacher ratings were missing for nine children, and five children did not complete the Stop Signal Task. Children with missing teacher data for the BRIEF scored significantly worse on the parent version of the BRIEF-Parent Monitor scale ($T = 2.8, p = .01$), and children
who did not complete the Stop Signal Task scored worse on the ANT-IICV ($T = 2.5, p = .02$), and Digit span ($T = -2.3, p = .03$).

Correlation of BRIEF-Parent and BRIEF-Teacher with EF tasks

The BRIEF-Parent Total score, Index scores, nor subscales were significantly related to any of the EF tasks ($r = -.24-.26, p > .01$). With respect to expected relations between BRIEF-scales and EF tasks that aim to measure the same construct, the BRIEF-Teacher Inhibit scale was not significantly related to the Stop Signal Task and the Shift scale was not significantly related to the ANT-Executive ($p > .01$), but the WM scale was significantly related to the Visual Sequencing ($r = -.31$) and Digit span ($r = -.36$), and the Monitor scale was significantly related to the ANT-IICV ($r = .35$). The Behavioral Regulation and the Total scale were significantly related to the ANT-IICV and Digit span ($r > .31$). The Meta-cognition Index was significantly related to the ANT-IICV ($r = .41$) and the Stop Signal Task ($r = .31$). Notably, the ANT-IICV was significantly related to all BRIEF-Teacher scales except Shift, Emotional control and Organization of materials; and the BRIEF-Teacher WM-scale was significantly related to all tasks except the ANT-Executive. See Table 2 for all correlations. (Note that all EF tasks were also significantly interrelated $r > .35, p < .01$)
Table 2. Correlation between questionnaires and tasks measuring neurocognitive functioning

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Tasks</th>
<th>Attention</th>
<th>Inhibition</th>
<th>Stop</th>
<th>Signal Task</th>
<th>SSRT(^a)</th>
<th>Visual memory</th>
<th>Working memory</th>
<th>Digit Span(^b)</th>
<th>Cognitive flexibility</th>
<th>ANT-Executive(^a)</th>
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<td></td>
<td>(r)</td>
<td>(r) (N = 77)</td>
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<td>(r)</td>
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<td>(r)</td>
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<td>Scales</td>
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<td>.31(^*)</td>
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</table>

Relation between scores on the BRIEF-Parent and BRIEF-Teacher

Only the Inhibition scales of the BRIEF-Parent and BRIEF-Teacher were significantly related \((r = .33, p < .01)\). The BRIEF-Parent and BRIEF-Teacher scores did not significantly differ on any of the scales, Indexes, nor on the Total scale. See Table 3 for all results.
EF task performance of children with clinical versus non-clinical scores on the BRIEF

We compared children who had a clinically elevated score (T > 65) on one or more of the BRIEF-Parent or BRIEF-Teacher Index scores or Total score, with children who did not have a clinically elevated score on any of these scales. There were no significant differences in EF task performance between children with and without a clinical score (see Table 4).

Based on the correlational findings (Table 3), we explored whether children who had clinically elevated scores (T > 65) on the BRIEF-Teacher WM scale, Index scores, or Total score (the scales that correlated best with the EF tasks) differed in EF task performance from children who did not have clinically elevated scores on these scales. Children with a clinically elevated score performed significantly worse on all EF tasks than children who did not have clinically elevated scores on these scales (d = 0.56 – 1.23, ps < .05; see Table 4).

Table 3. Comparison and correlation of BRIEF-Parent and BRIEF-Teacher T scores

<table>
<thead>
<tr>
<th></th>
<th>BRIEF-Parent</th>
<th>BRIEF-Teacher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Scales</td>
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<td></td>
</tr>
<tr>
<td>Inhibit</td>
<td>51.73</td>
<td>11.03</td>
</tr>
<tr>
<td>Shift</td>
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<td>9.17</td>
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<td>Emotional control</td>
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<td>Initiate</td>
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<td>Behavioral Regulation Index</td>
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<tr>
<td>Meta-cognition Index</td>
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<td>7.99</td>
</tr>
<tr>
<td>Total</td>
<td>53.77</td>
<td>8.38</td>
</tr>
</tbody>
</table>

Note: Higher scores indicate more executive functioning problems, ** p <.01, η² partial eta squared effect size: .01 = small, .06 = medium, .14 = large (Cohen, 1988), effect size of r: .1 = small, .3 = medium, .5 = large (Cohen, 1988)
Table 4. Comparison of EF task performance of children with and without clinical scores on the BRIEF-Parent or BRIEF-Teacher Total or Index scores

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Index scores or Total score BRIEF-Parent/ BRIEF-Teacher</th>
<th>Working memory scale, Index scores, or Total score BRIEF-Teacher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non clinical $N = 45$</td>
<td>Clinical $^5$ (T&gt;65) $N =31$</td>
</tr>
<tr>
<td>Attention ANT-II CV $^0$</td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Inhibition Stop Signal Task SSRT $^1$</td>
<td>256.01 $^{12}$</td>
<td>68.55</td>
</tr>
<tr>
<td>Visual memory Visual Sequencing $^6$</td>
<td>13.44</td>
<td>4.04</td>
</tr>
<tr>
<td>Working memory Digit Span $^7$</td>
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<td>3.49</td>
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<tr>
<td>Cognitive flexibility ANT-Executive $^8$</td>
<td>38.11</td>
<td>40.65</td>
</tr>
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</table>
DISCUSSION

We studied the correlation between parent- and teacher-rated EF problems, and test results on experimental, yet appropriate neuropsychological tasks, designed to assess core executive functions. The aim of our study was to explore whether EF in PBTS can be reliably screened by means of parent or teacher questionnaires, which are less expensive and therefore more feasible than extensive neuropsychological assessment. Parents’ ratings of EF problems were poorly correlated to the EF test performances, but the teachers’ ratings showed several significant correlations of medium size. Correlations between test performances and questionnaire ratings were highest for the compound Total Score on the BRIEF-Teacher. Parents’ and teachers’ ratings were poorly interrelated, though the means of their ratings were not significantly different either. Interestingly, children who showed clinically elevated scores on the BRIEF-Teacher WM scale, Index scale, and/or on the Total scale, performed significantly worse on all EF tasks than children who did not show clinically elevated scores on these scales.

The lack of significant relations between parent rated EFs and EF tasks is notable, particularly as parents appear to report more EF problems as compared to the normative population. One might expect that parents from PBTS could evaluate their child’s EF problems relatively well, as there is often a considerable difference in EF from before diagnosis to after treatment. In contrast, parents from children with a heritable condition, such as attention deficit hyperactivity disorder (ADHD), might consider EF problems less remarkable as they might exist since young age, and often are also seen in other family members. There are a number of explanations for the current poor relation between parent rated EF problems and children’s performance on EF tasks. Firstly, as all currently studied children had parent reported cognitive problems (such as affected attention, memory, speed, and/or information processing, or a clinical score on the attention scale of the DBD-RS), the variance in the parent ratings might have been too low to find correlations with other measures. However, this explanation seems unlikely as the standard deviations (SDs) of the BRIEF in the current study (7.99-12.01) are in line with the BRIEF T-score SDs (10). Secondly, parents of PBTS might condone deviant behavior more easily. This alteration in internal standards, known as response shift, might make parents less apt to rate their child’s EF reliably. On the other hand, teachers might also be prone to response shift, when they know what the child has been through in the past with their illness and the treatment. Finally, besides the advantages of computerized measures (such as ruling out the influence of the assessor, and precise, standardized, and reliably measuring EF), EF tasks may lack ecological validity compared to questionnaires. However, this also applies to teacher reports. The current findings confirm that experienced EF problems in daily life, particularly in the home situation, do not necessarily immediately derive from an assumed underlying cognitive (dys)function as measured with an EF task.
Chapter 6

The relation between teacher EF ratings and EF tasks was somewhat stronger. Teachers might be more competent to rate a child’s behavior, as they have other children in the classroom to compare the child with. This might particularly be true in the current sample, were 24% of the children received special education, with relatively small classes and specialized teachers (although these teachers might be more familiar with problem behavior, as expressed by other children within special education, and their evaluation might be biased). Moreover, teachers observe the child in an academic environment, and specific cognitive functions, such as focused attention, might largely influence schoolwork, but might not notably influence the home situation. Indeed, the BRIEF-Teacher more strongly relates to school functioning than the BRIEF-Parent, and the discrepancy between the parent and teacher reports might actually be meaningful.

There are some notable patterns in the BRIEF-Teacher. Firstly, many subscales of the BRIEF-Teacher were related to the attention task, even though the BRIEF does not include a specific attention scale (and the currently used Monitor scale as a measure of attention is hence negotiable). The current findings suggest that EF problems as reported by teachers might largely be influenced by a child’s attention abilities. Secondly, the BRIEF-Teacher WM scale was related to several EF tasks, and this scale might therefore be considered as a more broad EF measure, or daily experienced WM might be influenced by several underlying EFs. Thirdly, children with clinically elevated scores on the WM-, Index-, or Total scale performed worse on all EF tasks with medium to large effect sizes (note that this was not found with the BRIEF Parent). This suggests that the BRIEF-Teacher might be useful to screen for EF problems, although the explorative character of these findings require replication.

Different informants give distinct information and the use of a specific informant might depend on the goal of an assessment. The current findings suggest that EFs might be better assessed by teachers, but parent ratings should not be ruled out. As the BRIEF-Parent might not be the best measure of EFs in PBTS, alternative questionnaires could be explored to tap EF at home. Questionnaires that could be explored as possible screeners are Pediatric Perceived Cognitive Functioning (Peds-PCF) parent- or self-report, the Childhood Executive Functioning Inventory (CHEXI) parent-report, or the Subjective Awareness of Neuropsychological Deficits for Children (SAND-C) self-report. Self-reports might also give important, distinctive information. As Achenbach and Topplak suggested, it is important to consult multiple informants to get a good view on the behavior, and cognitive functioning of children or adolescents.
CONCLUSIONS

The current findings suggest that the BRIEF-Teacher might be a better screening tool for EFs in PBTS than the BRIEF-Parent. The BRIEF-Teacher does not seem specific enough to capture particular cognitive functions based on the subscales, but the Total and Index scores may be useful measures of general EF functioning. As a subclinical score on the BRIEF-Parent does not indicate that there are no EF problems, solely relying on parent ratings of EF as a screening of EF problems seems unreliable. Procedures to achieve structural screening of PBTS are important to explore, and it is relevant to explore alternative questionnaires.
REFERENCES


Neurofeedback not effective in pediatric brain tumor survivors: Results of a double-blind randomized placebo-controlled trial

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European Journal of Cancer 2016, 64, 62-73
Chapter 7

ABSTRACT

Background: Many paediatric brain tumour survivors (PBTS) suffer from neurocognitive impairments. Promising effects of neurofeedback (NF) on neurocognitive functioning have been reported, however research into NF for PBTS has not been conducted. We investigated the effects of NF on neurocognitive functioning in PBTS using a double-blind randomised placebo-controlled trial with a parallel-group design (Pediatric Research on Improving Speed, Memory, and Attention; the PRISMA study).

Methods: Eligible for inclusion were PBTS with neurocognitive complaints, aged 8–18 years, >2 years post-treatment. They were recruited from five medical centres in the Netherlands. A randomisation table assigned participants to 30 sessions (two per week) of either NF or placebo feedback (PF) (ratio 1:1). Participants, parents, trainers, and researchers handling the data were blinded to group assignment. Participants were assessed pre-, post- and 6 months post-training to determine whether NF training would lead to improved functioning as compared with PF training. Primary outcome measures were attention, processing speed, memory, executive functioning, visuomotor integration, and intelligence. Linear mixed models analyses were used to test differences between NF and PF training over time.

Results: A total of 82 children were enrolled (mean age 13.9 years, standard deviation = 3.2, 49% males); 80 participants were randomised (NF: n = 40, PF n = 40); 71 participants completed the training (NF: n = 34, PF: n = 37); 68 participants completed training and 6 months post-training assessment (NF: n = 33, PF: n = 35). Similar improvements were found over time for the two treatment groups on the primary outcomes (all p’s > 0.15).

Conclusion: Results indicated no specific treatment-effects of NF on neurocognitive functioning of PBTS.
INTRODUCTION

Paediatric brain tumour survivors (PBTS) often experience neurocognitive impairments, with attention being identified as a core problem.1 Neurocognitive impairments, in turn, lead to difficulties in acquiring new skills and knowledge. Ultimately this may lead to decreased academic and vocational achievements and may challenge social functioning and health related quality of life (HRQOL).2

So far, few interventions targeting neurocognitive impairments in PBTS have proven to be effective. Some training programs have been developed and investigated in the past, however, the studied groups were small and the efficacy limited.3,4 A recent study reported promising results of a computerised cognitive training as compared to a waiting list control group.5 The group who received the training showed improvements in neurocognitive functioning as compared to the control group, with large effect sizes. Due to the lack of a placebo control group, non-specific treatment-effects cannot be ruled out. Pharmacological interventions such as methylphenidate, have proven to be effective for neurocognitive deficits in PBTS.6 However, adverse side-effects have been reported, such as insomnia and loss of appetite.6

Neurofeedback (NF) is an intervention based on the principles of operant conditioning. In order to regulate brain activity, direct visual or auditory feedback of the brain activity is offered. Brain activity may be described in different frequency bands as depicted by a quantified electroencephalogram (qEEG), associated with different mental states. Beta frequencies (>12 Hz) are associated with a state of outwardly focused concentration.7 Reinforcing beta frequencies in healthy students leads to increased attention and arousal.8 The efficacy of NF in patients with attention deficit hyperactivity disorder (ADHD) has been studied extensively and promising results have been reported in uncontrolled and controlled studies.9,10 However, numerous reviews conclude that more blinded placebo-controlled randomised trials are warranted to establish efficacy of NF over non-specific treatment-effects.11,12 NF has not yet been studied in PBTS.

This paper describes the results of the first double-blind randomised placebo-controlled trial investigating the efficacy of NF in PBTS (Pediatric Research on Improving Speed, Memory, and Attention; the PRISMA-study). It was hypothesised that PBTS receiving NF would improve more on objective measures of neurocognitive functioning than PBTS who received placebo feedback (PF). Secondary, it was expected that PBTS in the NF group would experience enhanced subjective functioning regarding neurocognitive and psychosocial outcomes.
METHODS

Study design
This study used a double-blind parallel placebo-controlled design, with participants randomised 1:1 to either NF or PF. Participants of this study were recruited from five participating Dutch University hospitals: Emma Children’s Hospital/Academic Medical Center Amsterdam, VU Medical Center Amsterdam, University Medical Center Utrecht, Radboud University Medical Center Nijmegen, and Maastricht University Medical Center. Three children from other medical centres contacted us about participation independently. The study was approved by the local medical ethical committee (#W13_183). Data included in this manuscript were obtained in compliance with regulations of the Academic Medical Center Amsterdam and the Helsinki Declaration.

Participants
Participants were eligible for inclusion if they were treated for a brain tumour more than 2 years prior to enrolment, aged 8–18 years, and suffered from parent-reported neurocognitive complaints. Interested parents were provided with a screening questionnaire concerning their child’s neurocognitive functioning, including the attention scale of the disruptive behaviour disorders rating scale (DBDRS),¹³ and items regarding problems with attention, memory, information processing, and speed. If the score on the attention scale of the DBDRS was 14 (subclinical functioning) or higher and/or the parents indicated at least two problems, children were considered eligible. Exclusion criteria were a premorbid diagnosis of ADHD (the current study focused on cancer related impairments), a mental or physical condition that restricted neurocognitive assessment (e.g. blindness), and insufficient mastery of the Dutch language.

Potentially eligible children and their parents were informed about the study by their oncologist or psychologist and provided with written information on the study. Eligible children were subsequently invited for the first assessment. Written informed consent was obtained prior to the first assessment.

Randomisation and masking
Randomisation was done after selection of the most appropriate NF module based on the individual qEEG (Fig. 1). Three randomisation tables were generated using SPSS (fixed block size of four), one for each of the three NF modules. To ensure blinding, the three NF modules and three accompanying PF modules (Fig. 1) had identical interfaces and were randomly assigned a number between one and six as file name. Research team-member JO held the key to the codes of the training modules.
Neurofeedback in PBTS: Results RCT

One research team member analysed the qEEG and informed JO which NF module would be indicated. JO then randomised the participant to receive NF or PF, and notified MdR of the assigned, blinded, module (module 1–6; Fig. 1). MdR sent the module via email to the trainer. JO was not involved in training or testing participants or analysing the data. Participants, their parents, trainers and researchers handling the data were blinded regarding assignment of the participants until the analyses were finished.

**Figure 1.** Procedure of the PRISMA study.
Beta 1 up = reinforcing beta 1 frequency (15–20 Hz); SMR up = reinforcing sensory motor rhythm (12–15 Hz), with beta 1 inhibition; spindles down = beta 1 inhibition in case of beta spindles; qEEG = quantitative electroencephalogram.

**Intervention**

The intervention consisted of 30 sessions of 30 min, twice weekly at home or school. Each session was divided in ten times 3 min training, alternated with 1-min breaks, when the participant was required to sit with the eyes closed. All participants were trained with an electrode on location Cz with a portable Brainquiry PET NF device and a laptop equipped with BioExplorer software version 1.5. The design of the intervention was comparable to the majority of previous studies into the effects of NF.12

After comparison of the participant’s qEEG to a commercially available normative database (Brain Resource,14 data of >4000 healthy subjects, aged 6–100 years), standardised criteria determined the most appropriate NF module:8 (1) reinforcing beta 1 (15–20 Hz) when beta
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1 power <1 standard deviation (SD) below the normative age and gender specific mean; (2) reinforcing sensory motor rhythm (SMR, 12–15 Hz), with beta 1 inhibition when beta 1 power >1SD above the normative mean and SMR <1SD above normative mean; and (3) beta 1 inhibition in case of beta spindles, or if beta 1 was >1SD above the normative mean and SMR power was >1SD above the normative mean. A PF module was designed, which provided feedback based on the ‘random signal generator’ of the BioExplorer software.

All modules (NF and PF) were set to provide positive reinforcement 80% and negative reinforcement 20% of the time. A self-selected movie was used as positive reinforcement. A silent black screen was used as negative reinforcement. Positive reinforcement was based on an individually determined threshold, which was calculated from the amplitude of the brainwave frequency of interest (e.g. beta 1). The threshold was adjusted automatically during the session, based on the individual brain activity of the previous 30 s. This threshold was used to deliver positive reinforcement during the session. A threshold of 10 μV for muscular tension (>55 Hz) and 50 μV for noise (range 48–52 Hz) was used. If the muscular tension and/or the noise reached above the threshold, the movie stopped and the software produced a beeping sound until the muscular tension and/or noise were below the threshold again. This applied to the NF and PF modules.

The training was conducted by carefully trained trainers, according to an extensive standard operating procedure. After each session, the trainer filled out a checklist, providing information about the quality of the training; the duration, the time, the movie, the alertness, and anything aberrant from the standard procedure. The checklist was emailed weekly to the researchers. Assessment of the checklist did not show any major deviations of the procedure.

Procedures
Participants were assessed pre-training (T0), post-training (T1), and at 6-months follow-up (T2); see Fig. 1. Neurocognitive testing and qEEGs were conducted at three locations, using identical equipment, software and procedures. Questionnaires were completed online at home.

OUTCOME MEASURES

Primary outcomes
Well-validated, mostly computerised, (adaptations of) widely used tests were selected to provide a comprehensive assessment of neurocognitive functioning, according to recent recommendations: attention, processing speed, memory, executive functioning (EF), visuomotor integration (VMI), and intellectual functioning (Table 1). For a detailed description of the tests, see Appendix.
Secondary outcomes
Self-, parent- and/or teacher-questionnaires assessed HRQOL, social-emotional functioning, self-esteem, fatigue, behavioural EF, attention in daily life, and sleep disturbance. Widely used, reliable, and validated questionnaires were selected (Table 1).

Medical and demographic characteristics
Parents of participants provided information on demographics, medical data were obtained from the medical records; see Table 2. Limited medical and demographic data were available for a subsample of non-participants (n = 45): age at assessment, age at diagnosis, time since diagnosis, gender, tumour histopathology and grade, type of treatment, and tumour location.

Statistical analyses
Sample size calculation was based on previous research on NF in children with ADHD, using nQuery Advisor. With an effect size of 0.60, alpha set at 0.05 and a power of 0.80, a minimum of 35 patients were required in both groups. Analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, United States of America). Outliers on outcome measures were rescaled according to Tabachnick and Fidell. There were no missing data on any of the dependent measures. Independent-samples t-test and chi-square test were used to test differences on demographic and medical differences between: (1) participants and non-participants, (2) NF and PF, and (3) dropouts and non-dropouts. For (2) and (3), baseline differences on outcome measures were tested using one-sample t-tests. The short term (T1) and long term (T2) effects of NF were tested using linear mixed models analysis, accounting for the dependency of the data within subjects. Data of participants were included in the linear mixed models analyses if participants had completed the training as well as the pre-training and one post-training assessment. Differences between NF and PF at T0 regarding primary and secondary outcomes were controlled for by the use of a random intercept. For each outcome measure (except for the attention network task, ANT, and VMI task), a linear mixed model was fitted with a random intercept and fixed slopes for training (NF versus PF), time (T1 versus T0 and T2 versus T0) and the interaction term training × time. Training × time interaction effects tested the effects of NF compared to PF.

To analyse the effects of NF on the efficiency of three attention networks, ANT-trial type (Table 1) was added to the model as a repeated factor. The three-way interaction training × time × trial type was used to establish effects of NF. To analyse the effects of NF on VMI, structure and speed (Table 1) were added to the model as repeated factors. The three-way interactions of training × time × structure and training × time × speed were used to establish effects of NF.
### Table 1. Outcomes and measures.

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Measurement</th>
<th>Subject</th>
<th>Description</th>
<th>Dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Attention network task (ANT)</td>
<td>Child</td>
<td>Computerised response task with a neutral condition and three conditions to measure the three networks</td>
<td>Alerting, orienting and executive attention</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Baseline speed ANT</td>
<td>Child</td>
<td>Neutral condition ANT</td>
<td>Mean reaction time</td>
</tr>
<tr>
<td>Memory</td>
<td>Visual sequencing task</td>
<td>Child</td>
<td>Manually repeating a sequence of circles</td>
<td>Number of correct items</td>
</tr>
<tr>
<td></td>
<td>Digit span forward (WISC/WAIS)</td>
<td>Child</td>
<td>Verbally repeating a sequence of digits forward</td>
<td>Number of correct items</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Inhibition</td>
<td>Child</td>
<td>Response inhibition task</td>
<td>Stop signal reaction time</td>
</tr>
<tr>
<td></td>
<td>Working memory</td>
<td>Child</td>
<td>Verbally repeating a sequence of digits backwards</td>
<td>Number of correct items</td>
</tr>
<tr>
<td>Visuomotor</td>
<td>Tracking and pursuit task</td>
<td>Child</td>
<td>Following a moving target on a screen</td>
<td>Accuracy (structure, speed)</td>
</tr>
<tr>
<td>integration</td>
<td>Abbreviated WISC-III a</td>
<td>Child (8–16)</td>
<td>IQ test</td>
<td>FSIQ, PIQ and VIQ</td>
</tr>
<tr>
<td></td>
<td>Abbreviated WAIS-III b</td>
<td>Child (17–18)</td>
<td>IQ test</td>
<td>FSIQ, PIQ and VIQ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Respondent</th>
<th>Description</th>
<th>Dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRQOL</td>
<td>Kidscreen 27</td>
<td>Questionnaire</td>
<td>Physical well-being, psychological well-being, autonomy and parents, peers and social support, school environment, generic</td>
</tr>
<tr>
<td>Social-emotional</td>
<td>SDQ child version</td>
<td>Questionnaire</td>
<td>Total problem-score</td>
</tr>
<tr>
<td>functioning</td>
<td>SDQ parent version</td>
<td>Questionnaire</td>
<td>Total problem-score</td>
</tr>
<tr>
<td></td>
<td>SDQ teacher version</td>
<td>Questionnaire</td>
<td>Total problem-score</td>
</tr>
</tbody>
</table>

Note: a, b, c refer to additional information or notes related to the measurements.
### Primary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Measurement</th>
<th>Subject Description</th>
<th>Dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-esteem</strong></td>
<td>SPPC</td>
<td>Child (8–11) Questionnaire</td>
<td>Scholastic competence, social acceptance, athletic competence, physical appearance, behavioural conduct, close friendship (SPPA only), global self-worth</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>CIS</td>
<td>Child Questionnaire</td>
<td>See SPPC</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td>BRIEF parent version</td>
<td>Parent Questionnaire</td>
<td>Behavioural index, metacognition index, total score</td>
</tr>
<tr>
<td><strong>Attention daily life</strong></td>
<td>SWAN</td>
<td>Parent Questionnaire</td>
<td>Attention deficit, hyperactivity/impulsivity</td>
</tr>
<tr>
<td><strong>Sleep disturbance</strong></td>
<td>SDSC</td>
<td>Parent Questionnaire</td>
<td>Initiating/maintaining sleep, excessive somnolence, total score</td>
</tr>
</tbody>
</table>

**Notes.** Intellectual functioning is assessed pre-training at T0 and 6 months after training at T2 but not directly after training at T1. ANT = attention network task; BRIEF = behaviour rating inventory of executive functioning; CIS = checklist individual strength; FSIQ = full scale IQ; HRQOL = health related quality of life; PIQ = performance IQ; SDQ = strengths and difficulties questionnaires; SDSC = sleep disturbance scale for children; SPPC/SPPA = self perception profile for children/adolescents; SWAN = strengths and weaknesses of ADHD-symptoms and normal-behaviour; VIQ = verbal IQ; WISC-III = Wechsler intelligence scale for children – third version; WAIS-III = Wechsler adult intelligence scale – third version.

* The following subtasks were administered: arithmetic, similarities, block design, and picture completion.
* The efficiency of the alerting, orienting, and executive attention networks were assessed by contrasting the mean reaction times of correct responses on alerting, orienting and executive trials respectively, to the mean reaction time of the correct responses to neutral trials.
* The accuracy scores on two parts (structured and unstructured) on six different speed levels were used as measures of visuomotor integration.
Table 2. Demographics and medical characteristics of participants who completed the training.

<table>
<thead>
<tr>
<th></th>
<th>Neurofeedback N = 34</th>
<th>Placebo-feedback N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age and time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at assessment</td>
<td>14.45</td>
<td>2.99</td>
</tr>
<tr>
<td>Age diagnosis</td>
<td>6.81</td>
<td>3.65</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>7.64</td>
<td>4.04</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Girls</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>Tumour grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>Low grade</td>
<td>23</td>
<td>68</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Chemotherapy/Radiotherapy</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>20</td>
<td>59</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Country of origin mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>28</td>
<td>82</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Country of origin father</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Highest parental education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low or intermediate</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>High</td>
<td>20</td>
<td>59</td>
</tr>
</tbody>
</table>

Notes. None of the group differences reached significance (p > 0.05). High grade = medulloblastoma, supratentorial primitive neuroectodermal tumour (PNET), ependymoma, astrocytoma grade III, germ cell tumour; low grade = low grade glioma, craniopharyngioma, plexus papilloma; SD = standard deviation.

a Surgery, biopsy or cerebrospinal fluid pressure relief only
b Chemotherapy and/or radiotherapy with or without surgery
c Based on the parent with the highest education: low – intermediate = primary education, general secondary education and secondary vocational education; high = higher vocational education and university.
We also tested the possibility that beneficial effects of NF would be evident for the reinforcing beta 1 module (power did not allow examining the other two NF modules). This analysis included 55 participants (77%) who were allocated to receive the reinforcing beta 1 module (NF: n = 28, PF: n = 27).

For primary outcomes, p-values of <0.05 were considered significant. For secondary outcomes, the p-value was set on <0.01 due to the large number of outcomes.

An independent data monitoring safety board (DMSB) was installed to receive reports on serious adverse events (SAE), defined as seizures that are not controllable with conventional antiepileptic drugs and which require admittance to an intensive care unit. In case the total number of dropouts was >10% or the number of SAE was >5% of participants, the DMSB would receive information about which module (NF or PF) participants received and decide whether the study should be terminated. The trial is registered at clinicaltrials.gov: NCT00961922.

RESULTS

Participants
A total of 82 participants enrolled in the study (mean age 13.9 years, SD = 3.2, 49% males), 80 were randomised (NF: n = 40, PF: n = 40, refused qEEG: n = 2), 71 completed training and T1 (mean number of sessions = 30, range 28–33, NF: n = 34, PF: n = 37) and were included into the analyses, and 68 also completed T2 (NF: n = 33, PF: n = 35). Post-training and follow-up data were lacking for 8 of the 9 participants who dropped out. The analyses based on intention-to-treat (including one single subject for whom data were available) yielded highly similar results as the analysis without the data of the drop-out (data not shown).

Fig. 2 shows the flow diagram. Recruitment took place between November 2, 2009 and May 3, 2012. The assessments and intervention took place between January 5, 2010 and December 4, 2013.
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Figure 2. Flow diagram.
Beta 1 up = reinforcing beta 1 frequency (15–20 Hz); SMR up = reinforcing sensory motor rhythm (12–15 Hz), with beta 1 inhibition; spindles down = beta 1 inhibition in case of beta spindles; qEEG = quantitative electroencephalogram.
Demographic and medical variables are displayed in Table 2. Participants did not differ from non-participants regarding age at assessment, gender and tumour location ($p > 0.05$). The percentage of high-grade tumours, radiotherapy, and chemotherapy was higher in the participants ($p < 0.05$). Compared with non-participants, participants were younger at diagnosis ($p < 0.05$) and time since diagnosis was longer ($p < 0.05$). There was no difference between the dropouts ($n = 11$) and the non-dropouts at T0 ($n = 71$) on the demographic and medical variables and the primary outcomes ($p > 0.05$). On the secondary outcomes at T0, teachers reported more problems for dropouts ($n = 7$) on two of three behavioural EF scales and on social-emotional functioning ($p < 0.01$) than for non-dropouts ($n = 66$). No other differences were found ($p > 0.01$).

Regarding the primary neurocognitive outcomes (Table 3) no beneficial effects of NF were found; all interaction effects involving training × time, were not significant ($p > 0.15$). However, significant effects of time were found for processing speed ($p < 0.001$), visual short-term memory ($p < 0.001$), working memory ($p = 0.01$), and intelligence (FSIQ: $p < 0.001$; PIQ: $p = 0.01$; VIQ: $p = 0.01$), indicating that both groups improved over time.

Regarding secondary outcomes (Table 4), NF revealed no advantage over PF. Several significant effects of time suggested improvements on the ‘autonomy and parents’ subscale of the self-report HRQOL ($p = 0.002$; data not shown), self- and parent-report social-emotional functioning ($p = 0.001$), the ‘behavioural conduct’ subscale of self-report self-esteem ($p < 0.001$; data not shown), the ‘concentration’ subscale of self-report fatigue ($p = 0.001$; data not shown), and parent-report EF ($p < 0.001$). No SAEs were reported and <10% participants dropped out.

The exploratory analyses on reinforcing beta 1 yielded similar results: no significant intervention effects on neurocognitive outcomes. Only one secondary outcome measure showed significant training × time effects for NF resulting in worse self-reported self-esteem (subscale ‘athletic competence’, $p = 0.005$; data not shown).
Table 3. Primary, neurocognitive, outcomes of participants at T0, T1, T2: neurofeedback versus placebo-feedback.

<table>
<thead>
<tr>
<th></th>
<th>Neurofeedback (NF)</th>
<th>Placebo-feedback (PF)</th>
<th>Time</th>
<th>Training*time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0 N = 34</td>
<td>T1 N = 34</td>
<td>T2 N = 33</td>
<td>T0 N = 37</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT alerting attention</td>
<td>51.75 (28.57)</td>
<td>48.48 (35.21)</td>
<td>54.38 (32.30)</td>
<td>56.27 (32.30)</td>
</tr>
<tr>
<td>ANT orienting attention</td>
<td>−40.40 (30.31)</td>
<td>−43.13 (23.92)</td>
<td>−41.46 (19.33)</td>
<td>−39.32 (29.28)</td>
</tr>
<tr>
<td>ANT executive attention</td>
<td>28.12 (32.29)</td>
<td>30.83 (30.49)</td>
<td>34.20 (26.50)</td>
<td>45.74 (43.09)</td>
</tr>
<tr>
<td>ANT intraindividual</td>
<td>0.21 (0.06)</td>
<td>0.21 (0.05)</td>
<td>0.20 (0.05)</td>
<td>0.23 (0.06)</td>
</tr>
<tr>
<td>coefficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT mean reaction time</td>
<td>401.42 (104.92)</td>
<td>368.51 (99.83)</td>
<td>338.24 (87.73)</td>
<td>434.40 (127.65)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual short-term memory</td>
<td>14.44 (4.57)</td>
<td>14.76 (4.78)</td>
<td>15.79 (4.93)</td>
<td>13.03 (4.04)</td>
</tr>
<tr>
<td>Auditory short-term</td>
<td>7.97 (2.01)</td>
<td>8.09 (1.88)</td>
<td>7.91 (1.94)</td>
<td>7.95 (1.90)</td>
</tr>
<tr>
<td>memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>5.50 (2.09)</td>
<td>6.21 (2.36)</td>
<td>6.36 (2.33)</td>
<td>5.30 (2.33)</td>
</tr>
<tr>
<td>Stop task response</td>
<td>235.56 (49.54)</td>
<td>244.02 (39.14)</td>
<td>232.30 (36.13)</td>
<td>267.49 (62.47)</td>
</tr>
<tr>
<td>inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurofeedback (NF)</td>
<td>Placebo-feedback (PF)</td>
<td>Time</td>
<td>Training*time</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>T0 N = 34</td>
<td>T0 N = 37</td>
<td>T0–T1</td>
<td>T0–T2 Overall</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>p-Value</td>
<td>β β</td>
</tr>
<tr>
<td></td>
<td>91.18 (19.44)</td>
<td>93.21 (21.29)</td>
<td>0.01</td>
<td>0.25**</td>
</tr>
<tr>
<td></td>
<td>95.16 (19.22)</td>
<td>96.73 (20.00)</td>
<td>0.001</td>
<td>0.22**</td>
</tr>
<tr>
<td></td>
<td>90.51 (17.24)</td>
<td>91.00 (16.72)</td>
<td>0.01</td>
<td>0.22**</td>
</tr>
<tr>
<td></td>
<td>92.71 (18.18)</td>
<td>93.23 (18.11)</td>
<td>0.01</td>
<td>0.19*</td>
</tr>
<tr>
<td></td>
<td>91.33 (15.63)</td>
<td>95.06 (15.46)</td>
<td>0.01</td>
<td>0.25**</td>
</tr>
<tr>
<td></td>
<td>92.39 (15.69)</td>
<td>94.06 (16.46)</td>
<td>0.01</td>
<td>0.19*</td>
</tr>
</tbody>
</table>

Notes. Data of participants were included in the linear mixed models analyses if participants had completed the training as well as the pre-training and one post-training assessment. Placebo-feedback was the reference category in the analyses.
For all outcomes, except for intelligence, raw scores are reported. For intelligence, age standardised scores are provided. Scores based on reaction times are in ms (ANT, stop task). Outcomes were analysed after transformation into standard normal scores, expressing deviations from the overall mean at baseline (T0), so that the coefficients could be interpreted as standardised β coefficients. Higher scores reflect better functioning, unless stated otherwise.
Scores of the visuomotor integration task are not displayed, results of the analyses are described in the text. For intelligence, WISC and WAIS scores were combined. ANT = attention network task; FSIQ = full scale IQ; M = mean; PIQ = performance IQ; SD = standard deviation; T0 = baseline; T1 = post-training; T2 = 6-month follow-up; VIQ = verbal IQ; WISC = Wechsler intelligence scale; WAIS = WAIS-III = Wechsler adult intelligence scale. *p < 0.05; **p < 0.01; ***p < 0.001
β reported the in column Training × time are based on the three-way interaction Time × Training × ANT-condition.
*β reported the in column Time are based on the two-way interaction Time × ANT-condition.
Not assessed/not analysed
Lower scores reflect better functioning.
N = 34
* N = 33
Table 4. Secondary outcomes of participants at T0, T1, T2: neurofeedback versus placebo-feedback.

<table>
<thead>
<tr>
<th></th>
<th>Neurofeedback (NF)</th>
<th>Placebo-feedback (PF)</th>
<th>Time</th>
<th>Training × time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M(SD)</td>
<td>M(SD)</td>
<td>M(SD)</td>
<td>M(SD)</td>
</tr>
<tr>
<td></td>
<td>T0 N = 34</td>
<td>T1 N = 33</td>
<td>T2 N = 32</td>
<td>T0 N = 36</td>
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<tr>
<td>Self-report</td>
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<td></td>
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<tr>
<td>HRQOL</td>
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<td></td>
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<tr>
<td>Generic a</td>
<td>48.27 (7.10)b</td>
<td>48.50 (6.99)c</td>
<td>51.09 (7.54)d</td>
<td>49.18 (6.44)</td>
</tr>
<tr>
<td>Social-emotional functioning</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Total problem-score</td>
<td>9.62 (4.36)</td>
<td>8.64 (4.49)</td>
<td>7.97 (4.15)</td>
<td>10.64 (5.42)</td>
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<td>Self-esteem</td>
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<tr>
<td>Global self-worth a</td>
<td>52.47 (34.50)</td>
<td>48.64 (32.66)</td>
<td>49.13 (32.06)</td>
<td>57.92 (29.33)</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Total score</td>
<td>60.97 (22.52)b</td>
<td>60.06 (17.74)b</td>
<td>61.81 (22.49)</td>
<td>64.73 (21.46)f</td>
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<tr>
<td>Parent-report</td>
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<tr>
<td>Total problem-score</td>
<td>10.50 (4.31)</td>
<td>9.03 (4.63)</td>
<td>8.94 (4.83)</td>
<td>11.22 (5.18)</td>
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<td>Executive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Behavioural index</td>
<td>52.32 (9.68)</td>
<td>49.85 (11.61)</td>
<td>49.76 (11.35)</td>
<td>55.19 (12.56)</td>
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<td>Metacognition index</td>
<td>52.68 (8.85)</td>
<td>49.91 (9.21)</td>
<td>50.70 (9.23)</td>
<td>55.41 (7.80)</td>
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<tr>
<td>Total score</td>
<td>52.71 (8.37)</td>
<td>49.70 (9.91)</td>
<td>50.33 (9.81)</td>
<td>55.68 (8.98)</td>
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</table>
### Attention in daily life

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<th>0.34 (0.99)</th>
<th>0.14 (0.91)</th>
<th>0.33 (1.01)</th>
<th>0.77 (0.74)</th>
<th>0.54 (0.74)</th>
<th>0.41 (0.71)</th>
<th>0.02</th>
<th>−0.23</th>
<th>−0.06</th>
<th>0.12</th>
<th>0.03</th>
<th>0.36</th>
</tr>
</thead>
</table>

| Hyperactivity/impulsivity | −0.65 (0.92) | −0.77 (0.95) | −0.60 (1.00) | −0.09 (0.84) | −0.18 (0.79) | −0.16 (0.68) | 0.46 | −0.16 | −0.01 | 0.86 | −0.07 | 0.05 |

### Sleep disorders

| Total score (Teacher-report) | 40.18 (7.73) | 39.39 (8.40) | 39.00 (7.78) | 40.54 (6.44) | 40.47 (6.62) | 39.65 (6.76) | 0.41 | −0.08 | −0.12 | 0.82 | −0.10 | 0.02 |

### Social-emotional functioning

| Total problem-score (Teacher-report) | 8.91 (4.77) | 8.58 (5.63) | 8.29 (4.79) | 9.74 (6.18) | 9.18 (5.15) | 8.47 (4.46) | 0.22 | −0.12 | −0.19 | 0.92 | 0.08 | −0.00 |

### Executive functioning

| Behavioural index (Teacher-report) | 48.81 (10.83) | 46.70 (10.44) | 46.36 (9.56) | 48.94 (8.43) | 50.45 (11.04) | 51.69 (14.07) | 0.46 | −0.30 | −0.35 | 0.03 | −0.31 | −0.66** |
| Metacognition index (Teacher-report) | 48.44 (11.71) | 45.27 (10.70) | 47.96 (12.25) | 51.79 (10.45) | 52.12 (11.31) | 51.24 (10.94) | 0.12 | −0.35 | −0.16 | 0.31 | −0.29 | −0.04 |
| Total score (Teacher-report) | 48.47 (11.79) | 45.43 (10.48) | 47.46 (11.40) | 50.65 (9.64) | 51.42 (11.31) | 51.34 (12.41) | 0.15 | −0.35 | −0.21 | 0.28 | −0.31 | −0.24 |

Notes. Data of participants were included in the linear mixed models analyses if participants had completed the training as well as the pre-training and one post-training assessment. Placebo-feedback was the reference category in the analyses. For HRQOL, self-esteem and executive functioning standardised scores are reported, for other measures raw scores are provided. Outcomes were analysed after transformation into standard normal scores, expressing deviations from the overall mean at baseline (T0), so that the coefficients could be interpreted as standardised \( \beta \) coefficients. Lower scores reflect better functioning, unless stated otherwise. P-values of <0.01 are considered significant. For Self-Esteem, SPPC and SPPA scores were combined. HRQOL = health related quality of life; M = mean; SD = standard deviation; T0 = baseline; T1 = post-training; T2 = 6 months follow-up. **p < 0.01.

* Higher scores reflect better functioning.

** N = 32.

b ** N = 30.

c ** N = 29.

d ** N = 36.

e ** N = 33.
Chapter 7

DISCUSSION

The results of this first double-blind randomised placebo-controlled trial, aimed at investigating the efficacy of NF for PBTS, reveal no positive effects for NF over PF on any of the primary and secondary outcomes. In both groups, PBTS improved over time on the majority of primary and some secondary outcome measures, with small to medium effects. However, improvements over time have also been found in the four placebo-controlled studies in children with ADHD, potentially reflecting non-specific treatment-effects.33–36 The sound design of our study allows us to conclude that NF is not effective in improving neurocognitive functioning in PBTS. In agreement with our findings, the effects of NF in children with ADHD were found to be smaller in randomised controlled trials than in uncontrolled trials, and in double-blind trials no beneficial effects of NF in patients with ADHD were obtained, although similar to our study, improvements over time were found.12 In addition, our study had sufficient power to detect effects of medium size. Furthermore, a 6-month follow-up assessment was included to rule out a potential sleeper effect and lastly, dropout was low without evidence for selective dropout. The design of the NF and PF modules paralleled the mainstream of previous studies into the effects of NF. The NF modules used in this study were aimed at the beta 1 frequency, associated with focused attention. Attention has been identified as a fundamental neurocognitive domain that underlies higher order domains, such as working memory, intelligence and academic functioning.37 Reinforcing beta 1 in combination with theta inhibition has often been used for ADHD.38 It has been argued that treatment-induced white matter impairments cause neurocognitive deficits in PBTS and also that NF enhances white matter associated with increased attention, as was shown in a placebo-controlled trial where they reinforced beta 1 in healthy students.39 We found no evidence of an effect of NF on attention but information on white matter of the participants is lacking. The number of sessions of NF in our study has yielded large positive effects in earlier controlled studies performed in children with ADHD.38 We cannot rule out that PBTS would benefit from a more intensive training, however, in children and adults with traumatic brain injury, whose brain damage is of structural nature as in PBTS, similar numbers of sessions produced positive outcomes.40 It could be argued that using automatically adjusted thresholds is less effective than manually adjusted, however, a recent study did not find larger effect sizes when thresholds were switched from automatically to manually adjusted.45 Giving 80% positive feedback, as we did, has been criticised as possibly too high for optimal learning.41 However, the optimal percentage of feedback to optimise learning principles has yet to be investigated.41,42 The improvements we found over time in both training groups have also been reported in other NF studies,33–36 and in other intervention studies.43 The improvements may be a result
of non-specific treatment-effects, including the influence of positive expectations about the efficacy of the intervention, a substantial risk in a ‘high-tech’ setting like NF. Also personal attention of the trainer, the structured setting of the sessions, requiring participants to focus their attention for 30 min twice a week are potential non-specific treatment-effects. Regression to the mean, a well-known phenomenon in behavioural sciences, could also have caused the improvements. Another reason might be found in 1-min breaks, sitting with the eyes closed after every 3-min training block. This may have given the intervention an unintended mindfulness-like character, for which some evidence has been found for children in improving behavioural and psychosocial functioning. The year time between the T0 and T2 assessments may also have played a role in some improvements, due to maturation. Although it has been suggested that PBTS learn at a slower rate than their peers, (‘growing into deficit’), we did not find evidence for this, as the scores of PBTS improved also on age-corrected intelligence scores. It could not be ruled out that the improvements over time could have resulted from practice-effects, since most tests were repeated three times in a year’s time. To minimise the chance of practice-effects, neurocognitive measures with high test-retest validity were used, such as the inhibition task. Furthermore, intelligence was not tested after the intervention, increasing the interval between the intelligence tests to 1 year.

There are some limitations that should be taken into account when interpreting the results of this study. Patients were selected based on parent-reported complaints, not based on objective measures. This recruitment process could have led to inclusion of PBTS without ‘room for improvement’ in neurocognitive functioning. However, the results of the objective neurocognitive tests at T0 showed more problems in PBTS than in sibling controls, with effect sizes ranging from 0.40 to 0.82 ($p < 0.05$). Also, participants were more likely than non-participants to have high-grade tumours, to have been treated with radiotherapy and chemotherapy, and were on average younger at diagnosis with a longer time since diagnosis. This suggests that participants may have been at greater risk for neurocognitive late effects than non-participants. This might in turn limit the generalisation of the findings to a lower risk cohort. Regarding the intervention, a recent development is the application of transfer sessions, in which the participant does not receive feedback, while trying to maintain the desired brain activity to enhance generalisation from the training setting into daily life. We did not include this type of session.

Concluding, the results of this double-blind randomised placebo-controlled trial show that NF does not have favourable effects on neurocognitive and psychosocial functioning in PBTS as compared with PF. Both NF and PF were found to improve neurocognitive and psychosocial functioning, possibly due to non-specific treatment-effects. Thus far positive findings have been reported for several interventions, especially methylphenidate and the Cogmed training. However, interventions aiming to improve neurocognitive functioning of
PBTS remain to be developed that lack the possible side-effects of medication, remain to be studied using double-blind randomised placebo-controlled trials, to rule out confounding of results by non-specific training-effects.
REFERENCES


APPENDIX CHAPTER 7 – PRIMARY AND SECONDARY OUTCOME MEASURES

Primary outcome measures

Attention. The Attention Network Task is a computerized task that is designed to measure functioning of three independent neural networks that enable alerting, orienting, and executive attention. Reliability and validity has been established.\textsuperscript{1,2} In this study, we used a child-friendly adaptation of the Attention Network Task.\textsuperscript{3} In the Attention Network Task, children are required to push as quickly and accurately as possible one of two buttons corresponding to the location of a target stimulus presented at either the left or right side of a computer screen. There are four trial types: (1) neutral trials with a neutral cue in the center of the screen preceding the target stimulus; (2) alerting trials, with no cue provided before onset of the target stimulus; (3) orienting trials with a central cue pointing to the location of the subsequently presented target stimulus; and (4) executive trials in which the central cue points to the location opposite of the subsequently presented target stimulus (causing slower reaction times, due to the necessary shift in attention). The task consists of 312 trials, randomly presenting the four trial types. The efficiency of the alerting, orienting, and executive attention networks was assessed by contrasting the mean reaction times of correct responses on the alerting, orienting and executive trials respectively, to the mean reaction time of the correct responses to the neutral trials. In addition, the intraindividual coefficient of variation across all trials was used as measure of maintenance of attention. Intraindividual coefficient of variation is defined as standard deviation of reaction times on correct responses, divided by the mean reaction time of correct responses.\textsuperscript{4}

Processing speed. Processing speed was measured by the mean reaction time on correct responses on the neutral Attention Network Task trials.\textsuperscript{3}

Memory: visual short-term memory. A computerized version of a visual sequencing task was used to measure visual short-term memory. Psychometric properties have been reported in several studies.\textsuperscript{5,6} During a trial, a sequence of yellow circles appears one by one in a 4x4-grid. The participant is required to repeat the sequence by tapping the correct locations on a touch screen. Difficulty level is manipulated by increasing the number of circles to be repeated (2-9 circles), with each difficulty level comprising two trials. If a participant makes an error on both trials of a difficulty level, the task is terminated. The total number of correct trials was used as the outcome variable.
Memory: auditory short-term memory. Auditory short-term memory was measured by forward items of the Digit Span task of the age appropriate Wechsler Intelligence scale (Wechsler Intelligence Scale for Children, WISC-III, or Wechsler Adult Intelligence Scale, WAIS-III). In this task, participants are required to repeat verbally presented sequences of digits, increasing in length (2-9 digits). The task is terminated after an error on both items of a difficulty level. The number correct forward items (i.e. the raw score associated with Digit Span forward) on the Digit Span task was used as the outcome variable.

Executive functioning: working memory. The backward items on the Digit Span task of the age appropriate Wechsler Intelligence scale were used as a measure of working memory. During the backward items, the participants are asked to repeat verbally presented sequences of digits, increasing in length (2-9 digits), in the reverse order, requiring simultaneous and storage and processing of information. The task is terminated after an error on both items of a difficulty level. The total number of correct items (i.e. the raw score associated with Digit Span backward) was used as the outcome variable, with the number of correct forward items as covariate.

Executive functioning: response inhibition. The Stop Signal task was used to assess response inhibition. Reliability and validity have been established in several studies. The task presents participants with two kinds of trials; go trials and stop trials. The participant is required to press as quickly and accurately as possible one of two buttons corresponding to the location of a target stimulus presented either at the left or right side of a computer screen. On stop trials, the stimulus is followed by a stop signal, a cross superimposed on the stimulus, requiring participants to inhibit the response. The time between stimulus and stop signal (stop signal delay) is varied to accomplish on average 50% successful inhibition on stop trials. Stop signal reaction time (SSRT), measuring the speed of the inhibitory response, was calculated by the mean reaction time on correct go trials minus mean stop signal delay, and served as the outcome variable.

VMI. We used a computerized tracking and pursuit task to measure VMI, which had been adapted and extended for use with children. Psychometric properties have been detailed in de Sonneville (1999). The task comprises two parts, a structured and an unstructured part. In both parts, participants are required to follow the trail of a moving caterpillar with a computer pencil in their preferred hand. During the structured part, the caterpillar moves in a fixed circular way over the screen. In the unstructured part of the task, the caterpillar moves in random directions over the screen. Both parts consist of six trials of 30 seconds each, with increasing speed levels (40-140 mm/s). For each trial, accuracy was calculated as the mean distance (in mm) between the position of the pencil and the caterpillar. The
accuracy scores on the structured and unstructured part of the six different speed levels were used as measures of VMI.

**Intelligence.** Estimated Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) were estimated using a four-subtask short form of the age appropriate WISC-III or WAIS-III\(^6,7\) containing the subtests Arithmetic, Similarities, Block Design and Picture Completion (see Sattler).\(^8\) Satisfactory reliability (Cronbach’s Alphas>.80) and validity (rs with full test >.77) have been reported for this short form for both the WISC-III and the WAIS-III.\(^9\)

**Secondary outcome measures**

**Self-report**

**HRQOL.** The Kidscreen-27 was administered to evaluate HRQOL in children by means of 27 items, scored on a 5-point Likert-scale, divided over 5 dimensions: Physical Well-being, Psychological Well-being, Autonomy and Parents, Peers and Social Support, and School Environment.\(^14\) In addition, a Generic score was calculated by summing the ten items that comprise the Kidscreen-10, a shorter version of the Kidscreen, derived from the Kidscreen-27.\(^15\) Raw scores for each dimension were transformed into T-values with a mean of 50 and a standard deviation of 10 in a European sample.

T-values of a Dutch normative sample are available. Higher scores indicated better HRQOL. The Kidscreen-27 and Kidscreen-10 have good levels of validity and reliability (Chronbach’s alphas normative samples >0.70; Cronbach’s alphas PBTS 0.71-0.88).\(^14,15\) The Dutch normative sample did not differ in age and gender distribution from the PBTS group (p>0.10).

**Self-esteem.** We used the Self Perception Profile for Children (SPPC, age 8-12) and Adolescents (SPPA, age 12-18) to investigate self-esteem.\(^16–18\) The SPPC consists of 36 items, divided into six scales: Scholastic Competence, Social Acceptance, Athletic Competence, Physical Appearance, Behavioral Conduct and Global Self-worth. The adolescent version (SPPA) contains 35 items and comprises one additional scale: Close Friendship. Each item was presented on a 4-point Likert-scale, with higher scores indicating stronger self-esteem. The SPPC and SPPA have acceptable to good validity and reliability (Cronbach’s alphas Dutch manual >0.70; Cronbach’s alphas PBTS 0.62-0.91).\(^17,18\) The manual provided mean scores for males and females separately. For comparison with the total group of PBTS, scores of males and females in the normative population were combined after weighting by the gender distribution in the PBTS group. Age was not taken into account, as the SPPC and SPPA have separate norms, based on age.
Psychosocial adjustment. The Strengths and Difficulties Questionnaire (SDQ) was used to assess psychosocial adjustment. The items were scored on a 3-point Likert-scale. A Total Problem-score was calculated by adding the scores of 20 items, with a higher score indicating more problems. The SDQ Total Problem-score has good validity and reliability (Cronbach’s alphas Dutch controls =0.70; Cronbach’s alphas PBTS =0.77). Dutch norms were available for children aged 11-16 years; therefore analyses on the SDQ were restricted to PBTS aged 11-16 years. The gender distribution did not differ between the Dutch normative group and the PBTS, but mean age of the normative population was lower than of the PBTS. However, since Total Problem-score is not affected by age, age was not taken into account in the analysis.

Fatigue. Fatigue was measured with the Checklist Individual Strength (CIS). The CIS is a questionnaire that measures fatigue-related problems and consists of 20 items, scored on a 7-point Likert-scale. The four subscales were Subjective Fatigue, Concentration, Motivation and Physical Activity. A Total Score was calculated by summing up all items. Higher scores indicated more fatigue-related problems. The CIS has good reliability, with Cronbach’s alphas of the sibling controls and the PBTS 0.72-0.94. The data collected in the sibling control group were used for comparison with the PBTS. The sibling control group and the PBTS did not differ significantly \((p>0.10)\) in gender and age.

Parent-report

Psychosocial adjustment. The SDQ was used to measure the parental perspective of PBTS’ psychosocial adjustment; see “Self-report” for the description of the questionnaire. Reliability of the Total Problem-score is good (Cronbach’s alpha Dutch controls =0.70; Cronbach’s alpha PBTS=0.77). PBTS were compared to a Dutch normative sample of children aged 8-16. The Dutch normative sample did not differ in age and gender from the PBTS \((p>0.10)\).

Executive functioning. Parents rated their child’s behavioral executive functioning using the Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF contains 75 items, scored on a 3-point Likert-scale. The scores were summarized in 8 scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor), two indices (behavioral and metacognition index), and a Total Score. The raw scores of the scales and indices were transformed into age and gender specific standardized T-scores, as provided in the manual, with a mean of 50 and a standard deviation of 10. Higher scores indicated more problems. validity and reliability range from good to excellent, with Cronbach’s alphas reported in the manual between 0.78 and 0.96 and Cronbach’s alphas of the PBTS between 0.66 and 0.94.


**Teacher-report**

*Psychosocial adjustment.* The SDQ was used to measure the teacher perspective of psychosocial adjustment of the PBTS; see “Self-report” for the description of the questionnaire. The reliability of the Total Problem-score of the teacher-report is reported to be good (Cronbach’s alpha Dutch controls=0.88; Cronbach’s alpha PBTS=0.77).\(^2\) A Dutch normative population of children aged 8-11 was available, therefore the answers from teachers of PBTS within that age range were analyzed. The Total Problem-score was analysed separately for females and males, because the PBTS sample had more females than the normative population. The mean age of the Dutch normative population did not differ from the mean age of the PBTS aged 8-11.

**Executive functioning.** The BRIEF teacher-report version measures executive functioning of PBTS in the school situation; see “Parent-report” for the description of the BRIEF. Validity and reliability are good to excellent, with Cronbach’s alphas ranging from 0.88 to 0.98 as reported in the manual and between 0.82 and 0.97 of the PBTS.\(^2\)
REFERENCES


General Discussion
Chapter 8
AIMS

This thesis describes the PRISMA study; investigating neurocognitive and psychosocial late effects after a pediatric brain tumor and the efficacy of neurofeedback (NF) training as a possible intervention. In this final chapter, the results will be summarized and discussed. Furthermore, limitations of the study, clinical implications and suggestions for future research will be described.

MAIN FINDINGS

For an overview of the studies in this thesis, please see Table 1.

Neurocognitive late effects

This thesis clearly shows that many PBTS suffer from substantial neurocognitive late effects on many domains. First, we conducted a meta-analysis, described in Chapter 2, to determine the extent of the neurocognitive problems. We summarized results of 22 studies concerning intelligence and 7 studies on attention of pediatric brain tumor survivors (PBTS). The results of the meta-analysis show that the PBTS had significantly worse scores on IQ measures and worse attention as compared to normative data. Participants who were treated with radiotherapy and/or chemotherapy had lower intelligence scores than participants who had been treated with surgery only. Also, PBTS with a longer interval between diagnosis and treatment had lower intelligence scores than those with a shorter interval.

In Chapter 4, the results of pre-intervention neurocognitive functioning of a sample of PBTS with neurocognitive complaints are presented. A total of 82 PBTS and 43 sibling controls were assessed. Neurocognitive functioning was studied using a broad battery of computerized tests. PBTS showed problems in various domains: slower processing speed, lower intelligence, and more deficits in attention, short-term memory, executive functions, and visuomotor integration compared to the sibling control group.
Table 1. Main findings described in this thesis

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Short title</th>
<th>Sample</th>
<th>Methods</th>
<th>Outcome measures</th>
<th>Time point</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Meta-analysis of intelligence and attention in PBTS</td>
<td>Intelligence: 22 studies on 710 PBTS</td>
<td>Scores PBTS vs normative data</td>
<td>Intelligence: WISC-III&lt;br&gt;Attention: CPT, CPT II</td>
<td>n/a</td>
<td>PBTS show medium to large depressions in IQ. PBTS show large-sized increases in commission errors, indicating inattentiveness. Radiotherapy, chemotherapy, and longer time since diagnosis are related to worse intellectual outcome.</td>
</tr>
<tr>
<td>4</td>
<td>Neurocognitive functioning in PBTS</td>
<td>PBTS n=82, age in years M=13.85 (SD=3.15), males/females n=40/42&lt;br&gt;Sibling control group n=43, age in years M=14.27 (SD=2.44), males/females n=17/26</td>
<td>T0 scores PBTS vs scores sibling control group</td>
<td>Attention (ANT)&lt;br&gt;Processing speed (ANT)&lt;br&gt;Visual memory (visual sequencing task)&lt;br&gt;Auditory memory (Digit Span forward WISC/ WAIS)&lt;br&gt;Working memory (Digit Span backward WISC/ WAIS)&lt;br&gt;Response inhibition (Stop signal task)&lt;br&gt;Visuomotor integration (Tracking and Pursuit task)&lt;br&gt;Intelligence (abbreviated WISC-III/WAIS-III)</td>
<td>T0</td>
<td>PBTS have problems of medium to large effect size on the whole range of examined neurocognitive functions. Older PBTS at assessment performed better on the tasks than younger PBTS did. None of the medical risk factors were predictive of neurocognitive functioning. PBTS who were younger when they were diagnosed had lower estimated IQ-scores than PBTS who were older at diagnosis.</td>
</tr>
<tr>
<td>5</td>
<td>Psychosocial functioning in PBTS</td>
<td>PBTS n=82, age in years M=13.85 (SD=3.15), males/females n=40/42&lt;br&gt;Sibling control group n=43, age in years M=14.27 (SD=2.44), males/females n=17/26</td>
<td>T0 scores PBTS vs scores sibling control group or normative data</td>
<td>HRQOL (Kidscreen-27, self-report)&lt;br&gt;Social-emotional functioning (SDQ self-, parent- and teacher-report)&lt;br&gt;Self-esteem (SPPC/SPPA, self-report)&lt;br&gt;Fatigue (CIS, self-report)&lt;br&gt;Executive functioning (BRIEF-Parent and BRIEF-Teacher)&lt;br&gt;Attention daily life (SWAN, parent-report)&lt;br&gt;Sleep disturbance (SDSC, parent-report)</td>
<td>T0</td>
<td>PBTS showed decreased psychosocial functioning on HRQOL, social-emotional functioning, fatigue, and executive functioning. Despite the neurocognitive complaints, PBTS functioned within normal ranges in many psychosocial domains or showed only trends towards worse functioning. Physical subscales psychosocial functioning were specifically compromised in PBTS. PBTS behavioral conduct scores, a subscale of self-esteem, were higher than in the normative sample. PBTS did not report social-emotional problems, whereas parents and teachers did. Teachers reported no executive problems in PBTS, whereas parents did.</td>
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</table>
Table 1. Main findings described in this thesis

<table>
<thead>
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<th>Chapter Short title</th>
<th>Sample Methods</th>
<th>Outcome measures</th>
<th>Time point</th>
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<tbody>
<tr>
<td>Meta-analysis of intelligence and attention in PBTS</td>
<td>Intelligence: 22 studies on 710 PBTS Attention: 7 studies on 372 PBTS Average age 6-16 year</td>
<td>Scores PBTS vs normative data Intelligence: WISC-III Attention: CPT, CPT II</td>
<td>T0</td>
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<tr>
<td>Neurocognitive functioning in PBTS</td>
<td>PBTS n=82, age in years M=13.85 (SD=3.15), males/females n=40/42 Sibling control group n=43, age in years M=14.27 (SD=2.44), males/females n=17/26</td>
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<td>T0, T1, T2</td>
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<td>Psychosocial functioning in PBTS</td>
<td>PBTS n=82, age in years M=13.85 (SD=3.15), males/females n=40/42 Sibling control group n=43, age in years M=14.27 (SD=2.44), males/females n=17/26</td>
<td>T0 PBTS showed decreased psychosocial functioning on HRQOL, social-emotional functioning, fatigue, and executive functioning. Despite the neurocognitive complaints, PBTS had intact social-emotional functioning. Teachers reported no executive problems in PBTS, whereas parents did.</td>
<td>T0, T1, T2</td>
</tr>
<tr>
<td>Association BRIEF with neurocognitive tasks</td>
<td>PBTS n=82, age in years M=13.85 (SD=3.15), males/females n=40/42 Sibling control group n=43, age in years M=14.27 (SD=2.44), males/females n=17/26</td>
<td>T0 and T2 data of PBTS receiving neurofeedback training vs PBTS receiving placebo feedback training, controlling for T0 scores</td>
<td>T0</td>
</tr>
<tr>
<td>Neurocognitive functioning (see Chapter 4)</td>
<td>BRIEF-Parent and BRIEF-Teacher</td>
<td>Working memory (Digit Span WISC/WAIS) Response inhibition (Stop signal task) Visual memory (visual sequencing task) Executive attention (executive network ANT)</td>
<td>No significant associations were found between the BRIEF-Parent and the neurocognitive tasks. We found a significant relation between the BRIEF-Teacher Working Memory scores, index-scores and Total scores with neurocognitive tasks. No significant correlations were found between BRIEF-Parent and BRIEF-Teacher</td>
</tr>
<tr>
<td>Randomized controlled trial on neurofeedback in PBTS</td>
<td>PBTS n=71 NF: n=34, age in years M=14.45 (SD=2.99), males/females n=16/18 PF: n=37, age in years M=13.45 (SD=3.28), males/females n=19/18</td>
<td>Neurocognitive functioning (see Chapter 4) Psychosocial functioning (see Chapter 5)</td>
<td>T0, T1, T2</td>
</tr>
<tr>
<td>Neurofeedback training did not have a favorable effect on neurocognitive functioning in PBTS as compared with placebo-feedback training. Neurofeedback training did not have a favorable effect on psychosocial functioning in PBTS as compared with placebo-feedback training. Neurocognitive and psychosocial functioning of PBTS in both training groups were found to have improved over time, but no difference between the groups was observed. Effective interventions aimed at improving neurocognitive and psychosocial functioning of PBTS remain to be developed.</td>
<td></td>
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</table>

Note. The following subtasks of the WISC/WAIS were administered: Arithmetic, Similarities, Block Design, and Picture Completion. ANT=Attention Network Task; BRIEF=Behavior Rating Inventory of Executive Functioning; CISS=Checklist Individual Strength; CPT=Conner’s Continuous Performance Test; HRQOL=Health Related Quality Of Life; M=Mean; ICV=Intraindividual coefficient of variation; NF=Neurofeedback training; PBTS=Pediatric Brain Tumor Survivors; PF=Placebo feedback training; SD=Standard Deviation; SDQ=Strengths and Difficulties Questionnaires; SDSC=Sleep Disturbance Scale for Children; SPPC/SPPA=Self Perception Profile for Children/Adolescents; SWAN=Strengths and Weaknesses of ADHD-symptoms and Normal-behavior; T0=Pre-intervention assessment; T1=Post-intervention assessment; T2=6 Months post-intervention assessment; WISC-III = Wechsler Intelligence Scale for Children – Third version; WAIS-III = Wechsler Adult Intelligence Scale – Third version.
Chapter 8

Findings of our study seem to be in line with the hierarchical conceptual model of neurocognitive functions, that has been suggested by Palmer and colleagues. In this model, processing speed is a function that underlies other neurocognitive functions, and via attention and working memory, also underlies intelligence and academic achievement. In our study, slower processing speed appeared to be an underlying factor for many of the neurocognitive late effects, as scores of PBTS were more depressed on timed tasks as compared with untimed tasks. The low scores on intelligence we found in our sample of PBTS might in part, be a result of slower processing speed. Lower intelligence is a strong predictor of school achievement and vocational success in the general population, as has also been shown in PBTS. Therefore, lower processing speed and intelligence scores may have long lasting and far-reaching consequences for PBTS.

Predictors that may influence neurocognitive functioning of PBTS were also examined. Older age at assessment was associated with better neurocognitive functioning and younger age at diagnosis with lower intelligence. Medical risk factors, such as hydrocephalus or types of treatment, were not associated with worse neurocognitive functioning.

Executive functioning

Executive functions (EF) are called ‘higher order functions’ of the brain and comprise multi faceted neurocognitive functions, such as planning and working memory, and are mainly mediated by the frontal lobe. EF are important functions for daily living, especially in goal directed behavior. In PBTS, these functions are often depressed as a result of the tumor and/or the treatment. In our study, we included different ways to measure EF including performance based neurocognitive tasks and both parent- and teacher-rated EF using the BRIEF questionnaire (Behavior Rating Inventory of Executive Functions). On the neurocognitive tasks, PBTS showed worse working memory and attention functioning as compared to the sibling control group. These findings might be related to the decrease in scholastic performance seen over time in PBTS, as these executive skills are crucial for learning.

Regarding the BRIEF questionnaire (Chapter 5), there was a discrepancy between parent-report and teacher-report. Overall, parents reported more executive problems than the teachers did.

In Chapter 6, we tested the association between the BRIEF-questionnaire and neurocognitive tasks, to identify whether the BRIEF might be suitable as a screening tool to detect children that are at risk for deficits. If the BRIEF would show significant correlations with neurocognitive tasks, this would increase the feasibility to screen all PBTS for neurocognitive problems more frequently, since screening costs and time spent on testing are reduced dramatically.
There were no significant correlations between the BRIEF-Parent and the neurocognitive tasks, while the BRIEF-Teacher did reveal that inattention as measured by the ANT was correlated to the Monitor scale and working memory as measured by the Digit Span of the age appropriate Wechsler intelligence scale was related to the Working Memory scale. Also, there was no significant correlation between the BRIEF-Parent and BRIEF-Teacher, and the outcomes did not differ significantly either.

From our data, it can be concluded that teacher-reported EF problems is a better predictor of neurocognitive problems in PBTS than parent-reported EF problems. However, we should be aware that teachers report on the school situation and thus might not pick up problems as perceived at home. Also, it is important for a more comprehensive assessment of possible problems to include multiple respondents, as they might complement each other. Therefore, we would advise to use a parent-report questionnaire in addition to the BRIEF-Teacher as a screening tool for neurocognitive functioning in PBTS.

### Psychosocial functioning

Neurological late effects in PBTS may contribute to lower psychosocial functioning, especially social competence may be affected as reported in a review paper of Fuemmeler. But the review by Fuemmeler and a review by Nelson et al. both conclude that the findings are mixed as to whether and how psychosocial functioning is affected. Chapter 5 reports the psychosocial functioning of the 82 PBTS at baseline, which was assessed using self-, parent- and/or teacher-report questionnaires. The PBTS suffered from more psychosocial problems, health related quality of life, fatigue, and behavioral executive functioning problems compared to a sibling control group (n = 43) or normative data, as reported by themselves, parents, and teachers.

One of the main findings of our study on psychosocial functioning was the decreased subjective physical functioning. PBTS reported worse physical health related quality of life (HRQOL), a trend toward decreased athletic competence and decreased physical activity. PBTS often suffer from physical impairments, which may be related to lower physical self-esteem. Health care professionals working with PBTS should be aware of possible physical problems and accompanying self-esteem and HRQOL problems.

### Multiple respondents’ dilemma

The multidimensional approach we used, including multiple respondents, proved interesting also with respect to some discrepancies we found. The PBTS in our sample did not report psychosocial problems, but their parents and teachers did report such problems. Furthermore there was a discrepancy between teachers and parents regarding their reports on EF. Teachers reported no problems in PBTS, whereas parents did report problems on both the Behavioral index and the Metacognition index, as well as the Total Problems scale of the BRIEF questionnaire.
Self-report, parent-report, and teacher-report scores might all be influenced by different factors. Parents' perception of the child’s psychosocial functioning has been found to be influenced by their level of distress, whereas the child’s perception may be related to trait anxiety. Other possibilities are that childhood cancer survivors report less psychosocial problems than peers due to social desirability or positive coping. Age of the children could also play a role in the discrepancies in the scores of different respondents: the available normative data was not appropriate for our sample. The age-bands of the normative data differed for the different respondents.

The difference in parent- and teacher-report results regarding executive functioning might also be due to ‘observation environment.’ Teachers observe PBTS in a classroom situation, which is often more structured than the home situation. Possibly, some of the problems which parents observe at home, might not be as striking in structured settings like school. This leads us to believe that PBTS might benefit from a structured environment.

Parents and teachers also have a different frame of reference when perceiving the PBTS. Parents know the premorbid functioning or compare the child to healthy siblings, while teachers might be more prone to compare the child with peers. As many of our participants attended special education (24%), often classmates suffered from chronic conditions, which could also have affected teachers’ judgment of psychosocial functioning. The discrepancies between different respondents and the possible contributing factors illustrate the value of a multidimensional approach when investigating psychosocial functioning in PBTS.

**Intervention**

The neurocognitive deficits exhibited by PBTS call for an intervention to improve neurocognitive functioning. At present there are few effective interventions for PBTS. The interventions that have shown some efficacy in PBTS are a cognitive remediation program, a program that combines memory and attention exercises with cognitive behavioral training, a computerized working memory training, CogMed, and methylphenidate. NF training has shown promising effects in the past in other patient groups, e.g. children with ADHD, however, more recent studies did not show convincing effects of NF training in this group of patients.

**RCT**

The results of the randomized controlled trial (RCT) on NF training in PBTS are discussed in Chapter 7. We examined the effects of NF training on neurocognitive and psychosocial functioning, by randomizing 80 participating PBTS to receive NF training (feedback based on the brain activity) or to receive placebo-feedback training (PF; random feedback, based on a built-in signal generator of the software), and comparing the performance of the two training groups regarding neurocognitive functioning as primary outcome and psychosocial functioning as secondary outcome.
The results reveal no positive effects for NF training over PF training on any of the primary and secondary outcomes. In both groups, PBTS improved over time on the majority of primary and some secondary outcome measures, with small to medium effects (effect sizes between $d = .19$ and $d = .54$). However, no differences between the two groups were found. This finding is in line with recent double-blind RCTs that did not find an effect of NF training as compared to PF training in children with ADHD.\textsuperscript{22-26}

Based on characteristics of our design and the parallel of findings in randomized controlled trials with NF training in children with ADHD, we believe we can conclude the NF training is neither effective in improving neurocognitive functioning nor in improving psychosocial functioning in PBTS.

But what could have caused these improvements observed over time, if not the NF training? Improvements over time have been reported previously in trials investigating NF training,\textsuperscript{23-26} and in other interventions.\textsuperscript{27} Non-specific treatment-effects, such as positive expectations, regression to the mean or even the minutes of rest during the training sessions, could all have caused the improvements.\textsuperscript{28} The time that passed between the assessments may also contribute due to maturation effects, although the improvements were also found on age-corrected scores. It may also be speculated that with the structured frequent sessions we have trained focused attention, increasing functioning overall on neurocognitive domains.

Interestingly, attention did not improve over time, even though the NF training in present RCT focused on the beta 1 brain wave frequency, a frequency band that is strongly associated with attentional abilities. The fact that we did not find that NF training improved attention might also be related to the fact that the attention problems in our sample of PBTS were not pronounced enough. Perhaps there was not much room for improvement in attention functioning, or the selected task was not sensitive to the specific attention problems of the PBTS.

Also the majority of the participants, parents, and teachers reported that they did not think the training had been effective. Surprisingly, the percentage of participants and teachers that did report a potential benefit of the training, was even slightly but not significantly higher in the PF group than in the NF group, further strengthening our believe that the NF training was not effective in our group of PBTS.

**Key messages:***

- PBTS have more neurocognitive problems than the sibling control group
- Even PBTS without traditional risk factors, such as cranial irradiation and young age at diagnosis, may suffer from neurocognitive late effects
- PBTS with neurocognitive complaints suffer from more psychosocial problems than healthy controls, as reported by themselves, parents, and teachers. Specifically physical aspects seem to be affected, as reported by PBTS themselves.
- Parents report more EF problems in PBTS than teachers.
- Teacher-reported EF of PBTS shows some correlations with neurocognitive tasks and parent-reported EF does not.
- NF training is not more effective in PBTS than PF training in improving neurocognitive and psychosocial functioning.

**Limitations and strengths**

There are some limitations that should be taken into account when interpreting the results of this study. Regarding the sample, the results can not be generalized to PBTS without neurocognitive complaints, as study inclusion was based on the presence of parent-reported neurocognitive problems. Furthermore, after enrolment, parents reported larger (executive function) deficits than teachers did. Consequently, as inclusion was based on parent-report only, we might have included participants that had only little neurocognitive deficits as measured by standardized tests. The results in Chapter 4 of this thesis contradicts this though, as the PBTS in our sample had worse neurocognitive functioning as compared to the sibling control group.

The participants bore more risk factors for neurocognitive problems than non-participants. The participants were on average younger at diagnosis, had longer time since diagnosis and had more often had chemotherapy and radiotherapy than the non-participants. This seemingly higher risk for neurocognitive deficits, suggests that a more severely impaired group of PBTS participated in our study. This was expected, as the participants were included based on parent-reported neurocognitive complaints.

Regarding the intervention, increased effectiveness of the NF training might be seen when using newer NF approaches. Recent approaches include transfer sessions, in which the participant receives no feedback, while trying to continue to show the required brain activity. This is done to increase generalization from the training into daily life. Also, we used a 30 s epoch to adjust the threshold in the NF sessions, while a longer threshold of e.g. three minutes, or manually adjusted threshold might have led to a steeper learning curve than the PF training.

Regarding the outcome measurements we chose to use mainly experimental tasks that isolate a single neurocognitive domain, but these tasks are not used in clinical practice or many other brain tumor studies. Thus, for comparability reasons, it would have been interesting to see how the participants performed on widely-used multifaceted tasks that are common in clinical practice, such as the CPT (Conners’ continuous performance task) for attention or the trail-making task, for executive functioning. The usage of experimental tasks made it more difficult to compare our results to other studies.

Our study also has strengths. With the broad test battery that was used, we were able to assess a wide variety of possible neurocognitive and psychosocial problems. Also, the use of objective and subjective tests, as well as multiple informants, provided us with interesting
complementary information from different perspectives. The experimental tasks that were used had the advantage that they isolated the neurocognitive functions we were interested in, using built-in control conditions. Also, test reliability was increased by the use of computerized tests, versus traditional pencil-and-paper tasks.

For the neurocognitive tasks and the fatigue questionnaire, a sibling control group was included. This had the advantage over a non-related control group or normative data that it allowed controlling for genetic factors and socio-economic background.

The use of automatic thresholds for the NF training enabled us to conduct a double blind placebo controlled RCT preventing selection bias. Furthermore, using portable NF devices it was possible to train the participants at a time and location that was convenient for them. We believe this increased the commitment of the participants, reflected by the low attrition.

FUTURE RESEARCH AND CLINICAL IMPLICATIONS

Education and information on late effects for health care providers, parents and teachers
It is evident, from our study and other studies, that many PBTS suffer from neurocognitive and psychosocial late effects. This emphasizes the importance for parents and teachers of PBTS to be aware of the potential consequences of the tumor and the treatment. The Internet could be a good source of information; websites such as www.skion.nl (Dutch) or www.cancer.org (English) provide an overview of possible late effects of cancer treatment. Dutch parents might also www.vokk.nl a useful website, it provides all kinds of information for parents and families of children with cancer.

Besides education on which late effects might occur after successful treatment for a pediatric brain tumor, parents and teachers of PBTS should also be instructed on how to support PBTS that are suffering from poor neurocognitive functioning. From our results, it appears that PBTS with neurocognitive problems might benefit from a structured environment. Another conclusion that could be drawn from our findings is that some PBTS might profit from extra time in the classroom to complete exams or tasks.

Furthermore, it is essential that health care providers working with PBTS know about potential neurocognitive and psychosocial late effects. An important finding in our study on psychosocial functioning of PBTS, was a decrease on multiple physical aspects of psychosocial functioning, such as self-esteem and HRQOL. This could be related to physical late effects of the tumor or the treatment, such as weight gain, hair loss or scars. Health care providers should be aware of these potential problems. Psychosocial interventions might be supportive in increasing self-esteem and HRQOL.
Regular screening in clinical practices to monitor neurocognitive functioning

Screening can help identify possible problems. As a screening tool to assess neurocognitive functioning in PBTS, the BRIEF-Parent might not be the best option because this questionnaire did not show significant correlations with neurocognitive tasks. The BRIEF-Teacher could potentially be used as a screener, as it did show some significant correlations with PBTS neurocognitive functioning. However, in addition to the BRIEF-Teacher, parent reported questionnaires should be explored, as teachers might not be able to detect problems that manifest at home. Alternatives that could be explored include the parent-reported PedsPCF (Pediatric Perceived Cognitive Functioning) item-bank or the CCSS-NCQ (Childhood Cancer Survivors Study – Neurocognitive Questionnaire).  

By monitoring PBTS regularly, problems can be identified in time and the PBTS may be referred to receive appropriate care before problems escalate. Therefore, we would like to advocate using standardized monitoring systems to screen PBTS for problems, e.g. by using patient- and/or parent-reported outcomes (PROs). This could be done in clinical practices where PBTS are seen regularly. A fruitful way to conduct screening without increasing assessment time of the professional or burden for the patient is by using the KLIK system, an online system to monitor functioning of patients over time.

Development of interventions to decrease late effects

It is of utmost importance to develop and further study interventions to decrease neurocognitive late effects and psychosocial consequences in PBTS. The treatment of neurocognitive deficits requires a specific program, targeting processing speed and working memory. With CogMed a good start has been made. CogMed is a working-memory training with promising results shown in recently published randomized controlled trial. A group of childhood cancer survivors was trained with CogMed and compared to a waiting list group. The results showed large improvements, with effect sizes of up to .84, in neurocognitive functioning after the training as compared to the wait list control group. The researchers did not see the purpose of adding an active control group, which limits the possibility to eliminate non-specific training effects. Furthermore, the costs for the training can be substantial.

Besides working-memory training, mindfulness might be an optional intervention for PBTS to train attention. The improvements after the NF and PF training could have been due to the one-minute breaks during the training. During the training sessions, the participant was asked to sit still with eyes closed for one minute after every three minutes of training. This was similar in both training groups. These breaks may have given the training sessions and unintentional mindfulness-like character, which potentially contributed to the improvements in neurocognitive functioning. With TVs, computers, smartphones, and tablets with Internet available everywhere, people might take less time to sit quietly and be mindful in the
moment, reflecting their day. This lack of mindfulness in daily life might interfere with the processing of experiences and attention span. Mindfulness has shown preliminary favorable effects in children and adults with attention problems.\textsuperscript{32} Interventions to improve psychosocial functioning should also be pursued, given the psychosocial problems reported by the PBTS, their parents, and their teachers. Regarding the physical HRQOL problems reported by the PBTS, exercise based interventions should be explored, as suggested by previous studies.\textsuperscript{33,34} Physical exercise has been found to improve overall QOL, happiness, fitness and decrease depression in adult cancer survivors.\textsuperscript{35} Mindfulness or meditation in young adult cancer survivors has been explored in combination with an exercise program.\textsuperscript{36} This study showed improved physical activity, fitness and a trend towards improved mood in the young adult cancer survivors who received the mediation and exercise program as compared to a wait list control group.\textsuperscript{36} A recently updated Cochrane review summarized physical exercise related intervention studies (randomized and non-randomized controlled trials) for childhood cancer survivors.\textsuperscript{37} Small benefits for HRQOL were found, among other outcomes. However, the studies included small numbers of patients, and therefore the authors conclude that more studies are warranted to be conclusive.

**CONCLUSION**

In summary, the results of this study show that PBTS suffer from a wide range of considerable neurocognitive and psychosocial late effects. Results suggest that even PBTS that were traditionally viewed as having low risk for neurocognitive problems (e.g. surgery only, no prior hydrocephalus) may suffer from decreased neurocognitive functioning. The randomized controlled trial in this thesis convincingly shows that NF training does not have a favorable effect on neurocognitive and psychosocial functioning in PBTS above and beyond PF training. Interestingly, the NF as well as the PF training group improved regarding neurocognitive and psychosocial functioning, possibly due to non-specific training effects related to aspects of mindfulness. Continuous efforts are necessary to develop and test effective interventions for neurocognitive and psychosocial functioning of PBTS, as impairments are associated with decreased academic outcomes and vocational success. Some potentially useful programs are being developed and investigated, such as the working-memory training CogMed. Centers for pediatric neuro-oncology should incorporate monitoring of neurocognitive and psychosocial functioning. Conducting appropriate questionnaires via digital monitoring systems could increase feasibility. This will help professionals to identify those patients with specific deficits, who require advice for their home and schooling environment and to timely refer them when necessary.
REFERENCES


Summary
Samenvatting (Summary in Dutch)
List of contributions of all author
Portfolio
Financial Support
Dankwoord – Acknowledgements
Curriculum Vitae
SUMMARY

Summary of ‘Impact of a pediatric brain tumor: Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention’

Each year about 120 children are diagnosed with a brain tumor in the Netherlands (source: SKION). Fortunately, earlier detection and improved treatment options lead to an increasing number of children who survive the disease and its treatment. Survival differs per brain tumor type, but overall the five-year survival rate is up to almost 80%. However, the tumor and its treatment have been known to cause damage to the healthy tissue in the brain, which may cause a range of neurocognitive late effects. For example, many pediatric brain tumor survivors (PBTS) suffer from lower intelligence, which in turn may affect their quality of life.

With more children surviving, the consequences of damage to this growing group become apparent. With this, also the need grows to fully understand the extent of the neurocognitive late effects.

The First Chapter forms a general introduction to this thesis. It outlines the possible neurocognitive late effects PBTS may suffer from after being treated for a brain tumor. Impairments such as slower processing speed may cause to PBTS perform worse in school than peers. The neurocognitive late effects PBTS suffer as a result of the tumor and/or the treatment may lead to worse psychosocial functioning. In order to timely identify neurocognitive problems, it is important to regularly test PBTS. A suitable screener would increase feasibility for monitoring PBTS. Subsequently available interventions for PBTS with neurocognitive problems are described, such as medication. Neurofeedback (NF) training is introduced as a possible addition to the current options.

The aims of the current thesis were:
- To provide a systematic review of studies into intellectual and attention functioning of PBTS.
- To outline the neurocognitive functions that might be affected after treatment for a pediatric brain tumor, while potential predictors for neurocognitive functioning were also investigated.
- To assess the psychosocial functioning of the PBTS.
- To investigate the correlation between proxy-report questionnaires (parent and teacher) and tasks measuring neurocognitive functioning in PBTS.
- To investigate the effects of NF training on neurocognitive and psychosocial functioning in PBTS using a double-blind randomized placebo-controlled trial.
Summary

With Chapter 2, we were interested in the magnitude of the neurocognitive late effects in PBTS. To determine this, we included 29 trials into a meta-analysis: 22 studies on intelligence of 710 PBTS and seven on attention of 372 PBTS. The results show seriously declined intelligence and attention scores as compared to healthy peers. Risk factors for lower intelligence scores were radiation and/or chemotherapy and longer time since diagnosis.

The problems experienced by PBTS require an intervention to improve neurocognitive functioning. To date, few effective interventions for neurocognitive late effects in PBTS are available. The current options are cognitive remediation training, working memory training or pharmacological interventions. These options have some limitations, such as side effects of the pharmacological treatments or small effect sizes. Neurofeedback (NF) training could be an interesting addition to the existing interventions. NF training is based on operant conditioning, in which the participant acquired control over the brain waves measured on an EEG. NF training showed promising effects in other patient groups, such as children with attention deficit hyperactivity disorder (ADHD). Chapter 3 describes the design of the PRISMA study; a double-blind randomized placebo-controlled trial to investigate the effects of NF training on neurocognitive late effects in PBTS. The study was set up from the Emma Children’s Hospital/Academic Medical Center and we collaborated with four other Dutch University Medical Centers (UMC): the VUmc Amsterdam, UMC Utrecht, Radboud UMC Nijmegen, and Maastricht UMC. The intervention consisted of 30 sessions of NF or placebo-feedback (PF) training. For this, PBTS (8-18 years> 2 years after treatment) were invited to participate if they had neurocognitive complaints. Their neurocognitive and psychosocial functioning was tested before the intervention (baseline), immediately after and 6 months after the intervention. To gain insight into their functioning at baseline, we compared them with a sibling control group. A total of 82 PBTS (average age 13.9 years) and 43 siblings as control group (mean age 14.3 years) were enrolled into the PRISMA-study.

In Chapters 4 & 5, the baseline data of the PRISMA-study are presented. The neurocognitive functioning of the enrolled PBTS with neurocognitive complaints was compared to the functioning of a sibling control group in Chapter 4. Tests of attention, processing speed, memory, visuomotor integration, executive functioning, and intellectual functioning were used to create a detailed picture of the neurocognitive functioning. We also investigated the association between neurocognitive functioning and medical risk factors. PBTS showed that they had more difficulties than the sibling control group in the majority of the assessed domains. Especially tasks that were time-critical seemed to differentiate between PBTS and the sibling control group, with PBTS performing worse. There was no correlation between the medical risk factors and neurocognitive functioning. This suggests that even PBTS without the traditional medical risk factors for neurocognitive late effects, such as hydrocephalus, early age at diagnosis or cranial radiation, are at risk of neuro-cognitive problems.
The neurocognitive late effects PBTS suffer as a result of the tumor and/or the treatment may lead to worse psychosocial functioning in PBTS. Studies on different aspects of psychosocial functioning have been contradictory, some reporting no psychosocial problems and other studies reporting lower psychosocial functioning in PBTS. Therefore, studying psychosocial functioning, especially of PBTS with neurocognitive complains, is warranted. Psychosocial functioning can be measured using self-report or proxy-report, e.g. parent-report or teacher-report. These respondents have a different frame of reference, which may result in differing insights. By including several respondents, a more complete picture of the psychosocial functioning of the PBTS can be created. Psychosocial functioning of the PBTS with neurocognitive complaints was assessed using various self-, parent- and/or teacher-report questionnaires: health related quality of life (HRQOL), self-esteem, social-emotional functioning, fatigue, sleep disturbance, attention in daily life, and behavioral executive functioning (EF). The functioning was compared to normative data or the sibling control group (fatigue only). The results are described in Chapter 5. PBTS subjectively suffered more from social-emotional problems, fatigue, and behavioural executive functioning problems, as reported by themselves, parents and teachers. Especially physical aspects of psychosocial functioning appeared to be depressed. However, the difference between the PBTS and the normative data was less than a standard deviation, and therefore the scores appear to be within the normal ranges of psychosocial functioning.

The neurocognitive and psychosocial late effects can worsen over time as a result of difficulty to process new information and learn new skills. Therefore, it is important to monitor changes in neurocognitive functioning by testing PBTS regularly. Neurocognitive assessment is time consuming and expensive. A screener could be a cheaper, faster alternative to assess PBTS. The BRIEF (Behavior Rating Inventory of Executive Function) questionnaire could be a possible screener tool, as it is designed to assess behavioral executive functions in daily life. In Chapter 6, the utility of the BRIEF questionnaire as a possible screener for executive function problems in PBTS was researched. The correlation between the BRIEF-Parent and BRIEF-Teacher questionnaire and neurocognitive tasks measuring the same executive functions. The BRIEF-Parent seems unsuitable as a screener as the scores did not correlated to the tasks. The BRIEF-Teacher showed some significant correlations with EF tasks. PBTS with clinically elevated BRIEF-Teacher scores had worse scores on all executive function tasks, as compared to PBTS without elevated scores. The BRIEF-Parent and BRIEF-Teacher were not correlated to each other. The BRIEF-Teacher seems to be a better tool for screening executive functions in PBTS than the BRIEF-Parent, however, other questionnaires should be explored in the future.
Chapter 7 describes the results of the PRISMA-study. We examined the effects of NF training by treating half of the participants with NF training (on the basis of the brain activity) and the other half with placebo-feedback (PF) training (random), and comparing the two groups. Of the 82 PBTS who completed the baseline assessment, 80 PBTS were randomized to receive NF or PF training; 71 PBTS completed the training and post-training assessment; 68 PBTS completed the training and the 6 months post-training assessment. The results show no difference between the two groups. In short, we have found no positive effect of NF training on the functioning of PBTS above and beyond PF training. Based on these results, we cannot advise NF training for neurocognitive problems after treatment for a brain tumor.

In Chapter 8, a general discussion of the main findings of the studies is presented. The key messages are:

- PBTS have more neurocognitive problems than the sibling control group.
- Even PBTS without traditional risk factors, such as cranial irradiation and young age at diagnosis, may suffer from neurocognitive late effects.
- PBTS with neurocognitive complaints suffer from more psychosocial problems than healthy controls, as reported by themselves, parents, and teachers. Specifically, physical aspects seem to be affected, as reported by PBTS themselves.
- Parents report more EF problems in PBTS than teachers.
- Teacher-reported EF of PBTS shows some correlations with neurocognitive tasks and parent-reported EF does not.
- NF training is not more effective in PBTS than PF training in improving neurocognitive and psychosocial functioning.

We also reflect on the limitations of the studies in this thesis. As PBTS could only participate if they had neurocognitive problems, the results cannot be generalized to the entire group of PBTS. Also, the epoch to adjust the threshold of feedback in the training was short. Further, there were no ‘transfer sessions’, which are sessions to increase generalization from the training into daily life.

Recommendations for future research and clinical practice are made based on the findings in this thesis. Parents, teachers and health care providers that work with PBTS should be well aware of the possible late effects. Also, suggestions for parents and teachers of PBTS are made. They should provide structure for the PBTS and if indicated give extra time for completing a task. We, furthermore, stress the importance of monitoring neurocognitive and psychosocial functioning of PBTS, in order to timely identify problems, before they intensify. The BRIEF-
Teacher could be used as a screening tool, although other options should be explored. Some recommendations are made for systems that could increase feasibility of the monitoring, such as the KLIK-system. This is an online system to monitor patients over time using Patient or Parent Reported Outcomes (PROs).

Lastly, the quest for effective interventions to improve neurocognitive and psychosocial functioning of PBTS should continue. An intervention for neurocognitive functioning should be targeted at processing speed and working memory. CogMed and Mindfulness are mentioned as possible contenders. Regarding psychosocial functioning, physical exercises should be explored, as the psychosocial problems reported by PBTS seemed to be mainly physical, and also because exercises have been found to improve quality of life and increase happiness.

In summary, the results of this study show that PBTS have neurocognitive and psychosocial late effects as a result of the treatment. It is important to monitor these deficits in order to timely refer PBTS to proper care if indicated. New interventions that might be effective to decrease neurocognitive problems in PBTS should be developed and studied.
Samenvatting van ‘Impact of a pediatric brain tumor: Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention’

Elk jaar worden in Nederland ongeveer 120 kinderen gediagnosticeerd met een hersentumor (bron: SKION). Vroege diagnose en betere behandeling hebben ertoe geleid dat een groeiend aantal kinderen de ziekte en de behandeling overleven. Het overlevingspercentage verschilt per soort hersentumor, maar over het algemeen is het vijf-jaar-overlevingspercentage bijna 80%. Helaas is bekend dat de tumor en de behandelingen ook het gezonde weefsel in de hersenen kunnen beschadigen, wat tot neurocognitieve problemen kan leiden. Zo hebben veel kinderen na (behandeling van) een hersentumor een lagere intelligentie dan gezonde leeftijdsgenoten, wat een negatief effect kan hebben op hun kwaliteit van leven.

Met de stijging van het aantal kinderen dat een hersentumor overleeft, worden de neurocognitieve gevolgen van de tumor en de behandeling ook steeds duidelijker. Hiermee groeit de noodzaak om de omvang en de aard van de neurocognitieve problemen nog beter in kaart te brengen.

In het eerste hoofdstuk, een algemene inleiding op dit proefschrift, worden de mogelijke neurocognitieve en psychosociale gevolgen van een hersentumor op de kinderleeftijd beschreven. Problemen zoals een tragere verwerkingssnelheid kunnen ervoor zorgen dat deze kinderen slechter presteren op school dan leeftijdsgenoten. Deze problemen kunnen leiden tot problemen in psychosociaal functioneren. Het is van belang dat kinderen die zijn behandeld voor een hersentumor regelmatig worden getest, zodat problemen tijdig kunnen worden ontdekt. Een goede screener zou hierbij kunnen helpen. Vervolgens worden de beschikbare interventies, zoals medicatie, voor kinderen met neurocognitieve problemen na behandeling voor een hersentumor beschreven. Neurofeedback (NF) training wordt geïntroduceerd als mogelijke aanvulling op de huidige interventies.

We hadden voor dit proefschrift de volgende doelen voor ogen:
- Een systematisch overzicht geven van studies naar intelligentie en aandacht van kinderen die zijn behandeld voor een hersentumor
- De neurocognitieve functies die mogelijk zijn aangedaan na behandeling van een hersentumor op kinderleeftijd meten, alsmede mogelijke voorspellers voor neurocognitief functioneren
- Het psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor onderzoeken.
Samenvatting (Summary in Dutch)

- De correlatie meten tussen de proxy-vragenlijsten (ouder en docent) en taken die het neurocognitief functioneren van kinderen die zijn behandeld voor een hersentumor testen.
- De effecten van NF training op de het neurocognitief en psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor te onderzoeken met behulp van een dubbelblinde gerandomiseerde placebo-gecontroleerde studie.

In Hoofdstuk 2 worden de resultaten van de meta-analyse naar de omvang van de neurocognitieve problemen van kinderen die zijn behandeld voor een hersentumor beschreven. In de meta-analyse zijn 29 studies geïncludeerd: 22 studies naar intelligentie van in totaal 710 kinderen die zijn behandeld voor een hersentumor en zeven studies naar de aandacht van in totaal 372 kinderen die zijn behandeld voor een hersentumor. De uitkomsten laten zien dat kinderen die zijn behandeld voor een hersentumor een aanzienlijk lagere intelligentie en meer aandachtsproblemen hebben in vergelijking met gezonde leeftijdsgenoten. Risicofactoren voor lagere intelligentiescores waren: bestraling en / of chemotherapie en langere tijd sinds diagnose.

De neurocognitieve problemen die kinderen die zijn behandeld voor een hersentumor laten zien, vragen om een interventie om hun functioneren te verbeteren. Er zijn momenteel weinig effectieve interenties beschikbaar om het neurocognitief functioneren van deze kinderen te verbeteren. Huidige opties zijn cognitieve training, een geheugentraining, een werkgeheugentraining of medicijnen. Deze opties hebben een aantal beperkingen, zoals bijwerkingen van medicijnen, bovendien lieten studies slechts kleine effecten zien. NF training is een mogelijk interessante aanvulling op de bestaande interenties. NF training is gebaseerd op operante conditionering: de deelnemer leert controle te krijgen over de hersengolven met een EEG. NF training liet veelbelovende effecten zien bij andere patiëntengroepen, zoals kinderen met aandachtstoornis-hyperactiviteitstoornis (ADHD).

Hoofdstuk 3 beschrijft de opzet van de PRISMA-studie; een dubbelblinde gerandomiseerde placebo-gecontroleerde studie naar de effecten van NF training op de neurocognitieve problemen bij kinderen die zijn behandeld voor een hersentumor. Het onderzoek is opgezet vanuit het Emma Kinderziekenhuis/AMC en er werd samengewerkt met het VUmc Amsterdam, UMC Utrecht, Radboud UMC Nijmegen en Maastricht UMC. De training bestond uit 30 sessies van NF of placebo-feedback (PF) training. Hiervoor werden kinderen die zijn behandeld voor een hersentumor (8-18 jaar en > 2 jaar na de behandeling) uitgenodigd om deel te nemen als ze neurocognitieve klachten hadden. Hun neurocognitieve en psychosociale functioneren werd getest voor de interventie (voormeting), direct erna en 6 maanden na de interventie. Om inzicht te krijgen in hun functioneren voor de interventie, werden ze vergeleken met een controlegroep van broers en zussen. In totaal werden 82
Samenvatting (Summary in Dutch)

kinderen die zijn behandeld voor een hersentumor (gemiddelde leeftijd 13,9 jaar) en 43 broers en zussen (gemiddelde leeftijd 14,3 jaar) geïncludeerd in de PRISMA-studie.

De resultaten van de voormeting van de PRISMA-studie worden in de hoofdstukken 4 & 5 beschreven. In Hoofdstuk 4 werd het neurocognitief functioneren van de kinderen die zijn behandeld voor een hersentumor vergeleken met het functioneren van de controlegroep. Aandacht, verwerkingssnelheid, geheugen, visuomotorische integratie, executieve functies, en intellectueel functioneren werden getest om een gedetailleerd beeld te krijgen van het neurocognitief functioneren. We onderzochten ook de samenhang tussen neurocognitief functioneren en medische risicofactoren, zoals radiotherapie en tumorgraad. Kinderen die zijn behandeld voor een hersentumor bleken slechter te presteren dan de controlegroep op het merendeel van de onderzochte gebieden. Vooral op taken waarbij tijd een rol speelde, was er een substantieel verschil tussen kinderen die zijn behandeld voor een hersentumor en de controlegroep, waarbij kinderen die zijn behandeld voor een hersentumor slechter presteerden. Er was geen correlatie tussen de medische risicofactoren en neurocognitief functioneren. Dit suggereert dat zelfs kinderen zonder de klassieke medische risicofactoren voor neurocognitieve late effecten, zoals hydrocefaalus, jonge leeftijd bij diagnose of bestraling op het hoofd, toch risico lopen op neurocognitieve problemen.

De neurocognitieve problemen bij kinderen die zijn behandeld voor een hersentumor als gevolg van de tumor en / of de behandeling kunnen leiden tot problemen in het psychosociaal functioneren. Eerdere studies over het psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor lieten tegenstrijdige resultaten zien. Sommige studies vonden geen psychosociale problemen en andere studies vonden dat kinderen die zijn behandeld voor een hersentumor meer psychosociale problemen lieten zien dan leeftijdsgenoten. Daarom is het van belang om het psychosociaal functioneren van deze kinderen te onderzoeken, met name van de kinderen met neurocognitieve klachten. Psychosociaal functioneren kan worden gemeten met behulp van zelf-rapportage of proxy-rapportage vragenlijsten, bijvoorbeeld ingevuld door de ouder of docent. Deze respondenten hebben allemaal een eigen referentiekader, wat tot verschillende inzichten kan leiden. Door de informatie van verschillende respondenten te verzamelen, ontstaat een completer beeld van het psychosociaal functioneren van een kind. In Hoofdstuk 5 werd het psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor onderzocht met behulp van diverse vragenlijsten, ingevuld door verschillende respondenten: het kind zelf, een ouder en een docent. Met de vragenlijsten werd gezondheids-gerelateerde kwaliteit van leven, zelfvertrouwen, sociaal-emotioneel functioneren, vermoeidheid, slaapstoornissen, aandacht, en executief functioneren (EF) gemeten. De uitkomsten werden vergeleken met normatieve data of de controlegroep van broers en zussen (alleen voor vermoeidheid). Kinderen die zijn behandeld voor een hersentumor hadden significant meer last van
psychosociale problemen, zoals gerapporteerd door henzelf, ouders en leerkrachten. Vooral op fysieke aspecten van psychosociaal functioneren scoorden ze lager. Echter, het verschil tussen kinderen die zijn behandeld voor een hersentumor en normatieve data was minder dan een standaarddeviatie en dus lijken de scores binnen de grenzen van normaal psychosociaal functioneren te vallen.

Vaak verergeren de neurocognitieve problemen bij kinderen die zijn behandeld voor een hersentumor, door moeite met het verwerken van nieuwe informatie of het leren nieuwe vaardigheden. Daarom is het belangrijk om veranderingen in het neurocognitief functioneren door de tijd te volgen, door kinderen regelmatig te testen. Een neuropsychologisch onderzoek kost veel tijd en is duur. Een screeningsvragenlijst zou een goedkoper, sneller alternatief kunnen zijn om het functioneren van kinderen die zijn behandeld voor een hersentumor te onderzoeken. De BRIEF (Behavior Rating inventaris van Executive Function) vragenlijst zou een optie kunnen zijn, omdat de lijst is ontworpen om problemen met executieve functies in het dagelijks leven te meten. In Hoofdstuk 6 werd de bruikbaarheid van de BRIEF-vragenlijst onderzocht als mogelijke screener voor executieve problemen bij kinderen die zijn behandeld voor een hersentumor. De correlatie tussen de BRIEF-Ouder en BRIEF-Docent vragenlijst en neurocognitieve taken die EF meten (aandacht, cognitieve flexibiliteit, inhibitie, visueel geheugen, en werkgeheugen) werd bekeken. De BRIEF-Ouder lijkt niet geschikt als screener, omdat de scores niet correleerden met de EF taken. De BRIEF-Docent liet wel enkele significante correlaties zien. Kinderen met klinisch verhoogde BRIEF-Docent scores hadden slechtere scores op alle EF taken, in vergelijking met kinderen zonder verhoogde scores. De BRIEF-Ouder en BRIEF-Docent waren niet gecorreleerd met elkaar. Uit de resultaten lijk de BRIEF-Docent een beter instrument voor het screenen van EF bij kinderen die zijn behandeld voor een hersentumor dan de BRIEF-Ouder, maar andere vragenlijsten zouden moeten worden overwogen in de toekomst.

Hoofdstuk 7 beschrijft de resultaten van de PRISMA-studie. We onderzochten de effecten van NF training door de deelnemers met behulp van loting in twee groepen te verdelen. De ene helft van de deelnemers kreeg NF training (op basis van de hersenactiviteit) en de andere helft placebo-feedback (PF) training (met willekeurige feedback). Van de 82 kinderen die de voormeting deden, werden 80 kinderen gerandomiseerd om NF dan wel PF training te ontvangen. 71 kinderen maakten de training af en namen deel aan de nameting. Uiteindelijk werd na 6 maanden de nameting gedaan bij 68 kinderen. De resultaten lieten geen verschil zien tussen de twee trainingsgroepen. Kortom, we hebben niet gevonden dat NF training het functioneren van kinderen die zijn behandeld voor een hersentumor meer verbetert dan PF training. Op basis van deze resultaten kunnen we niet adviseren om NF training aan te bieden aan kinderen met neurocognitieve problemen na behandeling voor een hersentumor.
In **Hoofdstuk 8** wordt een algemene discussie van de belangrijkste bevindingen van het onderzoek gepresenteerd.

De belangrijkste boodschappen zijn:
- Kinderen die zijn behandeld voor een hersentumor hebben meer neurocognitieve problemen dan de controlegroep van broers en zussen
- Zelfs kinderen zonder de bekende risicofactoren, zoals bestraling van het hoofd en jonge leeftijd bij diagnose, kunnen last hebben van neurocognitieve problemen
- Kinderen met neurocognitieve klachten na behandeling voor een hersentumor hebben meer last van psychosociale problemen dan gezonde controles, zoals gerapporteerd door zichzelf, ouders en docenten. Vooral fysieke aspecten lijken een probleem te zijn, zoals gerapporteerd door henzelf.
- Ouders rapporteren meer EF problemen bij kinderen die zijn behandeld voor een hersentumor dan docenten.
- Door de docent gerapporteerde EF van kinderen die zijn behandeld voor een hersentumor toont enkele correlaties met neurocognitieve taken, door de ouder gerapporteerde EF niet.
- NF training is niet effectiever in het verbeteren van het neurocognitief en psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor dan PF training.

Deze studie heeft ook enkele beperkingen. Aangezien kinderen alleen konden deelnemen aan de studie als zij neurocognitieve problemen hadden, kunnen de resultaten niet worden gegeneraliseerd naar de hele groep van kinderen die zijn behandeld voor een hersentumor. Ook was de tijdspanne waarop de drempelwaarde van feedback werd aangepast vrij kort. Binnen de interventie werden er geen ‘transfer sessies’ gedaan, dit zijn sessies om overdracht van de training naar het dagelijks leven te vergroten.

Diverse aanbevelingen voor toekomstig onderzoek en de klinische praktijk worden gegeven op basis van de bevindingen in dit proefschrift. Ouders, docenten en zorgverleners die met kinderen die zijn behandeld voor een hersentumor werken moeten goed worden geïnformeerd over de mogelijke late effecten. Ook worden er suggesties voor de omgangswijze van ouders en leerkrachten van kinderen die zijn behandeld voor een hersentumor gedaan. Het is bijvoorbeeld belangrijk dat zij structuur aanbrengen voor de kinderen en dat zij, zo nodig, extra tijd geven voor een taak.

Het is van groot belang om het neurocognitief en psychosociaal functioneren van kinderen die zijn behandeld voor een hersentumor te monitoren door hen regelmatig te screenen op eventuele problemen. Zo kunnen problemen tijdig worden geïdentificeerd. De BRIEF-Docent kan worden gebruikt als een screener, hoewel ook andere vragenlijsten zouden moeten
worden onderzocht. We doen een aanbeveling voor systemen die de uitvoerbaarheid van het monitoren kunnen verhogen, zoals het KLIK-systeem. Dit is een online systeem om patiënten te monitoren over verloop van tijd met behulp van door de patiënt of ouder gerapporteerde uitkomsten.

Tenslotte is het belangrijk dat de zoektocht naar effectieve interventies om neurocognitieve en psychosociale problemen te verminderen bij kinderen na behandeling voor een hersentumor, doorgaat. Een interventie voor het verminderen van neurocognitieve problemen van kinderen na behandeling van een hersentumor zou vooral gericht moeten zijn op verwerkingssnelheid en werkgeheugen. Cogmed en Mindfulness worden genoemd als mogelijke opties. Wat betreft het psychosociaal functioneren kan lichaamsbeweging als interventie worden onderzocht, omdat de psychosociale problemen die door kinderen die zijn behandeld voor een hersentumor werden gerapporteerd vooral van fysieke aard lijken te zijn, en ook omdat in eerdere studies is gevonden dat lichaamsbeweging de stemming en de kwaliteit van leven kan verbeteren.

Samenvattend laten de resultaten van deze studie zien dat kinderen die zijn behandeld voor een hersentumor neurocognitieve en psychosociale late Effecten hebben als gevolg van de tumor en / of behandeling. Het is belangrijk om deze problemen te monitoren zodat deze kinderen tijdig kunnen worden verwezen naar de juiste zorg als dat nodig is. Nieuwe interventies die mogelijk effectief zijn bij het verminderen van neurocognitieve problemen van kinderen na behandeling voor een hersentumor dienen te worden ontwikkeld en onderzocht als aanvulling op de huidige opties.
LIST OF CONTRIBUTIONS OF ALL AUTHORS

Neurofeedback to improve neurocognitive functioning of children treated for a brain tumor: design of a randomized controlled double-blind trial
*BMC Cancer 12:581, 2012
*Chapter 2

*M.A. de Ruiter* conception and design of the study, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version
*A.Y.N. Schouten-van Meeteren* conception and design of the study, critical revision of the manuscript for important intellectual content, approved the final version
*R. van Mourik* conception and design of the study, critical revision of the manuscript for important intellectual content, approved the final version
*T.W.P Janssen* critical revision of the manuscript for important intellectual content, approved the final version
*J.E.M. Greidanus* data acquisition, critical revision of the manuscript for important intellectual content, approved the final version
*J. Oosterlaan* conception and design of the study, critical revision of the manuscript for important intellectual content, approved the final version
*M.A. Grootenhuis* conception and design of the study, critical revision of the manuscript for important intellectual content, approved the final version

Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis
*Chapter 3

*M.A. de Ruiter* conception and design of the study, data acquisition, analyses, and interpretation, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version
*R. van Mourik* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
*A.Y.N. Schouten-van Meeteren* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
*M.A. Grootenhuis* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
*J. Oosterlaan* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
List of contributions of all authors

Timed performance weaknesses on computerized tasks in pediatric brain tumor survivors: a comparison with sibling controls.
*J Child Neuropsych*, Epub ahead of print, 2015
*Chapter 4*

M.A. *de Ruiter* conception and design of the study, data acquisition, analyses, and interpretation, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version

M.A. *Grootenhuis* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

R. *van Mourik* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

H. *Maurice-Stam* conception and design of the study, analyses and interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

M.H.M. *Breteler* critical revision of the manuscript for important intellectual content, approved the final version

C. *Gidding* provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version

L.R. *Beek* provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version

B. *Granzen* provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version

D.G. *van Vuurden* provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version

A.Y.N. *Schouten-van Meeteren* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

J. *Oosterlaan* conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints
*Qual Life Res* 25(2):435-446, 2015
*Chapter 5*

M.A. *de Ruiter* conception and design of the study, data acquisition, analyses, and interpretation, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version
List of contributions of all author

A.Y.N. Schouten-van conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
D.G. van Vuurden provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version
H. Maurice-Stam conception and design of the study, analyses and interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
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B. Granzen provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version
J. Oosterlaan conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
M.A. Grootenhuis conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

The association between the behavior rating inventory of executive functioning and neurocognitive testing in children diagnosed with a brain tumor
Submitted
Chapter 6

M. de Vries data analyses, and interpretation, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version
M.A. de Ruiter conception and design of the study, data acquisition, critical revision of the manuscript for important intellectual content, approved the final version
K.J. Oostrom conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
A.Y.N. Schouten-van Meeteren conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
H. Maurice-Stam conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
J. Oosterlaan conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
M.A. Grootenhuis conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
Neurofeedback ineffective in pediatric brain tumor survivors: Results of a double-blind randomized placebo-controlled trial


Chapter 7

M.A. de Ruiter conception and design of the study, data acquisition, analyses, and interpretation, wrote the first draft, critical revision of the manuscript for important intellectual content, approved the final version

J. Oosterlaan conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

A.Y.N. Schouten-van Meeteren conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

H. Maurice-Stam conception and design of the study, analyses and interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version

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B. Granzen provided us with potential patients from their medical centres and provided us with the medical data of the participants and non-participants, approved the final version

H.N. Caron conception and design of the study, approved the final version

M.A. Grootenhuis conception and design of the study, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version
PORTFOLIO

AMC Graduate School for Medical Sciences PhD Portfolio

Summary of PhD training. Teaching and parameters of esteem

PhD student: Marieke Montgomery-de Ruiter
PhD period: December 2008 - December 2016
Supervisors: Prof dr MA Grootenhuis, Prof dr J Oosterlaan
Co-supervisors: Prof dr HN Caron, dr AYN Schouten-van Meeteren

1. PhD training

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General courses
- Basic course AMC World of Science
- Reference Manager
- Better use of PubMed
- Scientific writing in English
- Practical Biostatistics
- BROK: Basic course in Legislation and Organisation for Clinical researchers

Seminars, workshops and master classes
- Masterclass ‘How to publish in the Journal of Pediatric Psychology’ by dr. L. Barakat
- Elsevier workshop ‘Author and Reviewer’
- CV workshop by dr. K. Fijnvandraat

Presentations
The efficacy of neurofeedback to improve attention and memory in childhood brain tumour survivors: a randomized controlled trial.
- Poster presentation Dutch Society for Psychosocial Oncology (NVPO), Utrecht, the Netherlands
- Poster presentation International Society for Pediatric Oncology (SIOP), Boston, USA
- Poster presentation Emma Children’s Hospital scientific symposium, Amsterdam, the Netherlands
Neurocognitive consequences of treatment for pediatric brain tumors: a meta-analysis.
- Oral presentation Pediatric Neuro Oncological Platform (KNOP) research symposium, Amsterdam, the Netherlands 2010 - 0.5
- Poster presentation International Symposium on Pediatric Neuro-Oncology (ISPNO) Vienna, Austria 2010 - 0.5
- Poster presentation Dutch Pediatric Psychology Network (PPN) symposium, Amsterdam, the Netherlands 2011 - 0.5
- Poster presentation Emma Children’s Hospital scientific symposium, Amsterdam, the Netherlands 2011 - 0.5
- Oral presentation; NVPO, Utrecht, the Netherlands 2012 - 0.5

Attention networks in pediatric brain tumor survivors
- Oral presentation ISPNO, Toronto, Canada 2012 - 0.5
- Poster presentation SIOP, London, England 2012 - 0.5
- Poster presentation 2nd Amsterdam Pediatric Symposium (AKS). Amsterdam, the Netherlands 2013 - 0.5

Neurocognitive profile of pediatric brain tumor survivors: a comparison with siblings
- Oral presentation multidisciplinary meeting KNOP, the Netherlands 2012 - 0.5
- Poster presentation PPN symposium, Amsterdam, the Netherlands 2014 - 0.5
- Poster presentation SIOP, Toronto, Canada 2014 - 0.5

Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints
- Poster presentation PPN symposium, Amsterdam, the Netherlands 2014 - 0.5
- Poster presentation SIOP, Toronto, Canada 2014 - 0.5

Neurofeedback in children treated for a brain tumor: Results of a randomized controlled double-blind trial
- Oral presentation IPOS world congress, Washington, USA 2015 - 0.5
- Poster presentation AKS, Amsterdam, the Netherlands 2015 - 0.5
### (Inter-)national conferences

- Emma Children’s hospital (EKZ) Scientific Symposium 2010, 2011 0.5  
- International Society for Pediatric Oncology (SIOP) 2010, 2014 2  
- Pediatric Neuro Oncological Platform (KNOP) research Symposium 2010 0.25  
- International Symposium on Pediatric Neuro-Oncology (ISPNO) 2010, 2012 2  
- Dutch Society for Psychosocial Oncology (NVPO) 2011, 2012 0.5  
- Pediatric Psychological Network (PPN) Symposium 2011, 2014 0.5  
- Amsterdam Pediatric Symposium (AKS) 2013, 2015 0.5  
- International Psycho Oncology Society (IPOS) World Congress 2015 1  

### 2. Teaching

<table>
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#### Lecturing

- University of Leiden, guest lecture on neurofeedback training for the course Intervention Strategies in Clinical Neuropsychology in the Master Clinical Neuropsychology 2010 0.5  
- University of Amsterdam, guest lectures on psychosocial care and age appropriate communication with patients for residents in the Academic Medical Centre 2013-2014 2  
- VU University, guest lecture on the (neuro) psychological late effects of brain cancer and cancer treatment for the Master Clinical Neuropsychology 2014 0.5  

#### Supervising

- Zeliha Pekcan, master thesis Clinical Neuropsychology, VU University, ‘Attention functioning of childhood brain tumor survivors compared to their siblings’ 2012 1  
- Leontine Stolk, master thesis Psychology, University of Amsterdam, ‘De invloed van de behandeling van een hersentumor op responsinhibitie en snelheid van informatieverwerking’ 2013 1  
- Dora Csermak, master thesis Clinical Neuropsychology, VU University, ‘General well-being after a brain
tumour: the influence of psychosocial problems, fatigue and self-esteem on the quality of life of Dutch paediatric brain tumour survivors’
- Arnout Smit, master thesis Clinical Neuropsychology, VU University, ‘Pediatric brain tumors and IQ: The effects of age at diagnosis, radiotherapy, and chemotherapy’ 2014 1
- Sander Schippers, master thesis Clinical Neuropsychology, VU University, ‘Effects of neurofeedback on visuomotor functioning in children with a brain tumor’ 2015 1

3. Parameters of Esteem  Year

Scholarship
- Spinoza scholarship (UvA) €400 for ISPNO in Toronto, CA. 2012

4. Publications  Year

Peer reviewed

Neurofeedback to improve neurocognitive functioning of children treated for a brain tumor: design of a randomized controlled double-blind trial 2012
BMC Cancer

Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis 2013
M.A. de Ruiter, R. van Mourik, A.Y.N. Schouten-van Meeteren, M.A. Grootenhuis, J. Oosterlaan
Dev Med Child Neurol
Volume of white matter hyperintensities is an independent predictor of intelligence quotient and processing speed in children with sickle cell disease.


Br J Haematol 2014

Timed performance weaknesses on computerized tasks in pediatric brain tumor survivors: a comparison with sibling controls.


J Child Neuropsych 2015

Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints

M.A. de Ruiter, A.Y.N. Schouten-van Meeteren, D.G. van Vuurden, H. Maurice-Stam, C. Gidding, L.R. Beek, B. Granzen, J. Oosterlaan, M.A. Grootenhuis

Qual Life Res 2015

Neurofeedback ineffective in pediatric brain tumor survivors: Results of a double-blind randomized placebo-controlled trial

M.A. de Ruiter, J. Oosterlaan, A.Y.N. Schouten-van Meeteren, H. Maurice-Stam, D.G. van Vuurden, C. Gidding, L.R. Beek, B. Granzen, H.N. Caron, M.A. Grootenhuis

Eur J Cancer 2015

The association between the behavior rating inventory of executive functioning and neurocognitive testing in children diagnosed with a brain tumor

M. de Vries, M.A. de Ruiter, K.J. Oostrom, A.Y.N. Schouten-van Meeteren, H. Maurice-Stam, J. Oosterlaan, M.A. Grootenhuis

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Impact of a paediatric brain tumor
Research into neurocognitive late effects and psychosocial consequences and the evaluation of a potential intervention

Door Marieke A. Montgomery-de Ruiter

Op vrijdag 9 december om 10.00u in de Agnietenkapel, Oudezijds Voorburgwal 229-231 te Amsterdam
Aansluitend bent u van harte welkom op de receptie in Frenzi, Zwanenburgwal 232 te Amsterdam (5 minuten lopen)

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