Executive Functions in Survivors of Pediatric Brain Tumor and Consequences for Societal Participation

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS ....................................................................................................... 4

ABBREVIATIONS.................................................................................................................... 6

LIST OF PAPERS...................................................................................................................... 8

GENERAL SUMMARY............................................................................................................ 9

1. INTRODUCTION................................................................................................................ 12

  1.1 Pediatric brain tumors and their treatment ................................................................. 14
    1.1.1 Epidemiology and etiology ..................................................................................... 14
    1.1.2 Tumor classification ............................................................................................. 15
    1.1.3 Symptoms, treatment, and survival rates .............................................................. 15

  1.2 Late effects and long-term outcomes ......................................................................... 17
    1.2.1 Medical late effects .............................................................................................. 18
    1.2.2 Neurocognitive late effects .................................................................................... 20
    1.2.3 Mental health outcomes ....................................................................................... 23
    1.2.4 Fatigue .................................................................................................................. 25
    1.2.5 Long-term outcomes; psychosocial adjustment and socioeconomic outcomes ..... 26

  1.3 Executive functions ..................................................................................................... 28
    1.3.1 Conceptualizations and developmental models ..................................................... 28
    1.3.2 Hierarchical developmental models ....................................................................... 30
    1.3.3 Neurodevelopmental cascade models for declines in IQ and academic achievement in PBT survivors.......................................................................................... 30
    1.3.4 Adding temperature and context to the mix: the hot/cool distinction ................. 32
    1.3.5 Assessment of EFs ............................................................................................... 34

2. AIMS .................................................................................................................................... 36

  2.1 Paper I ............................................................................................................................ 36
  2.2 Paper II ............................................................................................................................ 36
  2.3 Paper III ........................................................................................................................ 36
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ABBREVIATIONS

ABCL – Adult Behavior Checklist (ASEBA)
ADHD – Attention deficit/hyperactivity disorder
ADL – Activities of daily life
ALL – Acute lymphoblastic leukemia
ASEBA – Achenbach System of Empirically Based Assessment
ASR – Adult Self-Report (ASEBA)
BRIEF – Behavior Rating Inventory of Executive Function – Parent report version
BRIEF-A – Behavior Rating Inventory of Executive Function – Adult version
CAVLT-2 – Children’s Auditory Verbal Learning Test – Second edition
CBCL – Child Behavior Checklist (ASEBA)
CCS – Childhood cancer survivors
CNS – Central nervous system
CWIT – Color-Word Interference Test
CPT 3 – Conners’ Continuous Performance Test – Third edition
CRT – Cranial/craniospinal radiation therapy
D-KEFS – Delis-Kaplan Executive Function System
EF – Executive functions
FQ – Fatigue Questionnaire
HPA – Hypothalamic–pituitary–adrenal (HPA) axis
HRQoL – Health-related quality of life
HRT BC – Hit Reaction Time Block Change (CPT 3)
ICCC-3 – International Classification of Childhood Cancer – Third edition
ICD-10 – International Classification of Disease - 10th edition
ICP – Intracranial pressure
IQ – Intelligence quotient
MRI – magnetic resonance imaging
pABI – Pediatric acquired brain injury
PBT – Pediatric brain tumor
PedsQL – Pediatric Quality of Life Inventory 4.0
PedsQL-MFS – PedsQL-Multidimensional Fatigue Scale
QoL – Quality of life
RAVLT – Rey Auditory Verbal Learning Test
SCL-90-R – Symptom Checklist 90 Revised
SES – Socioeconomic status
TBI – Traumatic brain injury
TMT – Trail Making Test
YSR - Youth Self-Report (ASEBA)
WAIS-IV – Wechsler Adult Intelligence Scale –IV
WASI – Wechsler Abbreviated Scale of Intelligence
WHO – World Health Organization
WISC-IV – Wechsler Intelligence Scale for Children –IV
LIST OF PAPERS

This thesis is based on the following papers which are referred to in the text by their Roman numbers I – III.

Paper I
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Paper II
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Paper III
GENERAL SUMMARY

Pediatric brain tumors (PBTs) are the second most common neoplasm after leukemia, and the most common of the childhood solid tumors, with about 40 new cases in Norway per year. The overall prognosis after treatment is encouraging and continuously improving, leading to an increasing number of long-term survivors. However, survivors of PBT often experience serious debilitating late effects, such as physical and sensory sequelae, persistent symptoms of fatigue, neurocognitive impairments, and psychological problems. This is particularly true of PBT survivors who have undergone complex treatment regimens, i.e., a combination of surgery, chemotherapy and/or cranial/craniospinal radiation therapy (CRT). These late effects may have major impacts on quality of life (QoL), and may potentially reduce survivors’ possibilities of functioning independently and participating in society. Neurocognitive impairments, and especially executive dysfunction, may play a special role in this respect.

Executive functions (EFs) refer to a subset of cognitive functions involved in controlling, organizing and directing neurocognitive activity, behavioral actions, emotional responses and social learning. They encompass cognitive (“cool”) skills that operate in emotionally neutral contexts, e.g., attention, working memory, planning, problem-solving, and behavioral (“hot”) skills, e.g., the ability to adapt to changes in one’s environment, to monitor and regulate emotions and behaviors, and to exert socially appropriate inhibitory control. EFs develop all through childhood and early adult life, paralleling the maturation of the brain, and disruptions to the development of these skills may have negative consequences for social functioning, academic/educational achievement, and vocational goal attainment.

The literature on the presence of executive dysfunction and how it affects psychosocial functioning and social attainment in this subset of childhood cancer survivors is sparse. Hence, this cross-sectional study aimed to provide a better understanding of EF and their associations to long-term functional outcomes in adolescent and young adult survivors of PBT, by utilizing self- and informant reports of EF, psychological and social functioning, fatigue, educational adjustments, employment/training status, and government benefit uptake. For a subgroup of participants, performance-based measures of neurocognitive functioning were also employed.

The purpose of this thesis was to investigate the presence of executive dysfunction and possible idiosyncratic EF profile in young adult survivors of PBT, as well as the presence of
psychological problems and symptoms of fatigue (Paper I), and the association between executive dysfunction, psychosocial adjustment, and social attainment (i.e., educational/vocational achievement and financial independence) in young adult survivors of PBT (Paper II) and adolescent survivors of PBT (Paper III).

The findings in Paper I demonstrated that young adult PBT survivors reported significantly more psychological and emotional difficulties and fatigue compared to a healthy control group. However, between group differences in these domains were small, and the largest effects were found on measures reflecting EF. Furthermore, the young adult PBT survivors reported significantly more difficulties with metacognitive (“cool”) aspects of EF compared to behavioral (“hot”) aspects. The findings also confirmed that certain PBT treatment-related factors and medical late effects are of particular concern for the development of negative long-term outcomes. A history of seizures represented a particular risk factor in the development of executive dysfunction, and surgery combined with CRT and chemotherapy was significantly associated with higher levels of reported mental fatigue in this survivor group. Other known medical and demographic risk factors such as younger age at diagnosis, hydrocephalus, and having undergone multiple surgeries (including patients with combined treatment), were not found to be associated with poorer outcomes in this sample.

In Paper II, the findings showed that young adult PBT survivors are at increased risk of poor social attainment compared to their healthy peers, as significantly more PBT survivors than controls reported to have received educational adjustments and substantial government benefits, and significantly more survivors than controls were currently not engaged in regular employment/training. However, young adult PBT survivors and healthy controls did not differ on educational level or living situation (i.e., living with caregivers vs. independently). Further, we expanded on the findings from Paper I by demonstrating that self-reported problems with EF, along with symptoms of fatigue, were most strongly associated with problems with social attainment, with psychological symptoms less impactful. Complex treatment regimens were significantly related to poorer social outcomes, and the presence of post-treatment psychiatric comorbidity was significantly associated with government benefit uptake.

In Paper III, we demonstrated the presence of executive dysfunction also in a group of adolescent PBT survivors, as evidenced by both parent and self-reports, as well as performance-based results. A similar EF profile to that of the young adult group emerged (i.e.,
more difficulties with metacognitive/"cool” aspects of EF compared to behavioral/”hot” aspects), and we again demonstrated a link between executive dysfunction and problems with psychosocial adjustment. Similar to the young adult PBT survivor group, surgery combined with CRT and chemotherapy was significantly related to higher rates of parent and self-reported problems on various questionnaires, as was male sex, and embryonal tumor or astrocytoma.

In summary, the findings from the three studies indicate the presence of impairments of both “hot” and “cool” aspects of EF in long-term survivors of PBT, but with relatively more prominent impairments in the “cool” domain, and that negative long-term social outcomes were strongly related to executive dysfunction.
1. INTRODUCTION

Half a century ago, Bloom, Wallace, and Henk (1969) of the Royal Marsden Hospital in London, UK, were among the first physicians to raise concern about the threat that PBTs and their treatment pose to the long-term quality of life (QoL) in children. They observed a high risk of “producing an impaired intellect, or disturbed emotions” in children with medulloblastomas treated with cranial or craniospinal radiotherapy, especially in children younger than 2 years. Since then, the PBT literature has become increasingly sophisticated, investigating factors and mechanisms related to adverse long-term outcomes, and expanding on physical and sensory late effects by also taking into account aspects of cognitive, emotional and social development. Initially, studies assessing neurocognitive late effects were focused primarily on intellectual ability, i.e., IQ, and its decline. More recently however, possible underlying processes of this decline have been recognized, acknowledging problems of attention, processing speed, and working memory as important mechanisms. As the number of aging PBT survivors is steadily increasing, the risk of adverse long-term outcomes that they carry into adulthood has become increasingly apparent. Compared to other childhood cancer survivors, this patient subset seems particularly vulnerable, as many struggle to negotiate the transition into adulthood and achieve adult milestones (e.g., independence, social adjustment, education, vocation). Although studies have identified several demographic, treatment-related and physical risk factors, there remains a need for more knowledge on the underlying mechanisms of poor long-term outcomes, such as the link between psychological factors, e.g., cognitive and emotional functioning, and how PBT survivors function in the “real world”. Do psychological problems contribute to poorer social engagement and less than optimal educational and vocational outcomes, and in which way? Are some psychological domains more essential than others in contributing to poorer long-term functioning?

Executive functions (EFs), a subset of higher-order cognitive functions dedicated to maintaining an overarching control over mental activity and behavior, are now firmly acknowledged for their importance for social adjustment and academic, educational and vocational success (Muscara, Catroppa, & Anderson, 2008; Sirois et al., 2017; Willard, Allen, Hardy, & Bonner, 2015; Wolfe et al., 2013; Zelazo, Blair, & Willoughby, 2016). The first descriptions of EF appeared in the mid 1800’s, with the famous case of Phineas Gage (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994), linking executive dysfunction, i.e., changes in personality and behavior, to frontal lobe pathology. The research field was
later expanded by descriptions of abnormal cognition and behavior after frontal lobe lesions in Luria’s (1966, 1973) influential work on victims of war injuries, and also case descriptions of frontal lobectomies performed in order to treat psychiatric conditions (Walsh, 1978). Fascinating case accounts thus became the starting point of a fast-growing research field within cognitive neuroscience, and knowledge about these functions is continuously refined. Today, the terms “executive functions” and “frontal lobe functions” are no longer used interchangeably, as it has become clear that these functions rely not only on the frontal lobes, but also on the intactness of multiple cooperating brain structures and networks (Gioia, Isquith, & Guy, 2001; Kalbfleisch, 2017; Stuss & Alexander, 2000). For example, the cerebellum, which is the most frequent location for PBTs, has rich neuroanatomical connections to the rest of the brain, including the frontal lobes, and thus plays a crucial role in EF and their development (Moberget et al., 2015; Stoodley & Schmahmann, 2009). Also, it has been acknowledged that the developmental trajectory of EFs is prolonged, spanning across the first three decades of life, paralleling the structural maturation and remodeling of the frontal lobes (Anderson, 2010; De Luca & Leventer, 2008). Therefore, sustaining a brain tumor at any time point during childhood, and in any location, may seriously hamper the development of EF.

For these reasons, EF has increasingly been the subject of studies in the PBT literature, especially over the past decade, and although still limited in numbers, findings indicate that survivors of PBT are at risk of executive dysfunction. However, although it is generally acknowledged that EF plays an important role in the successful navigation through life, there are currently few studies exploring the presence and degree of long-term executive dysfunction in PBT survivors beyond the neurocognitive domains processing speed, attention span and working memory. Moreover, few studies have investigated the extent to which executive dysfunction contributes to negative long-term social, academic and vocational outcomes in PBT survivors.

The main purposes of the study presented in this thesis are to explore the EF profile of adolescent and young adult PBT survivors, and to investigate the association between EF difficulties and long-term outcomes, such as living situation, social adjustment, educational level, and vocational and financial status, while also taking into account reports of fatigue and psychological and emotional problems. In this introduction, current knowledge regarding PBTs, PBT treatment and PBT-related late effects is summarized in chapters 1 and 2,
respectively. As EFs are the main outcome of interest in the thesis, chapter 3 is devoted to presenting EF conceptualizations and developmental models, methods of assessing EFs and related challenges, presence of executive dysfunction in PBT survivors, and the role of EFs in negotiating and achieving educational, vocational and social goals in this patient population.

1.1 Pediatric brain tumors and their treatment

1.1.1 Epidemiology and etiology

In Norway, the yearly incidence rate of central nervous system (CNS) tumors (i.e., intracranial and intraspinal tumors) in children is 3.9 per 100,000 (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018). CNS tumors are the most common form of solid tumors, and the second most common form of cancer in children after leukemia. For unknown reasons, the incidence of CNS tumors in the Nordic countries is the highest in the world (Johannesen, Angell-Andersen, Tretli, Langmark, & Lote, 2004; Schmidt et al., 2011, Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018). However, it is not unlikely that the high incidence rate reflects the completeness of the Nordic registries, as well as international variations in classification.

There are a few key differences between brain tumors that occur in adults and those that occur in children. For example, the histology of PBTs is different from that which is more commonly seen in adults, as children are more prone to developing astrocytomas, medulloblastomas and ependymomas, whereas adults are more likely to develop brain metastases, glioblastomas and meningiomas (see section 1.1.3 for tumor classification in children) (Gjerstad, Helseth, & Rootwelt, 2010; Helseth et al., 2003). Also, PBTs are more often localized infratentorially (brain stem and cerebellum), while brain tumors in adults are more often found supratentorially (the cerebrum) (Gjerstad et al., 2010; Helseth et al., 2003). Furthermore, brain tumors in children are more often benign than in adults, and have a better prognosis than adults with a similar condition.

The etiology of PBT is for a vast majority of patients poorly understood, and only for a few patients may the development of a brain tumor be linked to a genetic predisposition (e.g., tuberous sclerosis, neurofibromatosis types 1 and 2) (Gjerstad et al., 2010). Changes in environmental risk factors have been considered an unlikely explanation, as the incidence rates have remained stable over the last decades (Schmidt et al., 2011). The only well-
documented environmental risk factor is ionizing radiation, for example as a consequence of CRT for other malignancies (Wilne, Dineen, Domnett, Chu, & Walker, 2013).

1.1.2 Tumor classification
In the current standard classification system for childhood cancer, i.e., the third edition of the International Classification of Childhood Cancer (ICCC-3; Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005), diagnostic groups and subgroups are categorized according to tumor morphology (histological classification) and primary site of origin, with an emphasis on morphology. Diagnostic Group III in the ICCC-3 corresponds to CNS and miscellaneous intracranial and intraspinal neoplasms, with Diagnostic Subgroup IIIa-f corresponding to: ependymomas and choroid plexus tumors, astrocytomas, intracranial and intraspinal embryonal tumors, other gliomas, other specified intracranial and intraspinal neoplasms, and unspecified intracranial and intraspinal neoplasms, respectively (see Table 1). Astrocytomas (malignant and benign) are the most numerous of the PBTs, followed by intracranial and intraspinal embryonal tumors (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018).

For grading the severity of CNS tumors, the World Health Organization has four categories: grade I and II for non-cancerous, slow growing (benign) tumors, and grade III and IV for cancerous, faster growing (malignant) tumors that pose greater challenges to treatment (Louis et al., 2016). This classification is based on histological characteristics, and lately also more frequently on molecular markers.

1.1.3 Symptoms, treatment, and survival rates
Presenting symptoms of PBTs may include diffuse signs such as nausea, vomiting, headache, personality changes, irritability, and drowsiness. These symptoms may be due to an increase of intracranial pressure (ICP) caused by the tumor blocking one or more of the ventricles that drain cerebrospinal fluid (Ullrich, 2009). Depending on the localization of the tumor, focal symptoms may include uncoordinated muscle movements, problems walking (ataxia), seizures, endocrine problems (diabetes and/or hormone regulation), visual changes or double vision, hearing loss, facial paralysis, hemiparesis/-plegia, and changes in respiratory and cardiac function (Gjerstad et al., 2010). Several types of procedures aid the diagnostic process, and may include neurological examination, brain imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI]), lumbar puncture (cerebrospinal fluid
analysis), tumor biopsy, and analyses of genetic mutations and the molecular basis of the tumor.

**Table 1** Diagnostic Group III of the ICCC-3 (Steliarova-Foucher et al., 2005): CNS and miscellaneous intracranial and intraspinal neoplasms (simplified).

<table>
<thead>
<tr>
<th>ICCC-3</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa. Ependymomas and choroid plexus tumors</td>
<td>Ependymomas, choroid plexus tumors</td>
</tr>
<tr>
<td>IIIb. Astrocytomas</td>
<td>High and low grade gliomas, chiasmatic/optic gliomas</td>
</tr>
<tr>
<td>IIIc. Intracranial and intraspinal embryonal tumors</td>
<td>Medulloblastomas, medulloepitheliomas</td>
</tr>
<tr>
<td></td>
<td>Atypical teratoid/rhabdoid tumors (AT/RTs)</td>
</tr>
<tr>
<td>IIId: Other gliomas</td>
<td>Oligodendrogliomas, mixed and unspecified gliomas, neuroepithelial glial tumors of uncertain origin</td>
</tr>
<tr>
<td>IIIe: Other specified intracranial and intraspinal neoplasms</td>
<td>Pituitary adenomas and carcinomas, tumors of the sellar region (craniopharyngiomas), pineal parenchymal tumors, neuronal and mixed neuronal-glial tumors (dysembryoplastic neuroepithelial tumors [DNETs], gangliogliomas), meningiomas</td>
</tr>
<tr>
<td>IIIf: Unspecified intracranial and intraspinal neoplasms</td>
<td></td>
</tr>
</tbody>
</table>

Over the past decades considerable advances have been made in neurosurgery, CRT, and chemotherapy, and PBT treatment may include one or a combination of these approaches. Selection of treatment regimen depends largely on the type, size, and location of the tumor, as well as the age and overall health of the child. Neurosurgical resection of the tumor is usually considered the first and most important step in the treatment process, and total resection of benign tumors with clear borders is in many cases curative (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018). However, in many cases, chemotherapy and/or CRT is necessary, for example in cases where the tumor is inoperable or only partly operable (e.g., due to location in eloquent or vital regions), or not curative (i.e., malign tumors) (Ullrich et al., 2015). Proton beam radiation therapy has increasingly taken over for photon therapy in recent decades, as the former has been shown to minimize radiation to the healthy tissue.
surrounding the tumor, all the while maintaining the maximum dose to the tumor itself (Kahalley et al., 2016; King et al., 2017). In Norway, CRT is not administered to children below the age of four, due to the potential negative long-term sequelae such as neurocognitive decline, developmental delay and endocrine deficiencies (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018). Chemotherapy, which has significantly less severe long-term side effects than CRT, was initially used mainly as an adjuvant treatment to neurosurgery and CRT, but is now also used in order to postpone or replace radiation therapy in the youngest patients (Karajannis, Allen, & Newcomb, 2008). Advancements in the knowledge of molecular markers have led to personalized chemotherapy, which is showing promising results as a new treatment strategy (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018).

The overall prognosis after treatment for intracranial tumors in children is encouraging, as improved medical treatment has led to considerably higher 5-year survival rates, i.e., about 66-75% (Gatta et al., 2014; Noone et al., 2018). For Norway specifically, the 5-year survival rate is about 78% for all CNS tumors, but subgroup variations are considerable, as treatments and prognoses vary widely based on age, tumor location, size, histology, and staging (Nasjonalt kvalitetsregister for barnekreft, Årsrapport 2018).

1.2 Late effects and long-term outcomes
As the number of childhood cancer survivors is continuously growing, research efforts have increasingly been aimed at monitoring and managing late effects, applying both clinical and patient-reported outcome measures. Late effects may, separately and together, hamper normal development across the lifespan, and have a cumulative negative effect on educational attainment, employment, financial independence, independent living, social relationships and overall QoL (Brand, Chordas, Liptak, Manley & Recklitis, 2016; Brinkman et al., 2016; Hocking et al., 2015; Moyer et al., 2012; Zebrack et al., 2007; Zeltzer et al., 2008). However, children treated for brain tumors have often been excluded from childhood cancer research protocols because of probable brain pathology. Further, studies of pediatric acquired brain injury (pABI) do often not include PBT survivors, due to confounding cancer treatment effects (Brand et al., 2016; de Ruiter et al., 2016).
The question of which survivors are at risk of poor long-term outcomes is profoundly complex, involving a vast array of disease-related, individual and environmental factors. Figure 1 (adopted and modified from Stavinoha, Askins, Powell, Pillay Smiley, and Robert [2018]) summarizes factors that may contribute to and moderate late effects and long-term outcomes in PBT survivors, mirroring the cumulative burden of PBT and its treatment, as well as the developmental complexity involved in long-term outcomes. In the following sections, a summary of current knowledge on PBT-related late effects and associated risk factors is presented.

1.2.1 Medical late effects
Medical late effects may be summarized in 5 categories; physical, endocrinological, neurological, and sensory late effects, and secondary neoplasms (Turner, Rey-Casserly, Liptak, & Chordas, 2009), all of which have the potential to negatively impact long-term socioeconomic outcomes and overall QoL. Physical late effects may include changes to body image and physical appearance, i.e., either localized changes, such as scars from craniotomies, alopecia, and alterations in bone structure of the skull caused by CRT, or global changes, such as short stature (e.g., due to hypothalamic-pituitary axis disruption after CRT) (Turner et al., 2009). Physical late effects such as these will often represent a psychological burden for the young patient.

Disruptions to the hypothalamic-pituitary axis caused by the tumor itself or its treatment may lead to various endocrinopathies. Endocrinological late effects may include growth hormone deficiency, hypothyroidism, diabetes insipidus, obesity, osteopenia/osteonecrosis (especially after frequent use of glucocorticoids), long-term gonadotropin deficiency and deficiencies in sex hormones (e.g., hyperprolactinemia, central precocious puberty, premature ovarian failure in females), and are particularly common after CRT (Turner et al., 2009).
**Figure 1** Factors that may contribute to and moderate late effects and long-term outcomes in PBT survivors (adopted and modified from Stavinoha, Askins, Powell, Pillay Smiley, and Robert [2018]).
Neurological and sensory late effects such as vasculopathy (e.g., strokes, moyamoya disease), seizures, peripheral neuropathy, motor dysfunction (e.g., motor clumsiness, decreased distal sensation, ataxia, hemiparesis), and auditory and visual impairments, are relatively common in PBT survivors, and may occur as a consequence of tumor involvement, neurotoxicity caused by treatment, and/or neurological complications (seizures, hydrocephalus) (Ullrich & Embry, 2012). Cerebellar mutism, or posterior fossa syndrome, may occur postoperatively in 15% to 25% of patients (Ullrich & Embry, 2012), and involves a loss of speech, commonly accompanied by pseudobulbar dysfunction, irritability, ataxia, poor attention and eye contact, vomiting, and incontinence. Speech is typically regained within days to months, whereas difficulties with vomiting/appetite may take months to recover from. Emotional symptoms may possibly last for several years, although such symptoms are often confounded by other aspects of surviving a PBT and its treatment.

1.2.2 Neurocognitive late effects

Neurocognitive impairment, and more specifically, executive function (EF), may be of particular relevance to long-term functional outcomes in PBT survivors. EF and its definitions and theoretical conceptualizations will be addressed in more detail in chapter 3. In the following, knowledge on risk factors in PBT survivors associated with neurocognitive impairments in general is summarized.

Neurocognitive late effects are relatively common in PBT survivors (40-100 %), as PBT and its treatment disrupt the development of the immature brain and have a negative cascading impact on neurocognitive skills, intellectual ability (IQ) and academic learning (Bull & Kennedy, 2013; de Ruiter, van Mourik, Schouten-van Meeteren, Grootenhuis, & Oosterlaan, 2013; Duffner, 2010; King, Ailion, Fox, & Hufstetler, 2019; Palmer, 2008; Stavinoha et al., 2018). Over the last decade, several neurodevelopmental models explaining this cascade have been put forward, describing the interrelations between impairments of processing speed, attention, working memory and general EFs, and the combined and unique impact of these domains on IQ and academic achievement (King et al., 2019; Palmer, 2008; Wolfe, Madan-Swain, & Kana, 2012). As the impact of EFs is at the center of these models, they will be addressed in further detail in chapter 3.
Several risk factors for developing long-term neurocognitive sequelae have been identified, involving individual factors (e.g., age at diagnosis/treatment), tumor- and treatment variables, neurological comorbidities, and nondisease-related factors (e.g., environmental support, parental socioeconomic status [SES]) (Bull & Kennedy, 2013; Stavinoha et al., 2018). 

Younger age at diagnosis and treatment may put patients at higher risk of developing neurocognitive impairment (e.g., lower IQ, processing speed, working memory, attention and academic performance), due to the vulnerability of the immature brain and the interruption of development (e.g., rapid cell proliferation, dendritic and axonal outgrowth, myelination) (de Ruiter et al., 2013; Stavinoha et al., 2018). Furthermore, time lapse since treatment completion seems to be a significant influencing factor, with PBT survivors “growing into” deficits, especially as social engagement and academic demands increase (Anderson, Northam, & Wrennall, 2019; Stavinoha et al., 2018).

Several studies have investigated the effects of tumor location on long-term neurocognitive functioning. The cerebellum, with its connections to extensive regions of the cerebrum, is the most common site of PBTs, and is known to be involved in both motor and cognitive functions, including EF (Moberget et al., 2015). The cerebellum appears to play a crucial role during neurodevelopment, as lesions to the cerebellum and disruptions of the cerebello-cerebral connectivity in children generally lead to more pronounced neurocognitive deficits than in adults (Ailion et al., 2016; Moberget et al., 2015). Moreover, some findings suggest that patients with infratentorial tumors (i.e., below the tentorium) have greater neurocognitive impairments than those with supratentorial tumors (i.e., above the tentorium) (Stavinoha et al., 2018). A possible explanation for this difference may be that patients with infratentorial locations are more often treated with CRT (Corti et al., 2020; Raghubar, Mahone, Yeates, & Ris, 2017). However, studies on tumor location have in general shown mixed results, as both supra- and infratentorial tumor locations have been associated to poorer neurocognitive outcomes (Corti et al., 2020; de Ruiter et al., 2013; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Olsson, Lundgren, Hjorth, & Perrin, 2016; Raghubar et al., 2017; Stavinoha et al., 2018). Moreover, infra- and supratentorial tumor locations may show different patterns of neurocognitive outcomes, possibly because tumors and their treatment in either locations affect different neuroanatomical areas, and/or because of the different neuroplastic reorganization processes that take place after tumor occurrence (Corti et al., 2020). Also, not surprisingly, larger tumor size causing more widespread neuroanatomical effects, has been associated with poorer long-term neurocognitive outcomes (Stavinoha et al., 2018).
One of the most well-documented treatment-related risk factors for neurocognitive late effects in survivors of PBT is CRT, due to its severe neurotoxic effects on the immature brain, e.g., compromised white matter integrity and impaired growth of new neurons post-treatment (Ailion et al., 2016; Bledsoe, 2016; de Ruiter et al., 2013; Stavinoha et al., 2018). CRT is associated with deficits of attention, processing speed and EF, as well as yearly declines of two to four intelligence quotient (IQ) points. Patients with younger age at treatment, higher radiation doses, larger radiation fields, and CRT combined with chemotherapy, are at increased risk of poorer neurocognitive outcomes (Bull, Spoudeas, Yadegarfar, & Kennedy, 2007; Duffner, 2010; Kahalley et al., 2016; Raghubar et al., 2017; Stavinoha et al., 2018).

However, a growing body of literature on PBT survivors treated with proton therapy suggests a decrease in exposure to healthy brain tissue, and thereby overall toxicity, thus reducing the risk of neurocognitive impairment (Gross et al., 2019; Rey-Casserly & Diver, 2019).

The independent effects of chemotherapy on neurocognitive functioning is notoriously difficult to isolate, because of the confounding effects of the tumor mass itself and administration of other treatment paradigms (Stavinoha et al., 2018). Although chemotherapy is considered less neurotoxic than CRT, there are several chemotherapeutic agents that are known to increase the risk of neurocognitive impairments (e.g., Methotrexate) (Liu et al., 2015). Furthermore, studies on neurocognitive late effects in children treated chemotherapeutically for acute lymphoblastic leukemia (ALL) have shown long-term deficits of processing speed, attention, and aspects of EF, possibly due to disruption of white matter integrity (Kanellopoulos et al., 2016; McCurdy, Rane, Daly, & Jacobson, 2016; Raghubar et al., 2017).

Although patients treated with surgery only (i.e., without CRT or chemotherapy) have shown some advantage compared to those treated with CRT and chemotherapy, findings nevertheless show persistent neurocognitive dysfunction also in the surgery only subset, particularly for those who have undergone multiple surgeries (McCurdy, Rane, et al., 2016; Riva & Giorgi, 2000; Rønning, Sundet, Due-Tønnessen, Lundar, & Helseth, 2005).

Secondary neurological comorbidities and complications, such as seizures and hydrocephalus caused by the mass effect of the tumor, tumor treatment, or a combination of these, may result in damage and/or alterations to neuroanatomical structures and networks, and have also been
linked to poorer neurocognitive outcomes in adulthood (Aarsen et al., 2009; Brinkman, Krasin, et al., 2016; Liu et al., 2015; McCurdy, Rane, et al., 2016; Vingerhoets, 2006).

Nondisease-related factors such as pre-existing neurodevelopmental disorders and poorer premorbid developmental, neurocognitive, and neurological functioning, may be significant predictors of long-term neurocognitive dysfunction (Ullrich & Embry, 2012). Also, high stress levels and female sex have been associated to a risk of poorer neurocognitive outcomes, although studies have failed to replicate findings regarding sex (Olsson et al., 2016; Stavinoha et al., 2018; Ullrich & Embry, 2012). Environmental characteristics such as social support and family factors, e.g., parental health, education, and SES, and the impact of PBT on family interactions, may with time become increasingly important and contribute to observable differences between PBT survivors and peers (Klassen, Anthony, Khan, Sung, & Klaassen, 2011; Stavinoha et al., 2018; Ullrich & Embry, 2012).

1.2.3 Mental health outcomes
Although the majority of long-term childhood cancer survivors are psychologically well-adjusted, survivors of CNS tumors remain a vulnerable subset in this regard, and have been found to be at risk of experiencing significantly more psychological and emotional distress, including symptoms of depression, anxiety, posttraumatic stress, negative self-appraisal, suicidal ideation, psychoses, behavioral problems and somatization, compared to other CCS populations, siblings and healthy peers (e.g., Brinkman, Recklitis, Michel, Grootenhuis, & Klosky, 2018; Brinkman et al., 2013; Cousino et al., 2017; Shah et al., 2015; Zebrack et al., 2004; Zebrack et al., 2007; Zeltzer et al., 2008; Zeltzer et al., 2009). Further, it seems that PBT survivors may have a distinct pattern of psychological symptoms compared to other pABI populations, as they seem to struggle more with internalizing than externalizing problems (Brinkman, Li, et al., 2016; Poggi et al., 2005; Zebrack et al., 2004; Zebrack et al., 2007; Zeltzer et al., 2009). PBT survivors, particularly adolescent and young adult survivors, may be placed at increased risk of low self-esteem and self-identity issues due to social factors, such as the sense of being “left behind”, feeling disconnected from their peers, or having anxieties about altered physical appearance (Vetsch et al., 2017). Psychological problems may persist into adulthood, as findings indicate that psychological distress may emerge several decades after the original diagnosis (Brinkman et al., 2013).
Several risk factors for elevated distress symptoms in adulthood have been identified. Demographic and socioeconomic risk factors of psychological distress are much the same as for the general population, and include female sex, older age at diagnosis (i.e., during adolescence), single or divorced marital status, lower education, unemployment, and an annual household income of <$20,000 (Bitsko et al., 2016; Ness et al., 2008; Stavinoha et al., 2018; Zebrack et al., 2007; Zeltzer et al., 2008; Zeltzer et al., 2009). On the other hand, psychological symptoms may also mediate poorer QoL, lower income, lower education, and disability status, and the causal direction between these factors remains unclear (Bell, Ownsworth, Lloyd, Sheeran, & Chambers, 2018; Brinkman, Li, et al., 2016; Brinkman, Recklitis, et al., 2018).

Treatment-related and medical risk factors, such as severe medical late effects (e.g., relapses, secondary malignancies), functional or sensorimotor deficits, pain, and cardiovascular, endocrine, and/or pulmonary conditions subsequent to cancer treatment (particularly CRT) are linked to a risk of developing symptoms of depression, anxiety, and posttraumatic stress (e.g., Cousino et al., 2017; Greenberg, Kazak, & Meadows, 1989; Ozono et al., 2007; Vuotto et al., 2017). Also, self-perceptions of poor physical health status and physical symptoms has been linked to higher levels of psychological distress, along with other individual psychological characteristics such as inefficient coping styles, social skill development and temperament in both adolescent and young adult survivors (Brinkman et al., 2013; Kupst & Patenaude, 2016; Schwartz et al., 2012; Stavinoha et al., 2018; Vuotto et al., 2017). Furthermore, psychological distress may predict poor health behaviors, i.e., smoking, alcohol use, fatigue, and altered sleep (Zeltzer et al., 2009). Lastly, and importantly, neurocognitive dysfunction, particularly EF problems, has been consistently associated with emotional and behavioral health concerns (Stavinoha et al., 2018).

The importance of social factors, such as increased parental psychological symptoms, family dysfunction, and separation from peers and social networks, have increasingly been associated to negative impacts on psychological outcomes in survivors of childhood cancers (Cousino et al., 2017; Klassen et al., 2011). For example, one study showed an indirect effect of illness-specific family burden on the number of late effects and parent reported survivor internalizing problems (Cousino et al., 2017). Also, the influence of demographic factors, such as marital status and income, may underline the importance of
socioemotional and instrumental support for long-term psychological functioning. Altogether, these findings demonstrate that PBT survivors may, for a wide variety of reasons, be at risk of negative long-term psychological and emotional functioning.

However, there are some important shortcomings in the extant studies of long-term mental health in childhood cancer survivors that need to be considered. Compared to the literature on the adult PBT survivor population, current knowledge on mental health in adolescent PBT survivors is sparser, as only a few studies have examined mental health among adolescent CCS populations, especially among adolescent PBT survivors (Bell et al., 2018; Brinkman, Li, et al., 2016; Brinkman, Recklitis, et al., 2018). Furthermore, according to a systematic review by Bell et al. (2018) focusing on studies of younger PBT survivors, most of the extant studies of QOL and mental health have utilized proxy reports (i.e., parent/caregiver and/or teacher reports), with only a small number of studies investigating the children’s own reports of mental health or QOL. This is methodologically problematic, as several studies have found systematic discrepancies in child and parent reports for children suffering from cancer and other chronic illnesses, where parents typically have poorer reports of social or emotional functioning than their children (Jurbergs, Russell, Long, & Phipps, 2008; Sung et al., 2008). There have been offered different explanations for these discrepancies regarding report tendencies in both children and parents. For example, a repressive adaptive style of the child, psychological defense mechanisms (e.g., a need to move forward and to be “normal”) and possible impairments in self-awareness, may lead to the underreporting of difficulties in young survivors, whereas parental reports may become inflated due to parental distress (Jurbergs et al., 2008; Lund, Schmiegelow, Rechnitzer, & Johansen, 2011; Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; O’Leary, Diller, & Recklitis, 2007; Phipps, Steele, Hall, & Leigh, 2001). Therefore, the impact of PBT on subjective well-being in the younger survivors is not yet well known. Also, the studies that have employed subjective reports have shown mixed results (Bell et al., 2018). Whether the discrepancies between self- and proxy reports persist into adulthood, is not yet known.

1.2.4 Fatigue
One of most frequent and debilitating late effects following PBT treatment is excessive fatigue (van Deuren et al., 2020). Fatigue refers to the persistent, subjective experience of
physical, emotional, and/or cognitive tiredness and lack of energy, not proportional to recent activity, and interfering with usual functioning (Bower, 2014; Zeller et al., 2014). Furthermore, there are findings to suggest that survivors of PBT experience more fatigue than other childhood cancer survivors (e.g., patients with ALL) (Meeske et al., 2004).

While fatigue reduces upon treatment completion in many PBT survivors, for some the symptoms may persist several years, and the etiology of persistent post-treatment fatigue remains somewhat unclear (Boonstra et al., 2017; Brand et al., 2016; Clanton et al., 2011; Mulrooney et al., 2008). However, fatigue after childhood cancer has been linked to several predisposing, triggering, maintaining and modulating factors, such as demographic factors (e.g., age, sex, unmarried status, low income), genetic disposition (i.e., genetic components that affect proinflammatory cytokine activity), biological and treatment-related mechanisms (e.g., inflammatory processes, cytokine dysregulation, anemia, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, and alterations in ATP and muscle metabolism), medical factors (e.g., medical comorbidities, medications, nutritional issues), and psychological and biobehavioral factors (e.g., depression, coping and appraisal of the diagnosis and/or treatment, emotional support, sleep disturbance, physical inactivity and body mass) (Bower, 2014; van Deuren et al., 2020). Severe fatigue may in many cases be one of the most debilitating late effects, leading to lowered levels of societal participation (e.g., an inability to work or attend school, engage socially), and as such, having a negative impact on overall QoL (Bower, 2014; Brand et al., 2016; Meeske, Patel, Palmer, Nelson, & Parow, 2007; Zeltzer et al., 2009).

1.2.5 Long-term outcomes; psychosocial adjustment and socioeconomic outcomes

Separately or together, late effects after PBT and treatment exposure may have a cumulative negative impact on survivors’ long-term outcomes in terms of social engagement, educational achievement, vocational attainment, financial independence, and thus, overall QoL. Within all these areas, PBT survivors have been shown through several studies to be particularly vulnerable to adverse outcomes, compared to other CCS populations (Frederiksen et al., 2019).

Social difficulties are not uncommon among long-term PBT survivors (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Brinkman, Recklitis, et al., 2018; Warner et al., 2016).
Due to potentially lengthy treatment protocols and recovery periods, children/adolescents with PBT may have significant absences from the home environment, friends, and school. Because schools and educational facilities are vital arenas for social competence learning and achieving a sense of normality and participation, such absences, combined with the presence of late effects, can influence the development of age appropriate social behavior and skills. Social difficulties, such as poor peer acceptance, isolation, and difficulties developing and maintaining social relationships (friendship, partnership, family relationships), may have a fundamental negative effect on psychological well-being, QoL, and societal integration and participation.

Several studies have shown that PBT survivors are at risk of lower levels of academic and educational achievement compared to other CCS populations and the general population (e.g., Barrera et al., 2005; Brinkman, Recklitis, et al., 2018; Vetsch et al., 2017). Late effects, such as poor neurocognitive functioning, physical health problems, fatigue, and pain, significantly hinder successful engagement in schooling and academic learning. Social difficulties, low self-esteem, and self-identity issues may further impede survivors’ successful return to school (Fardell et al., 2018). The impact of neurocognitive impairments, more specifically executive dysfunction, on academic achievement is addressed further in chapter 3.

As a growing number of PBT survivors are aging into adulthood, negative long-term outcomes such as an inability to achieve independent living and poorer socioeconomic outcomes (e.g., vocational attainment, need for financial support), is becoming more apparent. These problems put psychosocial and financial strain on the individual survivor and his/her family, and place a financial burden on society. Studies of long-term survivors of CNS tumors have consistently reported lower income, lower occupational position, higher numbers of unemployment, and higher need of government disability benefits compared to siblings, the general population, and other CCS populations (Brinkman, Ness, et al., 2018; Brinkman, Recklitis, et al., 2018; Frederiksen et al., 2019; Ghaderi et al., 2013; Kirchhoff et al., 2011; Mader, Michel, & Roser, 2017). In fact, results from a large CCS study in the U.S., i.e., the Childhood Cancer Survivor Study, indicated that only 40% of adult CNS tumor survivors achieve complete independence, and that nonindependent survivors were more likely to be living dependently (e.g., with caregivers), to be unemployed, to require assistance with personal care and routine needs, to be unable to drive, and to be unmarried (Brinkman, Ness, et al., 2018). Associated factors to adverse socioeconomic outcomes are CRT, younger age at
diagnosis, impaired IQ, limitations in physical performance and adaptive physical function, female sex, and cancer-related late effects (Brinkman, Ness, et al., 2018; Brinkman, Recklitis, et al., 2018).

Although several important risk factors have been identified, few studies have investigated the unique contribution of psychological mechanisms in this patient population, such as EFs, which may be of particular importance for academic learning, social skills development, and educational and vocational outcomes (Frederiksen et al., 2019). In the following chapter, EF conceptualizations and developmental models are summarized (i.e., both general models, and models focusing on the PBT survivor population). These conceptualizations and models illustrate how this skill set plays a fundamental role in academic and social development, and further, how it is “necessary for appropriate, socially responsible and effectively self-serving adult conduct”, as described by Lezak, Howieson, Bigler, and Tranel (2012).

1.3 Executive functions

1.3.1 Conceptualizations and developmental models

In the early literature, EFs were mainly linked to (pre)frontal lobe functioning, as the patients that were observed with executive dysfunction had damages to frontal lobe regions (Lezak et al., 2012). Since then, knowledge on the underlying neural circuitry of these functions has expanded considerably. It is now generally acknowledged that EFs rely greatly on the intactness of multiple cooperating cortical and subcortical networks, and that the prefrontal regions may be viewed as analog to a “conductor” or orchestrator of EF skills (Gioia et al., 2001; Goldberg, 2001; Kalbfleisch, 2017; Stuss & Alexander, 2000). EFs are therefore vulnerable not only to frontal lobe lesions, but also to lesions in other parts of the brain, for example the cerebellum, a common site for PBT (Anderson, Jacobs, & Harvey, 2008; Moberget et al., 2015; Riva & Giorgi, 2000). Furthermore, as the structural maturation and remodeling of the frontal lobes is prolonged, spanning from infancy to young adulthood, so is the developmental trajectory of EFs, thus creating a vulnerability to damages at any time point of brain development (De Luca & Leventer, 2008).

Although there is no universal consensus on the definition of EF, it may be characterized as a multidimensional construct, consisting of collection of higher-order cognitive processes and skills that make up the natural human capacity to control, organize, and direct cognitive,
behavioral, and emotional responses in a dynamic environment (Gioia et al., 2001; Kalbfleisch, 2017; Lezak et al., 2012; Miyake et al., 2000; Stuss & Alexander, 2000). Lezak et al. (2012) describe the fundamental difference between EFs and other neurocognitive functions as follows: while the latter are related to the “what” and “how much” a person can do (e.g., “what/how much do you know?”), EFs are involved in the “how” and “whether” a person will go about doing something (e.g., “will you do x? If so, when and how will you do it?”). One of the purposes of EFs is thus setting and reaching goals in a dynamic environment (e.g., “will you reach your goal, and how?”), and goal attainment is therefore central in several definitions of EFs. For example, the International Neuropsychological Society’s dictionary of neuropsychology defines EFs as “cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands. Executive function includes the ability to plan and anticipate outcomes (cognitive flexibility), and to direct attential resources to meet the demands of nonroutine events” (INS dictionary of neuropsychology, 2015, p.143). Successful complex goal-directed behavior rely on EF processes such as the ability to identify, plan and organize steps involved; to be aware of one’s behavior in relation to situational demands; to initiate purposive action; to persevere in the presence of distraction; and to monitor and flexibly self-correct or shift to more effective strategies for achieving the anticipated outcome (Lezak et al., 2012). Put simply, EFs constitute capacities that enable the individual to manage and self-regulate him- or herself, and to engage successfully with the environment (Kalbfleisch, 2017).

Regardless of the definition one ascribes to, they generally have in common that they reflect shared, but diverse functions, a pattern that has been described as “unity and diversity” (Friedman & Miyake, 2017). Miyake et al.’s (2000) influential model expanded the knowledge on the relations between subdomains of EF, and showed how they, by controlling and coordinating specific cognitive processes, are involved not only in behavior regulation, but also in the performance of complex cognitive tasks. In their model, they focus on three of the most commonly discussed EFs in the literature; (a) shifting between mental tasks or sets, (b) updating, monitoring and manipulation of working memory representations (i.e., maintaining information active in consciousness while performing mental operations to achieve a goal), and (c) inhibitory control of dominant or prepotent responses (e.g., stopping automatic (incorrect) responses or resisting attending to irrelevant information). Their findings showed that these three processes are separable, but interrelated cognitive EF factors, and that each may be observed by employing certain neuropsychological tests. Since then,
several studies have replicated the unity and diversity of these three EFs. However, the authors did not intend for the model to be considered exhaustive, and maintain that it is likely that there are also other EF subdomains (Friedman & Miyake, 2017).

1.3.2 Hierarchical developmental models
The unity and diversity of EFs is reflected also in developmental models, and recently the literature has begun to move beyond describing the protracted developmental trajectories of individual EFs, to investigating the mechanisms for this development. Several developmental theories suggest that EFs may emerge hierarchically throughout childhood, i.e., that simple EFs with earlier developmental periods, such as sustained attention and inhibitory control, may facilitate and be the foundation for more complex EFs with more prolonged developmental curves, such as working memory and shifting (Tillman, Brocki, Sørensen, & Lundervold, 2013). More specifically, it is suggested that as inhibitory control becomes more efficient, sustained attention is consequently improved, thereby facilitating working memory resources. This theoretical perspective harmonizes with trajectory studies showing that, parallel to the maturation and remodeling of brain structures, inhibitory control is in active development between the early preschool years to about age 11 (e.g., Brocki & Bohlin, 2004; Garon, Bryson, & Smith, 2008; Romine & Reynolds, 2005, Tillman et al., 2013), whereas working memory and shifting, although also relatively early developing, seem to have a slower and more prolonged trajectory, developing into middle adolescence (e.g., Garon et al., 2008; Gathercole, Pickering, Ambridge, & Wearing, 2004; Huizinga, Dolan, & van der Molen, 2006; Luciana, Conklin, Hooper, & Yarger, 2005). The complexity and protraction of EF development is a likely explanation as to why studies in pABI populations have shown that although EF deficits may be subtle upon injury, there is a tendency to “grow into deficit” with time, with a delayed onset and increase of impairments (Anderson et al., 2019). Environmental factors no doubt contribute to this tendency, as difficulty levels and cognitive demands (e.g., in social and academic settings) gradually increase throughout childhood, adolescence and young adulthood (Anderson, Jacobs, & Harvey, 2008; de Vries et al., 2017).

1.3.3 Neurodevelopmental cascade models for declines in IQ and academic achievement in PBT survivors
Research findings in the field of child neuropsychology have repeatedly shown that EFs in childhood predict later academic achievement and educational level, and that this effect has
primacy over the effects of intelligence (Zelazo et al., 2016). Within the PBT literature, developmental models of neurocognitive mechanisms involved in the declines in both IQ and academic achievement have emerged over the past decade. Several models take into account tumor and treatment factors that interact with the child’s age, sex, and neurodevelopment, to predict the declines in core cognitive functions such as processing speed, attention span, and working memory that have been consistently demonstrated in the PBT population (Edelstein et al., 2011; King et al., 2019; Palmer, 2008; Rey-Casserly & Diver, 2019; Wolfe et al., 2012).

Based on a cognitive cascade model explaining IQ improvements in typically developing children (Fry & Hale, 2000), Palmer (2008) proposed a pathway model where impaired processing speed and selective attention disrupt working memory, which in turn leads to a negative cascading effect on IQ and academic achievement in survivors of medulloblastomas. Wolfe et al. (2012) later expanded on this work, arguing for a more comprehensive theoretical model, in which they incorporate similar core cognitive functions as the Palmer (2008) model (i.e., attention, processing speed, working memory), but also include general EFs, such as planning and metacognition. They argue that each core cognitive function has a unique, and potentially combined, impact on IQ and academic achievement in survivors of posterior fossa patients treated with CRT.

The models put forward by Palmer (2008) and Wolfe et al. (2012) both have strong scientific foundations. More recently, with the purpose of testing these models empirically, King et al. (2019) found evidence for Wolfe et al.’s (2012) theoretical model in a sample of survivors of pediatric posterior fossa tumors treated with CRT. However, they also showed that a hybrid model combining the two models had the best fit in their sample. In their hybrid model, neurodevelopmental risk factors have a direct impact on processing speed, in turn disrupting attention and working memory (cf., Palmer [2008]) model), and that all three core skills contribute to later declines in IQ and academic achievement (cf., Wolfe et al. [2012]). However, an important limitation to the hybrid model is that the authors were not able to include general EFs as contributing factors. Moreover, while these models offer strong explanations of factors culminating in negative long-term outcomes, neither take into account the social-affective or behavioral aspects of EF, which are equally important for everyday functioning. The significance of these aspects of EF is presented in the following section.
1.3.4 Adding temperature and context to the mix: the hot/cool distinction

Interestingly, although impaired control and regulation of behavior after frontal lobe lesions were initially the focus of research on EF (e.g., the well-known case of the unfortunate Phineas Gage), EF research continued for a long time to emphasize the cognitive aspects of EF, i.e., the abstract, decontextualized and non-emotional EFs, such as the three core skills in Miyake et al.’s (2000) influential model. However, to many authors, this conceptualization did not capture the executive processes that are needed additionally for successful interaction with everyday surroundings, and for behavior regulation in contexts that evoke emotions. Nor could adaptive decision making and goal-oriented behavior be explained solely on the basis of this traditional view. In response to this need, several authors called for a distinction between so-called “cool” and “hot” EF processes (Anderson, Jacobs, & Anderson, 2008, p. xxviii; Happaney, Zelazo, & Stuss, 2004; Metcalfe & Mischel, 1999; Peterson & Welsh, 2014; Zelazo & Carlson, 2012; Zelazo, Qu, & Kesek, 2010). Cool EF skills, i.e., the cognitive aspects of EF, operate in emotionally neutral contexts, and include functions such as attentional control, working memory, initiation, planning and organizing, selection of efficient problem-solving strategies, mental flexibility and utilization of feedback. Hot EF skills, on the other hand, operate in contexts that evoke emotions, motivation, and the competition between instant gratification and long-term rewards (Peterson & Welsh, 2014; Zelazo et al., 2010). They are involved in the ability to exert appropriate control and regulation of emotional and behavioral responses, e.g., by adapting to change, and by initiating, monitoring, and inhibiting impulses and responses in accordance with situational and social demands and expectations (Anderson, Jacobs, & Anderson, 2008, p. xxviii; Metcalfe & Mischel, 1999; Zelazo & Carlson, 2012). Hot EFs are essential components in empathy, emotion regulation, moral understanding, and affective decision-making (De Luca & Leventer, 2008). Importantly, despite the theoretical distinction between cool and hot functions, they are very much interconnected and work together in concert in everyday functioning. This may be the reason why research findings have not consistently been able to differentially predict adaptive “real-world” behaviors on the basis of hot or cool EFs, although there is some evidence that cool EFs are associated to academic performance (Peterson & Welsh, 2014).

Studies in brain injury populations lend strong scientific support to the hot/cool distinction, as findings show that impairments of hot EF may exist in the absence of impaired cool EF, and vice versa (Anderson, Anderson, Jacobs, & Smith, 2010). Further supporting this distinction are studies of adult patients with damages to orbitofrontal and ventromedial prefrontal...
regions. These are brain regions that are highly overlapping, with rich neuroanatomical connections to limbic areas involved in emotional and social processing. Patients with damages to these areas exhibit social regulation impairments, as well as an inability to consider future consequences during decision-making (Bechara, 2004; Beer, 2006; Peterson & Welsh, 2014; Yeates et al., 2007). Impairments such as these may occur in spite of relatively intact general cognitive abilities, and without significant impairment in traditional cognitive EF processes like working memory and planning, which are associated with dorsolateral areas of the prefrontal cortex. In a developmental perspective, some studies have shown that hot and cool EF skills are in active development in the age period of 3–5 years, and moreover, that cool processes may mature ahead of hot processes (Peterson & Welsh, 2014). Unfortunately, research efforts have yet to provide conclusive evidence for the developmental trajectories of these two EF domains, likely due to methodological challenges, and that the task of detangling this question is rarely undertaken.

The development of hot and cool aspects of EF are intimately related to the development of social information processing and social competence (Peterson & Welsh, 2014; Riggs, Jahromi, Razza, Dillworth-Bart, & Mueller, 2006; Ryan et al., 2016; Yeates et al., 2007). In several developmental models of social competence and interpersonal skills, EFs are key components underlying and facilitating this development (Beauchamp & Anderson, 2010). For example, Yeates et al. (2007) propose a heuristic model of social competence in children with brain disorder, where social–affective (hot EFs, e.g., emotional control) and cognitive–executive processes (cool EFs, e.g., working memory) facilitate social information processing, which in turn mediates social interaction and adjustment. Working memory and inhibitory control in particular have been found to be involved in social behavior. For example, a study in typically developing children found evidence that poor working memory is linked to social impairments such as peer rejection, poor overall social competence, and impaired conflict resolution skills (McQuade, Murray-Close, Shoulberg, & Hoza, 2013). Also, studies in various pABI populations, including PBT survivors, have shown a link between various aspects of executive dysfunction and impaired social functioning and societal participation (Muscara et al., 2008; Sirois et al., 2017; Willard et al., 2015; Wolfe et al., 2013).

Altogether, executive dysfunction, and its subsequent impact on other functional domains (e.g., social and academic difficulties), may contribute to account for poorer outcomes in survivors of PBT in terms of educational attainment, employment, financial independence,
independent living and social relationships. Further knowledge on the idiosyncratic EF profile of PBT survivors is needed, in order to help tailor suitable interventions.

1.3.5 Assessment of EFs

As challenging as it is to capture the complexity of EFs in a single definition, so is the task of operationalization and assessing these functions. Traditionally, performance-based neuropsychological measurements employing pencil-and/or-paper tests have been the “gold standard” for identifying and quantifying executive dysfunction. For example, neuropsychological tests such as the Trail Making Test 4 (i.e., number-letter switching) and the Color-Word Interference Test 3 (i.e., inhibition) from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) are frequently used to tap the domains “shifting” and “inhibitory control”, respectively, while the subtest Digit Span Backward from the Wechsler Intelligence scales Adult Intelligence Scale –IV (WAIS-IV; Wechsler, 2008 WISC-IV; Wechsler, 2003) may be utilized to tap the “working memory” domain.

However, the performance-based approach has been strongly criticized for lack of ecological validity, i.e., for not reflecting the complexity and demands of real life situations. The assessments are administered in a clinical laboratory-like setting that is structured, free from distractions, and lasting over a relatively short period of time. The examiner prompts the patient to comply with test requirements, leaving no need for initiative, self-regulation or creativity from the patient. Consequently, executive dysfunction may go undetected by the examiner. Moreover, while performance-based assessments are considered suitable for assessing cognitive (cool) aspects of EF, they do not as effectively capture the social-affective/behavioral (hot) aspects. For these reasons, performance-based results do often not match observed behavior in the home and/or school environment (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Gioia, Kenworthy, & Isquith, 2010).

In order to meet the need for a more comprehensive assessment of EFs, neuropsychologists and researchers have increasingly incorporated the use of questionnaires over the past two decades. Importantly, questionnaires reflecting both self-report and informant report are recommended, as executive dysfunction has been linked to diminished levels of self-awareness in several pABI populations, including PBT survivors (Krasny-Pacini et al., 2015;
McCurdy, Turner, et al., 2016; Sølsnes, Skranes, Brubakk, & Løhaugen, 2014). For example, studies have found that PBT survivors tend to overestimate their own EF skills, and underestimate peer relationship difficulties (Devine et al., 2016; McCurdy, Turner, et al., 2016). Also, as mentioned in chapter 1, several studies have identified reporter discrepancies in pediatric populations, including CCS populations, where chronically ill children tend to report fewer problems than their parents (Jurbergs et al., 2008; Lund et al., 2011). A commonly applied questionnaire both in clinical settings and research, is the Behavior Rating Inventory of Executive Function, for which there are several versions, including self-report, parent report, and informant report versions for most age groups (BRIEF; Gioia, Isquith, Guy & Kenworthy, 2000; BRIEF-A; Roth et al., 2005).
2. AIMS

The overall aim of this cross-sectional study was to determine the presence and degree of executive dysfunction in adolescent and young adult survivors of PBT compared to a healthy control group, and to explore the significance of executive dysfunction for long-term outcomes, i.e., adaptive functioning/psychosocial adjustment, academic and vocational achievement, and financial independence, compared to psychological problems and symptoms of fatigue.

2.1 Paper I

In the first paper, the aim was to investigate the presence and degree of self-reported long-term executive dysfunction, psychological and emotional problems in young, physically well-functioning adult survivors of PBT, and to determine whether this population has a specific profile of self-reported EF with respect to the hot and cool aspects of EF.

2.2 Paper II

In the second paper, the aim was to investigate self-reported social attainment in young, physically well-functioning adult survivors of PBT compared to the healthy control group, and to investigate how self-reports of executive dysfunction, psychological and emotional problems, and fatigue, were related to less favorable social outcomes.

2.3 Paper III

In the third paper, the aim was to explore the long-term neurocognitive consequences of PBT in adolescent survivors, with a special focus on the EF profile (i.e., regarding the “hot” and “cool” aspects of EF), as evidenced by parent and self-reports and performance-based measures. Furthermore, the purpose was to explore whether adolescent PBT survivors experience more problems with adaptive functioning (i.e., academic achievement and social functioning) compared to a healthy control group, and to which degree executive dysfunction was associated to poor adaptive functioning compared to psychological problems and fatigue.
3. METHODS

3.1 Participants and procedure

A flowchart of the study is shown in Figure 2. Survivors of PBT were identified by The Cancer Registry of Norway, and included when fulfilling inclusion criteria defined as treatment for PBT at 0-16 years, between 1990-2012, aged 13-30 at recruitment, and having completed treatment no later than 2 years prior to study participation. Exclusion criteria included self-/parent reported severe difficulties with activities of daily life (ADL), self-/parent reported severe sensory and motor disabilities, and pre-tumor cognitive/neurological deficits due to non-tumor diagnoses, evidenced in patient records. The exclusion criteria regarding ADL and sensory-motor functions are factors that may affect participation in society irrespective of the status of EF, and as such, could interrupt the main research goal. Participants were divided into two groups; an adolescent survivor group, aged 13-17 years, and a young adult survivor group, aged 18-30 years.

All eligible PBT survivors were invited to complete self-report forms on EF, psychological and emotional functioning. The adolescent PBT survivor group also received parent report forms. The young adult PBT survivors received informant forms, and were asked to distribute these forms to a person of their own choosing, i.e., a person who knows them well.

Information on tumor histology, location, age at diagnosis, and type of treatment was obtained from patient records, and the third version of the International Classification of Childhood Cancer (ICCC-3) was used to classify participants into larger diagnostic subgroups. Treatment regimens (e.g., surgery, CRT, chemotherapy), neurological late effects and psychiatric comorbidity (i.e., as classified by the International Classification of Disease -10 codes F01-F99) were registered as yes/no. Clinical characteristics for both age groups are presented in Table 2. For both age groups, healthy control groups were recruited from The National Population Register of Norway. The PBT survivor and control groups were matched for age and sex. The healthy young adults received self-report forms identical to those of the young adult PBT survivor group. In addition to identical self-reports, the healthy adolescent control group received parent report forms identical to that of the adolescent PBT survivor group.

Papers I and II present findings in the young adult survivor group, and paper III presents findings in the adolescent survivor group.
**Figure 2** Flowchart of the study

**Target population:**

452 eligible survivors from the Norwegian Cancer Registry

13-17 years: n=99, 18-30 years: n=353

Deceased: n=2

Non-tumor cerebri diagnoses: 18-30 years: n=30
(e.g., cortical dysplasia, cysts, extracranial tumors)

No longer living in Norway/unknown address: 18-30 years: n=6

Patient records unavailable: 18-30 years: n=3

**Survivors receiving self- and informant report forms:**

13-17 years: n=99, 18-30 years: n=312

Responded,

13-17 years: n=57 (57.6%)
18-30 years: n=131 (42.0%)

**Did not respond,**

13-17 years: n=42 (42.4%)
18-30 years: n=181 (58.0%)

**Treatment for recurrent/residual tumor < two years:**

13-17 years: n=3, 18-30 years: n=12

Pre-tumor cognitive/neurological problems:

13-17 years: n=2, 18-30 years: n=5

Non-tumor cerebri diagnoses: 13-17 years: n=4

Adolescent survivors invited for neuropsychological assessments:

n=36

**Total survey response:**

13-17 years:
Self- and parent reports: n=48 (53.3%)

18-30 years:
Self-reports: n=114 (38.6%)
Self- and informant reports: n=89 (30.2%)

Total participation, neuropsychological assessments:

n=26 (72.2%)
Table 2 Clinical characteristics

<table>
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<tr>
<th>Tumor diagnosis</th>
<th>N adolescent group (n=48)</th>
<th>%</th>
<th>N young adult group (n=48)</th>
<th>%</th>
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<tr>
<td>Ependymomas and choroid plexus tumors</td>
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</tr>
<tr>
<td>Astrocytomas</td>
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<td>47.9</td>
<td>49</td>
<td>43.0</td>
</tr>
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<td>Embryonal tumors</td>
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<td>33.3</td>
<td>32</td>
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</tr>
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<td>14</td>
<td>12.3</td>
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<tr>
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### Psychiatric comorbidity

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<td>43</td>
<td>84.3</td>
<td>95</td>
<td>83.3</td>
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</table>

a CRT=cranial/craniospinal irradiation therapy

b Ventriculoatrial shunt (VA), ventriculoperitoneal shunt (VP) or third ventriculostomy (3CVS),

c Hormone replacement treatment, e.g., growth hormone, cortisol, thyroid stimulating hormone, testosterone and estrogen, and antidiuretic hormone.

### 3.2 Long-term outcome measures

#### 3.2.1 Questionnaires (papers I, II and III)

The questionnaires utilized in this study were selected from the need to assess several domains, i.e., EF, psychological problems, fatigue and adaptive functioning. In order to cover all domains in both age groups, several questionnaires were needed, as no single questionnaire could suffice.

**Executive functioning**

The self- and informant report versions of the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A; Roth et al., 2005) and the parent report version of the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy & Kenworthy, 2000) were used to assess EF in everyday activities over the past 6 months. Three indices are generated: the Behavior Regulation Index (BRI), the Metacognitive Index (MI) and a Global Executive Composite (GEC). The BRIEF-A BRI contains subscales reflecting behavioral/emotional aspects of EF (Inhibit, Shift, Emotional Control, and Self-Monitor), as does the BRIEF BRI, although it does not contain the Self-Monitor subscale. The BRIEF-A MI subscales reflects cognitive aspects of EF (Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials), as do the BRIEF MI subscales, although instead of the Task Monitor subscale, the BRIEF MI contains the more general Monitor subscale. The BRI and the MI indices serve as measures of the hot and cool aspects of EF, respectively.
Psychological and behavioral problems and adaptive functioning

For psychological and behavioral problems, we used the Achenbach System of Empirically Based Assessment questionnaires (ASEBA; Achenbach & Rescorla, 2001; Achenbach & Rescorla, 2003), which is a family of screening tools for psychological symptoms and behavioral problems. We used the Youth Self-Report version (YSR), the Child Behavior Checklist (CBCL; parent report version), the Adult Self-Rating (ASR), and the Adult Behavior Checklist (ABCL; informant report version). The YSR and the CBCL consist of eight syndrome scales; Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. The ASR and ABCL yield similar syndrome scales; Anxious/Depressed, Withdrawn, Somatic Complaints, Thought Problems, Attention Problems, Aggressive Behavior, Rule-Breaking Behavior, and Intrusive Behavior. For all four versions, three composite scores are produced; Total Problems, Internalizing Problems (sum of the scales Anxious/Depressed, Withdrawn/Depressed [YSR, CBCL]/Withdrawn [ASR, ABCL] and Somatic Complaints), and Externalizing Problems (sum of the scales Aggressive [ASR, ABCL]/ Aggressive Behavior [YSR, CBCL], Rule-Breaking Behavior and Intrusive behavior [ASR, ABCL]). The subscales Attention (YSR, CBCL) and Attention Problems (ASR, ABCL) reflect subjective cognitive complaints. The ASEBA questionnaires also contain a subscale reflecting adaptive functioning, generating the subscale Total Competence for the YSR and the CBCL (i.e., items on the adolescent’s activities, social relations, and academic performance), and the Adaptive Functioning subscale for the ASR and the ABCL (i.e., items relating to friends, spouse or partner, family, education, and work).

For the adolescent survivor group, we also employed the self-report and parent report version of the Pediatric Quality of Life Inventory 4.0 (PedsQL; Varni, Seid, & Kurtin, 2001) measuring QoL, yielding the subscales Physical, Emotional, Social, and School Functioning, as well as a total score; PedsQL Total. For the young adult survivor group, we used the Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1994) to assess the presence and severity of psychological symptoms. Nine symptom scales are generated; Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism, and a measure of global symptom severity (Global Severity Index; GSI).
**Fatigue**

In order to assess the presence of fatigue in the adolescent survivor group, we employed The PedsQL-Multidimensional Fatigue Scale (PedsQL-MFS; Varni, Burwinkle, Katz, Meeske & Dickinson, 2002), which is a self-report questionnaire, consisting of the subscales General Fatigue, Sleep/Rest Fatigue and Cognitive Fatigue subscales, as well as a total score; PedsQL-MFS Total. For the young adult survivor group, we used the Fatigue Questionnaire (FQ; Chalder et al., 1993) which includes subscales reflecting mental fatigue (MF; 4 items) and physical fatigue (PF; 7 items), and yielding a total fatigue score (TF).

**Socioeconomic outcomes**

In addition to the questionnaires, the young adult PBT survivor group and young adult healthy control group were asked to provide personal data on social outcomes, i.e., living situation, education, work, and governmental benefits. More detailed descriptions of this personal data and the questionnaires employed in this study can be found in Papers I-III.

3.2.2 **Performance-based measures (paper III)**

A subgroup of the adolescent PBT survivors, who have been followed up with multiple neuropsychological assessments after treatment completion at Oslo University Hospital, also underwent cognitive retesting. Of 36 invited, 26 (72.2%) underwent retesting. For this subgroup, the mean age at diagnosis was 6.3 years (range=3-13.3, SD=3.97) and mean time since treatment completion was 8.9 years (range=4.0-14.1, SD=3.63). Mean age at cognitive retesting was 16.6 years (SD=1.37). Clinical characteristics for the retested subgroup are presented in Paper III. No survivors in the subgroup undergoing cognitive retesting reported sensory or motor impairments seriously disrupting everyday functioning. The tests were grouped into neurocognitive domains, i.e., estimated current IQ, processing speed, auditory attention span, sustained attention, verbal learning and recall, verbal fluency and executive functions, by calculating the average T-scores within each domain. Clinical cutoff was defined as a score of 1.5 standard deviations or more below the normative mean.

**Estimated current IQ**

The Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were employed to estimate current IQ.
**Processing speed**
The subtests Trail Making Test 2 (TMT 2; number sequencing) and 3 (TMT 3; letter sequencing), and Color-Word Interference Test 1 (CWIT 1; color naming) and 2 (CWIT 2; word reading), from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) were used to assess processing speed.

**Auditory attention span**
The Digit Span Forward scores from the Wechsler Adult Intelligence Scale –IV (WAIS-IV; Wechsler, 2008) for participants aged >16, and the Wechsler Intelligence Scale for Children –IV (WISC-IV; Wechsler, 2003) for participants aged 16-17, was employed in order to assess auditory attention span.

**Sustained attention**
The Hit Reaction Time Block Change measure (HRT BC) from the Conners’ Continuous Performance Test – Third Version (CPT 3; Conners, 2013), a well-known computerized test of different aspects of attention, was selected as a measure of sustained attention.

**Verbal learning and recall**
In order to assess the two domains verbal learning and recall, The Children’s Auditory Verbal Learning Test (CAVLT-2; Talley, 1993) was employed. For technical reasons, the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) was utilized for assessing verbal learning and memory in 8 participants.

**Verbal fluency**
The subtest Verbal Fluency 1 (phonemic fluency) and 2 (category fluency) from the D-KEFS battery was employed to assess verbal fluency, i.e., the ability to rapidly produce words according to required criteria.

**Executive functions**
For the assessment of the EF domain “shifting”, we utilized the subtests Trail Making Test 4 (TMT 4; number-letter switching) and Color-Word Interference Test 4 (CWIT 4; inhibition/switching) from the D-KEFS battery. For the “working memory” domain, we used the subtest Digit Span Backward (WAIS–IV, WISC–IV). For the EF domain “inhibitory
control”, we employed the commissions score from the CPT 3 and the subtest Color-Word Interference Test 3 (CWIT 3; inhibition) from the D-KEFS battery.

3.3 Statistical analyses
Data analyses were performed using the statistical package SPSS for Windows, version 25.0 (SPSS, Inc., Chicago, Illinois). Missing item scores in the questionnaires were replaced by the participant’s subscale mean where at least 2/3 of the subscale items were completed (Tabachnick & Fidell, 2007). Non-parametric statistics were conducted for questionnaire data due to non-normally distributed variables. Data from performance-based tests was normally distributed, and parametric analyses were performed.

Between-group differences were investigated by Pearson Chi Square and Mann-Whitney U test (Papers I, II and III). The Wilcoxon signed-rank test was applied for within-group differences and self- and informant report differences (Papers I and III). Bonferroni corrections for multiple comparisons were employed. Effect size (ES) is reported as $r$ for continuous data, and as $\phi$ for categorical data, in both cases defining small ES as $=.1 - .3$; medium ES as $=.3 - .5$; large ES as $>.5$ (Field, 2009). Associations between various questionnaire subscales, and between performance-based test scores and questionnaire subscales reflecting neurocognitive functioning and adaptive functioning, were investigated by Spearman’s rho ($r_s$) test (Paper III). One sample T-tests were conducted in order to investigate deviations from the normative mean ($T=50$) in performance-based test scores (Paper III). The social outcome variables for which there were significant between group differences were retained for univariate and logistic regression analyses within the young adult PBT survivor group (Paper II). The questionnaires for which there were significant differences between the various social outcome subgroups of young adult PBT survivors, were retained as variables for social outcome models. Associations between questionnaire data (i.e., indices, composite scores and total scores) and demographic (sex, age at time of survey), tumor-related (age at diagnosis, location [i.e., supra- vs. infratentorial locations], tumor type), and treatment-related (time since treatment completion, type of treatment [surgery only vs. complex treatment regimens combining CRT treatment and/or chemotherapy]), were explored by univariate analyses (Papers I, II and III).
3.4 Ethical considerations

The study was conducted in compliance with the Declaration of Helsinki by the World Medical Association Assembly, and was approved by the Regional Committee for Medical Research Ethics in Norway (REC; 2014/379). Written informed consent was obtained after a complete description of the study.
4. RESULTS

4.1 Paper I

Self-reported executive dysfunction, fatigue, and psychological and emotional symptoms in physically well-functioning long-term survivors of pediatric brain tumor (Puhr et al., 2019a).

Paper I investigates the presence and possible distinct profile of executive dysfunction in the young adult subgroup of the PBT sample, reporting four main findings:

i. Young adult survivors of PBT reported significantly higher levels of psychological and emotional problems and mental fatigue compared to matched healthy controls, as evidenced by significant group differences in scale scores and caseness frequency on measures surveying these domains.

ii. Significant group differences were found on measures of most EFs, and ESs were generally larger for EF measures than for psychological and emotional problems and mental fatigue. Moreover, although problems of behavioral regulation (hot) aspects of EF were reported, the PBT survivors had relatively more complaints concerning metacognitive (cool) aspects.

iii. Informants reported significantly less EF problems than the PBT survivors themselves.

iv. PBT survivors who had undergone surgery combined with CRT and chemotherapy, and for whom the time interval since treatment completion was shorter, had significantly higher levels of mental fatigue complaints.

4.2 Paper II

Social attainment in physically well-functioning long-term survivors of pediatric brain tumour; the role of executive dysfunction, fatigue, and psychological and emotional symptoms (Puhr et al., 2019b).

In paper II, building on the findings from paper I, we investigate self-reported social attainment in young, physically well-functioning adult survivors of PBT compared to healthy controls, and to which degree self-reports of executive dysfunction, psychological and emotional problems, and fatigue, are related to less favorable social outcomes. We reported three main findings:

i. Compared to healthy controls, significantly more PBT survivors reported having received educational adjustments and substantial government benefits, and were currently not engaged in regular employment/training.
ii. In general, poor social outcomes were most strongly associated to subscales measuring self-reported executive dysfunction, difficulties with adaptive functioning, and fatigue.

iii. Complex treatment regimen (i.e., multiple surgeries, chemotherapy, CRT, and/or hormone therapy) was significantly related to poorer social outcomes, and the presence of post-treatment psychiatric comorbidity was significantly associated with government benefit uptake.

4.3 Paper III

Executive function and psychosocial adjustment in adolescent survivors of pediatric brain tumor (Puhr et al, 2020, in revision for publication).

Paper III presents three main findings on the presence and possible distinct profile of executive dysfunction in the adolescent PBT survivor group, the association between EF difficulties and adaptive functioning complaints in the PBT survivors, and the association between demographic and tumor and treatment-related variables and questionnaire measures of EF, psychological problems and fatigue:

i. Significantly elevated rates of neurocognitive impairment, including executive dysfunction, were found both in PBT survivors’ parent reports of EF compared to matched controls, and on performance-based tests of EF compared to normative data.

ii. Adolescent PBT survivors and their parents reported significantly more adaptive functioning complaints (i.e., academic and social difficulties) than healthy controls and their parents. These difficulties were most strongly associated with parent reported problems with executive dysfunction, internalizing symptoms of withdrawal/depression and thought problems, and physical functioning, as well as to self-reported problems with EF, physical functioning and sleep/need for rest.

iii. Being male, having sustained an embryonal tumor or an astrocytoma, and having undergone surgery combined with CRT treatment and chemotherapy was significantly related to higher levels of parent and self-reported problems on the questionnaires assessing EF, QoL and fatigue.
5. DISCUSSION

5.1 Discussion of main findings

5.1.1 Executive function in the PBT survivor sample

The results presented in papers I and III confirm earlier findings of poorer neurocognitive functioning, including poorer EF, in long-term survivors of PBT. This was evidenced by young adult PBT survivor self-reports and adolescent PBT survivor parent reports, showing significantly higher levels of EF complaints compared to matched healthy controls (Papers I and III), as well as by performance-based tests of EF compared to normative data in the adolescent PBT survivor sample (Paper III). Complex treatment regimens, including surgery combined with CRT and chemotherapy, were significantly associated with higher rates of parent reported problems on a composite scale reflecting cognitive aspects of EF and a global EF scale (Paper III). However, treatment effects for self-reported EF were not found in the young adult PBT survivor group, although post-treatment psychiatric comorbidity and postoperative seizures were related to significantly more self-reported problems on the global EF scale (Paper I). These findings are in line with previous studies demonstrating the association between the added burden of complex treatment regimen involving CRT, and late effects on long-term neurocognitive functioning (de Ruiter et al., 2013; Duffner, 2010; King et al., 2019; Palmer, 2008; Stavinoha et al., 2018). However, contrary to past studies, the present findings did not reveal significant effects regarding tumor location, age, or time since treatment completion.

Along with physical problems and fatigue, the largest ESs in the adolescent group were for between group differences in neurocognitive complaints, including problems with aspects of EF in everyday life (Paper III). Parents of PBT survivors generally reported more EF problems than parents of controls, but only differences on a subscale measuring working memory problems survived correction for multiple comparisons, with a near to medium ES. Nonetheless, the presence of EF weaknesses was also found in performance-based neuropsychological results, with significant deviations from the normative mean within the processing speed domain, and in two out of the three EF domains from Miyake et al.’s (2000) model; shifting and inhibitory control. Furthermore, for the cognitive domains processing speed, auditory attention span, verbal learning, verbal recall, and shifting, there was a larger percentage of PBT survivors than expected from the normal distribution performing in the clinically impaired range (i.e., with T-scores 1.5 standard deviation below the normative
mean). These are all domains positively correlated and interrelated with EF skills (Zelazo et al., 2016). Unfortunately, the number of participants who underwent neuropsychological assessments was not large enough to enable subgroup analyses based on tumor- and treatment-related variables.

The young adult PBT survivors reported a significantly higher rate of EF problems compared to their healthy peers, with medium ESs (Paper I). Significant group differences in T-scores were identified on almost all scales assessing EF skills, i.e., subscales reflecting shifting, self-monitoring, initiating action/activity, working memory, planning/organizing tasks/activities, and task monitoring, as well as composite scales indexing behavioral and cognitive aspects of executive function, and a global EF scale. In addition to significant group differences in T-scores, a significantly higher frequency of caseness was found for the young adult PBT survivor group compared to the control group for the same EF domains, including problems with emotional control.

Although the PBT sample’s mean scores on subscales reflecting aspects of EF are within one standard deviation from the normative mean (i.e., within the normal range by clinical standards) in both age groups, there are several studies showing that mean scores in Norwegian and non-U.S. healthy samples on both the BRIEF and BRIEF-A are significantly below the U.S. normative mean of T = 50 (Grane, Endestad, Pinto, & Solbakk, 2014; Hovik et al., 2017; Løvstad et al., 2012; Løvstad et al., 2016; Sølsnes et al., 2014). This raises concern about the appropriateness of these norms in a Norwegian setting, and indicates that mean scores from a matched Norwegian sample of healthy controls are a more suitable basis for comparisons, both in clinical and research settings. Altogether, the present findings are in line with the PBT literature, consistently demonstrating impaired functioning in these neurocognitive/EF domains, not only in survivors treated with CRT and chemotherapy, but also after surgery only (Edelstein et al., 2011; King et al., 2019; Krivitzky, Walsh, Fisher, & Berl, 2016; Moberget et al., 2015; Palmer, 2008; Rey-Casserly & Diver, 2019; Rønning et al., 2005; Wolfe et al., 2012).

In the young adult PBT group, informants (consisting of mainly parents) reported significantly less problems with EF than the PBT survivors themselves (Paper I). Although the opposite pattern has generally been found in pediatric populations (i.e., parents reporting higher rates of problems in various domains compared to their child, especially for
subjective symptoms) (Brinkman, Li, et al., 2016; Jurbergs et al., 2008; Lund et al., 2011; Sung et al., 2008), for the EF domain specifically, there are a few studies that are in line with the findings from this study. For example, studies have demonstrated low levels of parental endorsement of EF problems in survivors of PBT, even in the presence of performance-based findings of executive dysfunction (Krivitzky et al., 2016; Wochos, Semerjian, & Walsh, 2014). In comparison, teacher reports have been found to be more in accordance with performance-based data (Wochos et al., 2014). This discrepancy may be explained by a possible rater bias in parents, such as psychological defense mechanisms and adjusting to the needs/challenges of their medically fragile child, and/or differences in EF demands across the home and school settings.

Altogether, the findings presented in Papers I and III provide evidence for the presence of EF difficulties in long-term survivors of PBT, not only in adolescent survivors who are temporally closer to treatment completion, but also in young adult survivors, indicating that these are long-term weaknesses persisting into adulthood.

**EF complaints vs. reports of psychological problems and fatigue in the PBT survivor sample**

Interestingly, in both the adolescent and young adult PBT survivor groups, there emerged a pattern where neurocognitive concerns, including EF concerns, showed generally larger ESs compared to psychological and emotional problems (Papers I and III). ESs in both age groups were small for psychological and emotional problems, and compared to normative data, the mean scores were well within one standard deviation from the normative mean.

For symptoms of psychological distress in the adolescent group, the between group differences with the largest ESs were found for parent reports, with parents of PBT survivors reporting significantly more problems than parents of controls on subscales and indices reflecting internalizing problems (i.e., symptoms of withdrawal, depression and somatization) relative to externalizing problems (Paper III). This is in line with earlier findings noting that PBT survivors may exhibit more internalizing than externalizing problems compared to other pABI and adolescent CCS populations (Brinkman, Li, et al., 2016; Poggi et al., 2005). This pattern was less apparent in the young adult PBT survivor group, probably due to relatively few reported psychological distress symptoms in general. However, informants in the young
adult PBT survivor group did report significantly fewer problems on subscales and indices reflecting externalizing problems (i.e., aggressive and rule-breaking behavior) compared to the young adult PBT survivors themselves.

Importantly, the adolescent PBT survivors themselves did not report a significant increase of psychological distress compared to the healthy controls (Paper III). Earlier studies have shown a tendency of parent-child report discrepancies in pediatric populations, with parents typically reporting poorer emotional functioning than their child (Brinkman, Li, et al., 2016; Jurbergs et al., 2008; Lund et al., 2011; Sung et al., 2008). It is therefore unclear whether the findings reflect an actual risk of psychological problems, or inflated parental reports due to parental distress and sensitivity to changes in their child after serious illness, or alternatively, a repressive adaptive style in the adolescent leading to underreporting of difficulties (Brinkman, Li, et al., 2016; Jurbergs et al., 2008; Meeske et al., 2004). Further uncertainty concerning this question is brought on by the fact that there are few significant discrepancies between parent and self-reports of psychological distress in this study, with the only exception of subscales reflecting somatization (i.e., PBT survivor parents reported significantly more problems than their adolescent) and externalizing problems (i.e., PBT survivor adolescents reported significantly more problems than their parents). Interestingly, a review of the CCS literature by Bitsko et al. (2016) indicated that survivor self-report may be the most accurate way to assess emotional functioning. In the case of our adolescent sample, emphasizing the findings from the PBT survivors’ self-reports would indicate no significantly increased risk of psychological problems compared to healthy peers.

The findings in Papers I and III indicating low levels of reported psychological distress symptoms is in conflict with earlier findings showing an increased risk of psychological problems in PBT survivors compared to other CCS populations and the general population (Bitsko et al., 2016; Brinkman, Li, et al., 2016). There are several possible explanations for the findings. One possible explanation for the low levels of psychological distress observed in the young adult PBT survivor group may be that the participants in this age group were physically well-functioning, as physical and sensory late effects have previously been associated with higher rates of global and internalizing symptoms (e.g., self-isolation) (Brinkman, Li, et al., 2016; Cousino et al., 2017; Ozono et al., 2007). Alternatively, promising psychological outcomes in this subset of the CCS population may gradually become more common with the continuous improvement of modern treatment modalities.
(Macartney, Harrison, VanDenKerkhof, Stacey, & McCarthy, 2014). Also, findings from several studies in other CCS populations reflect a tendency towards resiliency, posttraumatic growth, and benefit finding after life-threatening illness (Bitsko et al., 2016; Brinkman et al., 2013; Vetsch et al., 2017; Zebrack et al., 2012). Altogether, these findings may indicate that the PBT survivors in our sample are at relatively low risk of psychological and emotional problems.

In both age groups, PBT survivors reported significantly more symptoms of fatigue than their healthy peers (Papers I and III). Our findings suggest that fatigue seems to be a more salient problem in the adolescent PBT survivor group compared to the young adult PBT survivor group, i.e., with medium and small ESs for between group differences, respectively. Smaller ESs for fatigue in the young adult group may be due to longer time since treatment completion, with initial symptoms of fatigue having subsided with time. This is consistent with previous findings showing that although there is a subgroup for whom symptoms may persist several years upon treatment completion, in many PBT survivors fatigue reduces post-treatment (Boonstra et al., 2017; Brand et al., 2016; Clanton et al., 2011; Mulrooney et al., 2008; van Deuren et al., 2020).

Presence of fatigue is associated with neurocognitive impairment in CCS populations and brain injury populations, e.g., impaired processing speed, attention, memory and EF (Clanton et al., 2011; Ponsford, Schönberger, & Rajaratnam, 2015), and thus may have contributed to neurocognitive problems reported in the adolescent PBT survivor group. However, for the young adult PBT survivor group, EF concerns are present despite low levels of subjective fatigue, indicating that fatigue cannot be the full explanation. Moreover, the cognitive and mental fatigue scales utilized in the adolescent and young adult PBT survivor groups, respectively, mainly contain items reflecting subjective cognitive complaints. Moreover, two out of six items on the general fatigue scale utilized in the adolescent group reflect problems with initiating and completing tasks, which in addition to fatigue includes involvement of EF.

Although symptoms of fatigue were significantly present in the adolescent PBT survivor group, the findings in general seem to suggest that the long-term PBT survivors in our sample struggle relatively more within the EF domain, compared to psychological problems and symptoms of fatigue. Within the EF domain, difficulties with certain aspects of EF seem to be more prominent than others in the present PBT survivor sample, and in the following,
evidence for a distinct EF profile in light of the hot/cool distinction of EF processes is presented.

5.1.2 What’s hot and what’s not; towards an idiosyncratic executive function profile

PBT survivors constitute a subset of both the CCS population and the pABI population, i.e., two patient populations known to be neurologically compromised and demonstrating a range of impairments in the neurocognitive domain (e.g., Anderson, Jacobs, & Anderson, 2008; Beauchamp & Anderson, 2013; Beauchamp, Dooley, & Anderson, 2010; Kanellopoulos et al., 2016; McCurdy, Rane, Daly, & Jacobson, 2016; Raghubar, Mahone, Yeates, & Ris, 2017). Our findings are in line with numerous past studies demonstrating neurocognitive difficulties in long-term PBT survivors (de Ruiter et al., 2013; Duffner, 2010; King et al., 2019; Palmer, 2008; Stavinoha et al., 2018). However, fewer studies have focused specifically on EF in this particular population, and even fewer on the different aspects that make up the EF construct. Our findings are not only in line with past studies demonstrating EF problems in the PBT survivor population (King et al., 2019; Palmer, 2008; Wolfe et al., 2012), but also expand on the current knowledge. Our studies identify a possible distinct EF profile compared to that of other CCS and pABI populations, and explain it within the theoretical hot/cool framework for understanding EF. For instance, do long-term PBT survivors struggle relatively more with metacognitive, i.e., cool aspects of EF, compared to emotional and behavioral, i.e., hot aspects of EF? Our findings indicate that this may be the case, as this pattern was found in both the adolescent and the young adult PBT survivor group.

Cool versus hot EF domains

In the adolescent PBT survivor group (Paper III), although there were significant between group differences on parent reports of EF for both cool and hot EF processes, most of these differences had small ESs, and only parent reported problems with working memory, i.e., a cool EF aspect, survived corrections for multiple comparisons, having a near to medium ES. Evidence for weaknesses within cool EF processes in the adolescent PBT survivor group was further found in data from performance-based assessments, i.e., for the EF domains shifting and inhibitory control, as well as for the domains processing speed, auditory attention span, and verbal learning and recall.
Self-report data from young adult PBT survivors and healthy controls showed the same pattern, i.e., self-reports of problems with both hot and cool aspects of EF, but with more problems reported for cool EF processes (Paper I). Furthermore, in the young adult PBT survivor group, the “cool pattern” in the self-report data seemed to be more prominent than in the parent report data from the adolescent PBT survivor group. On several of the measures of hot aspects of EF, i.e., subscales measuring aggressive and intrusive behavior, and problems of emotional control and behavioral inhibition, there were no significant differences between the young adult PBT survivor group and the healthy control group. Conversely, there were significant differences between the two groups on all but one of the subscales measuring cool aspects of EF, i.e., a subscale reflecting the ability to keep one’s surroundings in an orderly manner. Moreover, within group analyses in the young adult PBT survivor group, showed that significantly more difficulties in the cool EF domain than in the hot EF domain were reported by both the survivors themselves, and their informants. Also, as noted in the previous section, informants reported significantly less problems with EF than the young adult PBT survivors themselves. Taking into account that difficulties with cognitive aspects of EF may be less detectable to the surroundings than behavioral symptoms, but more readily experienced by the PBT survivors themselves, this discrepancy may support the notion that executive dysfunction experienced by PBT survivors is of a more cognitive/cool than behavioral/hot nature. Notably, there were no significantly higher rates of reported problems with behavioral inhibition, i.e., an important hot EF aspect, either in the adolescent or in the young adult PBT survivor group. This is in line with previous findings noting that PBT survivors are less likely to demonstrate clinically significant problems with behavioral inhibition, even compared to healthy controls (Brinkman, Li, et al., 2016; Krivitzky et al., 2016).

A pediatric brain tumor survivor profile?
The present findings lend support to studies demonstrating that PBT survivors, survivors of ALL, other pABI populations (e.g., traumatic brain injury [TBI]), and congenital brain disorder populations (e.g., attention deficit/hyperactivity disorder [ADHD]) may share some executive dysfunction similarities. However, PBT survivors seem to have a distinct cognitive/EF profile, somewhat unique compared to the aforementioned clinical populations (Anderson et al., 2002; Araujo et al., 2017; Krivitzky et al., 2016; Pennington & Ozonoff, 1996; Poggi et al., 2005; Winter et al., 2014). For example, although patients with ADHD, TBI, and PBT may have deficits in working memory in common, patients with ADHD and
TBI (i.e., especially focal frontal lobe lesions) exhibit more behavioral/hot EF problems, e.g., difficulties with behavioral inhibition (Anderson et al., 2002; Gioia, Isquith, Kenworthy, & Barton, 2002; Konrad, Gauggel, Manz, & Schöll, 2000). Our results indicate that this seems not to be the case for PBT survivors. Furthermore, within the CCS population, studies have shown that, although both the PBT and the ALL subset demonstrate lower-level EF problems (i.e., simple processing speed), PBT survivors who more global and higher-level EF problems (i.e., inhibitory control, planning, and flexibility) (Kahalley et al., 2013; Krivitzky, Blaufuss, & VanDenHeuvel, 2015; Winter et al., 2014). This might be due to the differences in the amount and type of damage to the developing brain caused by the respective illnesses and treatment regimens.

Treatment effects (e.g., Araujo et al., 2017; Brinkman et al. 2016), cerebellar tumor location (Moberget et al., 2015), and neurological complications such as hydrocephalus (Anderson et al., 2002), which may cause more diffuse damage, including white matter pathology and compromised cerebral wiring, may play a contributing role in the development of an idiosyncratic EF profile in the PBT population. For example, although executive dysfunction is frequently noted in the CCS population, some studies have noted an absence of an externalizing profile among survivors treated with CRT, as many show impaired inattention, slowed processing speed, and lack of initiation rather than hyperactivity or impulsivity (Brinkman, Li, et al., 2016). It has been suggested that impairments in processing speed, and what has been described as “sluggish cognitive tempo”, defined by lethargy, impaired focus, and disorganization, may in part preclude disinhibited behavior (Kahalley et al., 2013; Krivitzky et al., 2016; Willard et al., 2013). Although the number of PBT survivors having received CRT was small in our sample (11 [22.9 %] in the adolescent group and 27 [25.3%] in the young adult group), reports from this subgroup may have contributed to the distinctive EF profile observed in our sample. Indeed, parents of adolescent PBT survivors who had undergone complex treatment regimens including CRT reported significantly more problems on a composite scale reflecting cognitive/cool EF processes compared to parents of adolescent PBT survivors who had undergone surgery only, whereas the composite scale reflecting behavioral/hot aspects of EF showed no such subgroup differences.

Altogether, our findings may support previous findings demonstrating that it is mainly the cognitive/cool aspects of EF that are affected by PBT and PBT treatment, sooner than the emotional and behavioral/hot aspects of EF. However, further studies are needed to better
understand the idiosyncratic EF profiles of PBT survivors. Although the literature does not place the EF impairment within the hot/cool EF framework, findings seem generally to be in line with the notion that they struggle more with the cool EF processes relative to the hot. Furthermore, whether nuances in the EF profile of PBT survivors are due to differential damage to the specific frontal–subcortical circuits that underlie these abilities warrants further research, for example by utilizing advanced neuroimaging techniques. For instance, while hot EF processes (e.g., inhibitory control, emotional and social processing), may be more greatly affected by damage to ventromedial prefrontal regions, problems in cool EF processes (e.g., working memory, shifting, planning) may be more prominent as a result from damage to dorsolateral prefrontal regions (Anderson et al., 2002; Araujo et al., 2017; Bechara, 2004; Beer, 2006; Peterson & Welsh, 2014; Yeates et al., 2007). Nonetheless, in a “real life” perspective, the integrity of and cooperation between both hot and cool functions is essential for everyday functioning and long-term psychosocial adjustment and socioeconomic outcomes. In the following, findings of long-term adaptive functioning and socioeconomic outcomes in the present PBT survivor sample are presented, as well as the importance of EF in regard to these outcomes.

5.1.3 Executive function involvement in long-term adaptive functioning and socioeconomic outcomes

Interestingly, compared to most measures of subjective symptoms (with the exception of measures reflecting neurocognitive/EF problems), the largest between group differences in both age groups were found for measures of adaptive functioning and socioeconomic outcomes. This includes social relations (e.g., number of friendships, getting along with peers), educational functioning (e.g., completing school work efficaciously, need for educational adjustments), employment/training status (i.e., engagement in regular work, studies or military service), and financial independence (i.e., need for government benefits) (Papers II and III). More specifically, the only difference between the adolescent PBT survivor group and the healthy control group to survive corrections for multiple comparisons on a self-report measure of psychological problems, was for a subscale assessing adaptive functioning, i.e., difficulties with social adjustment and academic performance (Paper III). Similarly, on a screening measure of QoL, the largest ESs were found for subscales reflecting social and school functioning. In our sample of young adults, significantly more PBT survivors compared to healthy controls reported having received educational adjustments and
substantial government benefits, and were currently not engaged in regular employment/training (Paper II). This was particularly true of the survivors that had undergone complex treatment regimens (i.e., multiple surgeries, chemotherapy, CRT, and/or hormone therapy). These findings confirm conclusions from previous studies demonstrating that PBT survivors struggle in negotiating important adult milestones, and that they are at risk of experiencing social difficulties (e.g., poor peer acceptance, isolation), lower academic/educational achievement, and poor socioeconomic attainment (e.g., employment and financial independence) compared to other CCS populations and to the general population (Boman, Lindblad, & Hjern, 2010; Brinkman, Krasin, et al., 2016; Brinkman, Ness, et al., 2018; Brinkman, Recklitis, et al., 2018; de Boer, Verbeek, & van Dijk, 2006; Frederiksen et al., 2019; Ghaderi et al., 2016; Ghaderi et al., 2013; Mader et al., 2017; Ness et al., 2008).

However, the study showed also some encouraging findings; the young adult PBT survivors did not differ from the healthy controls regarding educational level or living situation, i.e., living independently or with parents/caregivers. Furthermore, although there was a difference between the groups in activity status, it is worth noting that more young adult PBT survivors than not were currently engaged in regular work, studies or military service. Because the participants in our young adult sample are relatively young, this may in part account for why there were no significant differences in living situation between PBT survivors and healthy controls, as participants in either groups may not yet have established an independent living situation (e.g., for financial reasons). However, similar levels of education in the groups is most likely a reflection of the equality of the Norwegian welfare and educational system, as all citizens are entitled to education at a high school level, and educational services and adjustments are offered to those who are struggling academically. Indeed, some studies demonstrate significant geographic variations in educational attainment among childhood cancer survivors, arguing that these differences are due to substantial differences between countries regarding educational systems and accessibility of special education and rehabilitation services (Boman et al., 2010; de Boer et al., 2006; Frederiksen et al., 2019; Lund et al., 2011; Mader et al., 2017; Mehnert, de Boer, & Feuerstein, 2013). For example, survivors of childhood cancer in Europe have been found to have significantly better educational outcomes compared to survivors in the U.S., with many survivors showing similar educational levels to the background population. Similar variations have been shown for employment outcomes, with European countries showing more positive outcomes than the U.S. (Boman et al., 2010; de Boer et al., 2006; Frederiksen et al., 2019; Lund et al., 2011;
Mader et al., 2017; Mehnert et al., 2013). In addition to differences in educational possibilities, differences in access to health care, (vocational) rehabilitation services and labor markets may be significant contributors in this respect. For example, it is plausible that many childhood cancer survivors are, to a larger extent, rejected as employees in the U.S., due to employer-sponsored health insurance coverage and the high risk of late effects that this patient population carries (Frederiksen et al., 2019).

Altogether, the present findings show that not only medical late effects and physical disabilities impede PBT survivors from academic achievement, educational and vocational success and financial independency, and that psychological and psychosocial aspects are important for long-term outcomes in these domains. This is demonstrated by the fact that the participants in the young adult PBT survivor group were all physically well-functioning, as survivors with severe difficulties with activities of daily life (ADL) and sensory and motor disabilities were excluded. In spite of this, there were striking differences between the young adult survivors and their healthy peers with regard to educational adjustments, substantial government benefits, and the number of survivors who were currently not engaged in regular employment/training.

**The impact of executive function impairment on long-term adaptive functioning and socioeconomic outcomes**

The present findings confirmed past studies demonstrating the negative impact of CCS late effects such as emotional and physical problems and persistent fatigue on their possibilities to participate in social and educational settings (Bell et al., 2018; Boonstra et al., 2017; Brand et al., 2016; Brinkman, Li, et al., 2016; Brinkman, Recklitis, et al., 2018; Ness et al., 2005). However, in both age groups, there emerged a pattern where poor adaptive functioning and academic and vocational outcomes were most strongly related to difficulties within the EF domain, with emotional and psychological distress less impactful. In the adolescent group, problems of adaptive functioning in the PBT survivors were most strongly related to parent reported problems with executive dysfunction, internalizing symptoms of withdrawal/depression and thought problems, and physical functioning, as well as to self-reported cognitive problems (e.g., attention problems), physical functioning and sleep/need for rest. However, parent reported neurocognitive complaints, including executive
dysfunction (i.e., problems with attention, working memory, mental shifting, and initiation), exhibited the strongest correlations to parent reported problems with adaptive functioning.

Similar findings were uncovered across most of the administered self-report measures in the young adult PBT survivor group: along with symptoms of fatigue, cognitive and executive dysfunction were more strongly associated to poorer social outcomes, with emotional and psychological distress showing less impact. Specifically, neurocognitive complaints including aspects of EF (e.g., problems with attention, working memory, and the ability to initiate activity) were significantly associated with educational adjustments and substantial government benefits, and reduced employment/training. These findings, along with findings from several past studies, confirm the interrelation between impairments of EF and poor long-term adaptive functioning and socioeconomic outcomes (Evans, 2008; Ness et al., 2008; Papazoglou, King, Morris, & Krawiecki, 2008a, 2008b; Wolfe, Vannatta, Nelin, & Yeates, 2015; Wolfe et al., 2013).

Although we were not able to establish any age effects (i.e., younger age at diagnosis resulting in poorer outcomes) in either age group, the findings are interesting in a lifetime perspective. The present findings indicate that in adolescence, difficulties with adaptive functioning and EF may still be relatively subtle compared to early adulthood. Problems seem to gradually arise as the PBT survivors leave the support of caregivers and the educational system, and transition into adulthood, with all the demands of independency that this entails (Anderson et al., 2019; Stavinoha et al., 2018). Also, considering the protracted nature of EF development and hierarchical developmental models maintaining that the development of more complex EFs build on simple, earlier developing EFs, it is plausible that findings may reflect what has been described as “growing into deficit” in pABI populations (Anderson et al., 2019; Tillman et al., 2013). Thus, adolescents may present with more difficulties as they get older, with a delayed onset and increase of impairments combined with increasing expectations for independent work, organization, and self-regulation (Anderson, Jacobs, & Harvey, 2008; Anderson et al., 2019; de Vries et al., 2017; Krivitzky et al., 2016).

The present findings harmonize well with neurodevelopmental cascade models of the neurocognitive mechanisms (i.e., impaired processing speed, attention span, and working memory) involved in the declines in both IQ and academic achievement in long-term PBT survivors (Edelstein et al., 2011; King et al., 2019; Palmer, 2008; Rey-Casserly & Diver,
2019; Wolfe et al., 2012). However, the present thesis expands on these models in two ways. First, we took a step further by including not only academic achievement, but also data on socioeconomic outcomes (e.g., work/training status and financial situation). Second, neither of these models includes emotional/behavioral, or hot, EF processes, but focuses mainly on the cool, cognitive processes. Thus, several EF processes that are crucial for successful interaction with the everyday surroundings and long-term goal achievement in “the real world” are not taken into account by these models. Our findings demonstrate the association between both cool/cognitive and hot/behavioral aspects of executive dysfunction and academic and occupational concerns, thus lending support to, but also expanding on the current neurodevelopmental cascade models.

Interestingly, in the adolescent PBT survivor group, difficulties within the hot EF domain seemed more impactful on outcomes compared to the young adult PBT survivor group. Within the adolescent PBT survivor group, subscales reflecting the cool EF domain, i.e., initiation, working memory, planning/organizing skills and monitoring, and subscales reflecting the hot EF domain, i.e., shifting between activities and emotional control, were all significantly correlated with poorer adaptive functioning outcomes, although subscales reflecting problems with emotional control and monitoring did not survive corrections for multiple comparisons. Thus, although hot EF processes were significant for adaptive functioning outcomes, associations between measures assessing cool EF processes and poorer adaptive functioning were both more numerous and yielded in general somewhat stronger correlations than the subscales assessing hot EF processes. This tendency, i.e., for cool EF processes to have greater impact on negative functional outcomes, was found more clearly within the young adult PBT survivor group: on a self-report measure of EF problems, only difficulties with cool EF processes were significantly associated to poorer socioeconomic outcomes, with working memory and initiation most impactful. Thus, our findings seem to yield support for the neurodevelopmental cascade models, but underscore the importance of attending also to difficulties within the hot EF domain, especially in the adolescent years.

Although significant, the differences between the PBT survivors and the controls on a majority of measures of executive dysfunction, psychological and emotional problems, and physical and mental fatigue generally displayed generally small ESs (with the exception of measures neurocognitive/EF complaints). This stands in contrast to the fact that they simultaneously report struggling significantly more with academic performance, education,
work and financial independency. A similar discrepancy was found in a CCS study by Brinkman, Krasin, et al. (2016) where severe performance-based neurocognitive impairment was associated with lower educational attainment, unemployment and non-independent living, yet only a few of the survivors’ self-reports reflected a similar degree of cognitive and behavioral impairment in daily life. This discrepancy may have several explanations. For example, even though scores on questionnaires were within a standard deviation below the normative mean, the difference was nonetheless significant, and the findings may reflect the total accumulation of subtle problems over time translating into bigger and more concrete issues of independent functioning, similar to that noted in adult survivors of pABI (Beauchamp et al., 2010). Furthermore, diminished impairment awareness, which is often related to executive dysfunction, has been found in several pABI populations, possibly accounting for the close to normal levels of self-reported functioning (Krasny-Pacini et al., 2015; McCurdy, Turner, et al., 2016; Sølnes et al., 2014). The issue of impairment awareness may be further exacerbated by the fact that PBTs occur in the earliest years of life, often leading survivors to habituate and gradually adapt to a subnormal level of functioning (Beauchamp et al., 2010). In this case, this subnormal functioning level may become a subjective normality, not necessarily perceived by the survivor as impaired, or different to that of their peers. Also, a systematic tendency to underreport or deny difficulties frequently noted in CCS populations, which has been linked to a repressive adaptive coping style and psychological defense mechanisms (e.g., a need to be “normal” and move past the illness), may result in an overly positive impression of outcomes (Lund et al., 2011; O’Leary et al., 2007; Phipps et al., 2001).

In summary, the present findings confirm earlier studies demonstrating that disruptions to EF development may lead to serious negative functional outcomes (Ness et al., 2008; Wolfe et al., 2012; Ylvisaker & Feeney, 2008), and that both the cognitive and the behavioral aspects of executive dysfunction are related to social, academic and occupational concerns (Zelazo et al., 2016). However, there are several important methodological concerns and limitations that need to be taken into account, and these issues are discussed in the following section.

5.2. Methodological issues, strengths and limitations
A few methodological issues have already been discussed in the previous sections; i.e., report discrepancies (e.g., self- and proxy report discrepancies, discrepancies between self-reports of
subjective symptoms versus socioeconomic attainment). In the following, issues regarding study design, outcomes measures, response rates, sample size and generalizability of findings are discussed.

5.2.1 Cross-sectional design and possible impact of environmental factors

The present study employed a cross-sectional design (Papers I, II and III). This type of design precludes the possibility of making causal inferences, and therefore there may be alternative explanations for the observed differences between the PBT survivors and healthy controls other than those presented in this thesis. For example, data on socio-environmental factors like coping style, family factors (e.g., parental responsiveness, health, education and socioeconomic status, and impact of serious illness on family interactions), and social support was not collected. These are all factors that may become increasingly important with time, and contribute to observable differences between PBT survivors and peers (Klassen et al., 2011; Kupst & Patenaude, 2016; Ryan et al., 2016; Van Schoors et al., 2017). In the developmental psychology literature, it has long been known that the development of cognitive and socio-emotional skills and behaviors, including EF skills, is to a large extent dependent on the quality of the home environment and the role models provided by parents (Anderson et al., 2019). Within the CCS population, family dysfunction and parental stress has been associated with more functional impairment, including a greater number of medical and psychosocial late effects experienced (Cousino et al., 2017; Hile, Erickson, Agee, & Annett, 2014; Peterson, Cousino, Donohue, Schmidt, & Gurney, 2012). A longitudinal design including socio-environmental information would have been more appropriate for isolating the contributory effects of socio-environmental factors, and for establishing how the symptoms and outcomes may vary over time (e.g., increase vs. reduction of impairment/symptoms). However, such an approach was not possible within the scope and time frame of the present study.

5.2.2 Response rates and generalizability of study findings

For the young adult PBT survivor group, the response rate was relatively low (38.6%, Paper I), which raises questions of the representativeness of the sample and the validity of the findings. Unfortunately, as data collection on non-responding survivors was limited by ethical regulations, an analysis of non-response bias which, in part, could explain possible variations between responding and non-responding participants, was not possible in the present study.
However, all PBT survivors in Norway meeting diagnostic and age criteria were identified by
The Cancer Registry of Norway (a database of all cancer cases in Norway), and were invited
to participate, ensuring a high level of representativeness.

There are several plausible explanations for the relatively low response rate in the young adult
PBT survivor group. Because the goal of the study was to explore how EF impairment may
affect PBT survivors’ level of societal participation, only physically well-functioning PBT
survivors were included, as severe ADL, sensory and motor disabilities are factors that may
have a negative impact participation in society regardless of the status of EF. The relatively
low response rate may, to some extent, be explained by these exclusion criteria, as past
studies on long-term outcomes in this CCS population have demonstrated relatively frequent
performance and participation limitations, with up to 26% of adult PBT survivors reporting
limitations in physical performance and daily activities (Ness et al., 2005). Although
information on physical and sensory impairments in non-responding survivors was not
available, the actual response rate for our target population may therefore be considerably
higher than 38.6%, considering that up to 26% of the original 295 invited PBT survivors may
not have met the inclusion criteria. In light of this, it is possible that the PBT survivors that
did respond constitute a relatively representative sample of this specific PBT survivor
population. Furthermore, as established throughout this thesis, the presence of EF
impairments has repeatedly been noted in the PBT survivor population. Considering that the
process of completing and returning the questionnaire by mail is in essence an “EF task”, it is
not unlikely that PBT survivors with more serious cognitive impairments and executive
dysfunction may have found participation too demanding, and therefore refrained from
responding. However, alternate methods of survey distribution, e.g., electronic surveys, may
not have yielded any higher response rates, as people today are continuously inundated with
surveys of all kinds, subsequently lowering response rates in general. Indeed, a meta-analysis
comparing response rates in e-mail and paper surveys distributed to healthy respondents,
found paper survey more efficient than e-mail survey in terms of response rates (Shih & Fan,
2009). Also, the response rate in the present young adult PBT survivor sample seems
comparable to previous studies in the child brain injury literature. Moreover, the response rate
in the adolescent PBT survivor sample was substantially higher than that of the young adult
group (53.3%, Paper III), and is, as such, relatively high compared to previous studies in the
child brain injury and CCS literature, ensuring an adequate level of representativeness in this
age group. Nonetheless, the issues concerning the low response rate caution the
generalizability of the findings, as they may provide a different and/or overly optimistic picture of long-term outcomes for the PBT population in general.

5.2.3 The use of self-reports and performance-based data for assessing EF

In this study, self-report and parent report measures were employed for the exclusion criteria and for the key variables and outcomes (Papers I, II and III). There are several possible sources of confounding influence on the findings associated with this methodological approach, such as psychological defense mechanisms/coping style, demand characteristics, cognitive deficits, social desirability bias, acquiescent responding, and extreme responding (Logan, Claar, & Scharff, 2008; Lund et al., 2011; McCambridge, de Bruin, & Witton, 2012; O’Leary et al., 2007; Phipps et al., 2001). These issues may be present in both self- and proxy reports, and threaten the accuracy and validity of the information obtained. In this population, the possibility of impaired self-awareness is a particularly relevant issue, potentially having had a confounding influence on the findings. For example, it is possible that some of the young adult PBT survivors may not have had a realistic perception of the severity of their physical limitations, and as such, may not in fact have met the inclusion criteria. Alternatively, considering the possibility of impaired awareness of cognitive deficits and social functioning, the difference between the healthy controls and the adolescent and young adult PBT survivors may in reality be greater than what the current findings have shown.

Despite these limitations, self- and proxy reports offer the advantage of efficiently collecting large amounts of information from many participants, i.e., from those persons who have first-hand knowledge and experience with the participants’ functioning in their everyday settings, without the interference of the researcher (Manchester, Priestley, & Jackson, 2004). Moreover, there are currently few other available methods to assess EF processes in real-world settings as efficiently as questionnaires, especially with regard to social-emotional/behavioral skills and hot EF processes.

For a subgroup in the adolescent PBT survivor group, performance-based measures were administered in addition to questionnaires (Paper III). Unlike questionnaires, performance-based assessments are regarded more suitable for assessing the cognitive aspects of EF, and are administered in laboratory-like settings. Previous findings from these two different methodological approaches confirm that they most likely tap separate, but related, constructs within the EF domain, and that performance varies across settings that place different and/or
higher demands on cognitive functioning (Anderson et al., 2002; de Vries et al., 2017; McCurdy, Turner, et al., 2016). In this study, the self- and proxy report assessing EF were the BRIEF and BRIEF-A. These methods have shown to be powerful tools in assessing EF, distinctive from performance-based measures (Anderson et al., 2002; Toplak, West, & Stanovich, 2013), including accounting for variance in neuroimaging findings in studies of both typically developing and patient populations (Wang et al., 2012; Warren et al., 2013; Ziegler, Dahnke, Winkler, & Gaser, 2013). Indeed, the present findings demonstrated only a few significant correlations between performance-based data and questionnaire data. Only the verbal fluency domain was significantly associated with parent and self-reported problems of neurocognitive functioning, i.e., problems with attention, working memory, initiation, ability to plan and organize, and overall problems with EF in everyday life. However, these correlations did not survive corrections for multiple comparisons. Furthermore, although parents of PBT survivors reported significantly more problems with working memory, significant deviations in this EF domain were not found in the performance-based data. For these reasons, the two approaches cannot simply replace one another without risking loss of valuable information, and both were therefore employed in the present study in order to capture both cool and hot EF processes. Unfortunately, the subgroup for which performance-based data was collected was small, and the results should therefore be viewed as exploratory. However, as discussed in the previous sections, despite the small number of participants in this subgroup, the findings are in line with the broader literature on neurocognitive functioning in survivors of PBT.

5.2.4 Sample size for subgroup analyses
Another area of concern is the small number of participants for some of the subgroup analyses, which could account for why age, tumor type and location, and treatment-related effects on long-term outcomes measures were not consistently found in the present PBT survivor sample. The results from these analyses should therefore be considered merely exploratory, also because the variables were less well defined (e.g., information regarding treatment regimen registered as yes/no, and tumor location defined as either supra- or infratentorial). Nonetheless, the present study invited all eligible survivors in the Norwegian patient population, in order to enhance the number of participants as much as possible.
5.3 Clinical implications

Despite these limitations, the findings from this study provide important insights into long-term adaptive functioning, socioeconomic attainment and societal participation in PBT survivors. The study contributes to provide a more comprehensive picture of the psychological and psychosocial mechanisms underlying poor social outcome in this CCS subset, for which there traditionally has been limited research. Further, the findings provide important insights into the difficulties experienced by adolescent PBT survivors, for which there traditionally has been limited knowledge. These insights have important clinical implications. The findings confirm the need for clinical follow-ups both shortly after treatment completion, and years after treatment is completed, i.e., as survivors enter adulthood, as problems such as neurocognitive decline, including EF impairment, and psychological and emotional distress symptoms may gradually develop years after treatment completion. Furthermore, PBT survivors both with and without severe physical sequelae after treatment completion should be followed.

Due to its complex and dynamic nature, executive dysfunction may remain undetected by professionals, and is often misinterpreted, e.g., as negative volitional aspects dependent on the individual’s character and psychological functioning (Anderson et al., 2010; Lezak et al., 2012), underlining the need for assessing EF in follow-ups. Also, the findings demonstrate the importance of awareness of the tendency of underreporting difficulties, and caution that even discrete problems may gradually accumulate and cause serious negative consequences for social attainment across the lifespan.

Long-term assessments may help to uncover EF impairments, to form a basis on which to implement suitable compensatory strategies and educational/occupational adjustments, and for advising health and education professionals on appropriate intervention strategies. The importance of suitable, tailored interventions is reflected in the findings: although a majority of the PBT survivors had received educational adjustments, they nonetheless had poorer outcomes compared to their healthy peers. In light of findings from this study, to improve outcome from the educational and rehabilitation resources offered, future efforts should focus more on improving EF skills and tailoring compensatory strategies for executive dysfunction. Fortunately, EFs are relatively malleable, and may be improved by supportive caregiving and EF skills practice (Zelazo et al., 2016; Zelazo & Carlson, 2012).
Furthermore, the findings indicate the presence of a distinct EF profile in this population, with cool EF processes more strongly affected than hot EF processes, which is important information when tailoring interventions to the specific needs of PBT survivors. Encouragingly, interventions aimed at improving hot and cool aspects of EF in pediatric populations are rapidly emerging. For example, a recent meta-analysis found that caregiver involvement may improve the effectiveness of rehabilitation interventions aimed at hot EF processes, while high intervention session frequency may be essential in improving cold EF processes (Chavez-Arana et al., 2018). However, so far the findings are mixed as to the effectiveness of current interventions, warranting further research (Godfrey, Catroppa, Kaizar, Yeates, & Robinson, 2014; Riccio & Gomes, 2013).

6. CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH
In conclusion, our findings suggest that PBT survivors with well-preserved sensory and physical function are at increased risk to develop neurocognitive impairments that persist into adulthood compared to healthy peers. This includes executive dysfunction, and within the EF domain, problems with cognitive/cool aspects of EF seem to be greater than problems with emotional and behavioral/hot aspects of EF. Also, the findings demonstrate that survivors in the present PBT sample struggle with symptoms of fatigue years after treatment, as well as problems in the areas of psychological and emotional functioning, although the latter to a lesser degree compared to problems with EF and fatigue. Further, our findings suggest that PBT survivors, although physically well-functioning, have significant long-term problems with adaptive functioning and achieving important adult milestones such as occupational success and financial independency, and that these problems are associated with self-reports of executive dysfunction, cognitive problems, and fatigue, in addition to having undergone complex treatment regimens.

Future research efforts should focus on further discerning the possible idiosyncratic EF profile in this CCS and pABI subset, e.g., with more finely tuned hot vs. cool EF measures, and with longitudinal studies demonstrating their respective developmental trajectories and associated real-world outcomes. Also, further research into the effectiveness of tailored interventions is essential in order to optimize PBT survivors’ chances of succeeding in the transition to adulthood and of participating in society, and to prevent social inequity for survivors of PBT in a lifetime perspective.
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Executive function and psychosocial adjustment in adolescent survivors of pediatric brain tumor

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Abstract

Adolescent survivors of pediatric brain tumor (PBT) are a sparsely studied subset of childhood cancer survivors. Sustaining a PBT may complicate the development of executive functions (EF), which play a vital role in long-term psychosocial adjustment. In this study, 48 adolescent survivors and their parents completed questionnaires assessing EF, psychological symptoms, fatigue and adaptive functioning, and 26 survivors underwent neuropsychological assessment. Survivors reported significantly more problems with adaptive functioning than a healthy control group, and executive dysfunction was most strongly associated to problems with adaptive functioning, compared to psychological symptoms and fatigue. The findings have important implications for long-term follow-ups.
1. Introduction

Adolescence is a critical period for the development of executive functions (EF), emotional functioning, and social skills, laying the foundation for the transition into adulthood and for achieving adult milestones, such as social independence and socioeconomic attainment (e.g., education, vocation, financial independence). Having sustained a brain tumor at an early stage in life may complicate these normative developmental processes in several ways. Studies have repeatedly shown that compared not only to the general population, but also other childhood cancer survivors (CCS), survivors of pediatric brain tumors (PBT) are at increased risk of negative functional outcomes, such as fatigue, emotional problems, greater challenges with social relationships (e.g., poor peer acceptance, isolation), and poorer socioeconomic attainment (Bell, Ownsworth, Lloyd, Sheeran, & Chambers, 2018; Boonstra et al., 2017; Bower, 2014; Brand, Chordas, Liptak, Manley, & Recklitis, 2016; Brinkman, Li, et al., 2016; Brinkman, Recklitis, Michel, Grootenhuis, & Klosky, 2018; Clanton et al., 2011; Husson, Zebrack, Block, et al., 2017; Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; Poggi et al., 2005; Puhr et al., 2019b; Speechley, Barrera, Shaw, Morrison, & Maunsell, 2006; Walter, Nixon, Davey, Downie, & Horne, 2015; Zeltzer et al., 2009). This vulnerability may likely be due to brain pathology caused by treatment or the tumor itself, and within PBT survivor population, irradiation therapy, physical and sensory sequelae, hydrocephalus, younger age at diagnosis, and infratentorial tumor location, have been associated with poorer social outcomes and quality of life (QoL) (Barrera et al., 2017; Bell et al., 2018; Frederiksen et al., 2019; Husson, Zebrack, Aguilar, Hayes-Lattin, & Cole, 2017; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Ness et al., 2005; Robinson et al., 2015; Turner, Rey-Casserly, Liptak, & Chordas, 2009). However, findings are mixed as to the effects of tumor location and age, and negative outcomes (i.e., neurocognitive dysfunction) have also been found in patients treated with surgery only (Bell et al., 2018; Riva & Giorgi,
Optimal executive functioning may play a particularly significant role in long-term functional outcomes, as even in the context of preserved intellectual, perceptual, communication and memory skills, impairments in EF may cause the greatest handicap for adaptive functioning and social attainment (Evans, 2008).

Although there is no consensus on the definition of EF, they are often described as the human capacity to control, organize and direct cognitive, behavioral and emotional responses, which, although linked to prefrontal lobe functioning, rely greatly on the intactness of multiple cooperating brain networks (Gioia, Isquith, & Guy, 2001; Stuss & Alexander, 2000). Traditionally, the cognitive aspects of EF has mainly been understood as abstract, decontextualized and non-emotional functions, often referring to Miyake et al.’s (2000) influential model comprising three separate, but interrelated cognitive EF core factors: (a) shifting between tasks or mental sets, (b) updating and monitoring of working memory representations, and (c) inhibitory control of dominant or prepotent responses. However, it is becoming increasingly more common to use the umbrella term ‘EF’ to refer to both cognitive functions and behavioral and social/affective skills, and furthermore, to consider different methodological approaches to the clinical assessment of EF in light of this diversity. This distinction is often referred to as the “cool” and “hot” EF. “Cool” EFs operate in affectively neutral contexts (e.g., attentional control, working memory, initiation, planning and organizing, selection of efficient problem-solving strategies, mental flexibility and utilization of feedback), whereas “hot” EF operate in situations that evoke emotion, motivation, and the contest between immediate gratification and long-term rewards, and involve the capacity to exert appropriate control and regulation of emotional and behavioral impulses and responses (Zelazo, Qu, & Kesek, 2010). Although linked to different developmental trajectories, both “hot” and “cool” EF develop rapidly throughout early childhood into adolescence and early
adulthood; paralleling the development and maturation of neuroanatomical structures and networks (Peterson & Welsh, 2014; Zelazo & Carlson, 2012). Damage to the developing brain at any time and in any location can cause persistent impairments in EF along with social dysfunction, as the development of “hot” and “cool” aspects of EF are closely related to the development of social information processing and social competence (Peterson & Welsh, 2014; Riggs, Jahromi, Razza, Dillworth-Bart, & Mueller, 2006; Ryan et al., 2016; Yeates et al., 2007).

While performance-based neuropsychological tasks are generally considered as methodologically suitable measures for assessing the “cool” aspects of EF (Peterson & Welsh, 2014), more ecologically valid measures are needed to assess the “hot” aspects, considering that these functions are more readily observed in everyday settings, than in standard, highly structured neuropsychological test settings. Questionnaires reflecting both self-report and informant report are therefore recommended, to address the confounding influence of possible impairments in self-awareness and reporter discrepancies, which is not uncommon in pediatric acquired brain injury (pABI) and CCS populations (Jurbergs, Russell, Long, & Phipps, 2008; Krasny-Pacini et al., 2015; Lund, Schmiegelow, Rechnitzer, & Johansen, 2011; McCurdy et al., 2016; Roth, Isquith, & Gioia, 2005).

Studies focusing on EF in PBT survivors have shown that this population are at risk of developing problems with EF, both in the short and long term, and impairments in EF may be of particular significance for long-term outcomes (de Ruiter, van Mourik, Schouten-van Meeteren, Grootenhuis, & Oosterlaan, 2013; Koustenis, Hernaiz Driever, de Sonneville, & Rueckriegel, 2016; Netson et al., 2016; Wolfe, Madan-Swain, & Kana, 2012). In a recent study of long-term outcomes among physically well-functioning adult PBT survivors compared to healthy controls, the largest effect sizes were for group differences in self-reported EF, along with fatigue, compared to self-reported psychological and emotional
problems (Puhr et al., 2019a). Furthermore, a study following up on these findings, showed that negative adaptive functioning and poor socioeconomic attainment (e.g., employment outcome, financial independence) was most strongly associated to executive dysfunction, with psychological and emotional problems showing less impact (Puhr et al., 2019b). The survivors in these studies had all been treated for a PBT during the first 16 years of life, and, although historical data were not available, it is plausible that impairments in EF with the potential to hamper the negotiation of adult milestones were present already in adolescence, post treatment. These findings point to the need for further knowledge on the presence of impairments in EF in adolescent PBT survivors, in order to prevent negative long-term outcomes and enhance psychosocial adjustment.

The purpose of this study is threefold. The primary aim was to explore the long-term neurocognitive consequences of PBT in adolescent survivors, with a special focus on executive dysfunction, by comparing parent-reports of EF and performance-based neuropsychological assessments to matched controls and normative data, respectively. Based on previous findings, we expected parents of adolescent PBT survivors to report more overall problems with EF than parents of healthy peers, and that the presence of executive dysfunction would be further confirmed by the survivors’ results on performance-based tests. Also, we explored possible associations between performance-based measures and self- and parent-reports of neurocognitive functioning, expecting few significant associations, as these methods assess different aspects of EF. The second aim was to explore whether PBT survivors experience more problems with adaptive functioning (i.e., academic achievement and social functioning) compared to healthy controls, and to what degree executive dysfunction is associated to adaptive functioning compared to psychological problems and fatigue. As we have previously reported (Puhr et al., 2019b), EF is linked to adaptive functioning and social attainment in adult PBT survivors. In this study, we focused on the
association between adaptive functioning and EF in adolescent PBT survivors. We also expected this association to be confirmed by performance-based assessments of EF in the PBT subgroup. The third aim was to investigate how reports of executive dysfunction, psychological and behavioral problems and fatigue are associated with tumor-related factors (age at diagnosis, location, and tumor type) and treatment-related factors (type of treatment, time since treatment completion). We expected younger age at onset, infratentorial tumor location, and complex treatment regimens to be more strongly associated with negative self- and parent-reported outcomes.

2. Methods

2.1 Study participants

Figure 1 shows a flowchart of the study. Survivors of PBT fulfilling inclusion criteria defined as treatment for PBT at \( \leq 16 \) years, aged 13-17 at the time of recruitment, and having completed treatment \( \geq 2 \) years prior to study participation, were identified by The Cancer Registry of Norway. Exclusion criteria were self-reported severe difficulties with activities of daily life (ADL), self-reported severe sensory and motor disabilities, and pre-treatment cognitive/neurological deficits unrelated to the tumor diagnosis, evidenced in patient reports and/or patient records.

Ninety-nine teenage PBT survivors received self-report and parent-report forms by mail to assess EF, psychological and emotional functioning, and fatigue. Of the 99 PBT survivors, four were excluded due to non-tumor diagnoses (e.g. cysts, lipomas), three due to treatment for recurrent/residual tumor within last two years, and two because of pre-tumor cognitive/neurological problems due to non-tumor diagnoses. In total, 48 of 90 (53.3%) of eligible PBT survivors and their parents/caregivers completed the self-report and parent-report forms, respectively. Mean age at time of survey was 15.7 (SD=1.37), 54.2% of the
survivors were female. Mean age at illness debut was 6.8 years (range: 0.1-14.1, SD=4.13) and mean time since treatment completion was 8.4 years (range=2.7-17.0, SD=3.98). Seventeen survivors (35.4%) reported minor sensory and/or motor impairments partly disrupting everyday functioning.

A subgroup of the PBT survivors, who have been followed up with multiple neuropsychological assessments after treatment completion at Oslo University Hospital, also...
underwent cognitive retesting. Of 36 invited, 26 (72.2%) underwent retesting. For this subgroup, the mean age at diagnosis was 6.3 years (range: 0.3-13.3, SD=3.97) and mean time since treatment completion was 8.9 years (range=4.0-14.1, SD=3.63). Mean age at cognitive retesting was 16.6 years (SD=1.37). No survivors in the subgroup undergoing cognitive retesting reported sensory and/or motor impairments seriously disrupting everyday functioning.

Clinical characteristics for the PBT survivor group and the PBT subgroup that underwent cognitive retesting are presented in Table 1. Information on age at diagnosis, histology, location, and treatment type was collected from patient records. For the purpose of classifying PBT survivors into larger diagnostic subgroups, the third version of the International Classification of Childhood Cancer (ICCC-3) was used. The following information on treatment and late effects was registered as yes/no: surgery, CRT, chemotherapy, hormone replacement treatment (i.e., growth hormones, cortisol, thyroid stimulating hormones, testosterone and estrogen, or antidiuretic hormones), postoperative seizures (i.e., ≥1 seizure after tumor surgery), postoperative hydrocephalus treatment (ventriculoatrial shunt, ventriculoperitoneal shunt, or third ventriculostomy), and psychiatric comorbidity (i.e., as classified by the International Classification of Disease -10 codes F01-F99).

A group of healthy controls was recruited from The National Population Register of Norway, and received self-report and parent-report forms identical to those of the patient group. Of the 300 controls invited, 73 (24.3 %) controls and caregivers/parents returned completed self-report and parent-report forms, respectively. There was a significant age difference between the PBT survivor group and the control group: mean age at time of survey was 15.7 (SD=1.4) in the PBT survivor group and 14.7 (SD=1.4) in the healthy control group.
The groups were matched for sex: 55.1 % of the survivors and 50.7 % of the controls were female \( (p=.632) \).

**Table 1. Clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>N survey group ((n=48))</th>
<th>%</th>
<th>N retested subgroup ((n=26))</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ependymomas and choroid plexus tumors</td>
<td>6</td>
<td>12.5</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Astrocytomas</td>
<td>23</td>
<td>47.9</td>
<td>13</td>
<td>50.0</td>
</tr>
<tr>
<td>Embryonal tumors</td>
<td>16</td>
<td>33.3</td>
<td>6</td>
<td>23.1</td>
</tr>
<tr>
<td>Other gliomas</td>
<td>1</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other CNS-tumors</td>
<td>2</td>
<td>4.2</td>
<td>3</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Tumor location</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Supratentorial</td>
<td>14</td>
<td>29.2</td>
<td>7</td>
<td>26.9</td>
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<tr>
<td>Infratentorial</td>
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<td>4.2</td>
<td>1</td>
<td>3.8</td>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Surgery only</td>
<td>28</td>
<td>58.3</td>
<td>17</td>
<td>65.4</td>
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<td>9</td>
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<td>-</td>
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<tr>
<td><strong>Postoperative hydrocephalus treatment(^b)</strong></td>
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<td></td>
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<td>7</td>
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<td>43</td>
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<td>23</td>
<td>88.5</td>
</tr>
</tbody>
</table>

\(^a\) CRT=cranial/craniospinal irradiation therapy  
\(^b\) Ventriculoatrial shunt (VA), ventriculoperitoneal shunt (VP) or third ventriculostomy (3CVS),  
\(^c\) Hormone replacement treatment, e.g., growth hormone, cortisol, thyroid stimulating hormone, testosterone and estrogen, and antidiuretic hormone.
2.2 Long-term outcome measures

2.2.1 Self- and parent-reports of neurocognitive functioning, psychological symptoms, and fatigue.

**BRIEF.** The parent-report version of the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy & Kenworthy, 2000) contains 86 items surveying teenagers’ EF in everyday activities over the past 6 months. The items are rated on a three-point scale (1=never; 2=sometimes; 3=often) and three indices are generated: the Behavior Regulation Index (BRI), the Metacognitive Index (MI), and a Global Executive Composite (GEC). The BRI subscales Inhibit, Shift, and Emotional Control, reflect behavioral and social/affective aspects of EF, i.e., the “hot” EF aspects, whereas the subscales Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor, reflect cognitive, or “cool”, aspects of EF. Higher scores on the subscales and indices reflect more problems with EF. The BRIEF questionnaire showed high levels of internal consistency; Cronbach’s alpha of =.96 for both the survivor and control group, respectively.

**YSR, CBCL.** The Achenbach System of Empirically Based Assessment (ASEBA; Achenbach & Rescorla, 2001) is a family of screening tools for psychological symptoms and behavioral problems, which, amongst others, include the Youth Self-Report (YSR), and the parent version Child Behavior Checklist (CBCL). The YSR and the CBCL consist of 112 questions, scored on a three-point Likert scale (0 = statement not true; 1 = statement sometimes true; 2 = statement very true), yielding the eight syndrome scales Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. Three composite scores are produced; Total Problems, Internalizing Problems (sum of the scales Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints), and Externalizing Problems (sum of the scales Rule-Breaking Behavior and Aggressive Behavior). Higher
scores on the syndrome scales reflect more psychological symptoms and behavioral problems. The subscale Attention reflects subjective cognitive complaints. The YSR and the CBCL also measure competence and adaptive functioning, generating the subscale Total Competence which is comprised of items on the teenager’s activities, social relations, and academic performance, with lower scores reflecting more problems in these areas. The YSR and CBCL had high internal consistency for both survivor and control groups; Cronbach’s alpha of =.92 and .94, and .91 and .87, respectively.

**PedsQL.** The self-report and parent-report version of the Pediatric Quality of Life Inventory 4.0 (PedsQL; Varni, Seid, & Kurtin, 2001) measure QoL over the past month in teenagers aged 13 to 18. The 23 items are rated on a five-point Likert scale (0=never; 1=almost never, 2=sometimes; 3=often, 4=almost always), and items are reverse-scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that lower scores reflecting more problems. Four subscales are generated: Physical, Emotional, Social, and School Functioning, as well as a total score; PedsQL Total, and subscale scores are computed as the sum of the items divided by the number of items answered. Varni, Burwinkle, Seid, and Skarr (2003) recommend a cutoff score of 1 standard deviation below the population mean. However, the appropriateness of this cutoff score has been questioned because of its sample-dependence, as is its applicability across age and diagnostic groups and cultural contexts (Huang et al., 2009; Petersen, Hägglöf, Stenlund, & Bergström, 2009). Internal consistency was high; Cronbach’s alpha of =.89 and =.75 for the PedsQL parent version for the survivor group and control group, respectively, and = .92 and .90 for the PedsQL self-report version.

**PedsQL-MFS.** The PedsQL-Multidimensional Fatigue Scale (PedsQL-MFS; Varni, Burwinkle, Katz, Meeske & Dickinson, 2002) is a self-report questionnaire that consists of 18 items measuring problems with fatigue during the last month. The items are scored as for the
PedsQL, with lower scores reflecting more problems. From the 18 items, the subscales General Fatigue, Sleep/Rest Fatigue and Cognitive Fatigue are generated, as well as a total score; PedsQL-MFS Total. The subscale Cognitive Fatigue may be considered a measure of subjective cognitive complaints rather than a measure of fatigue, as it comprises items all reflecting everyday cognition. To the best of our knowledge, there are currently no recommended clinical cutoff scores for the PedsQL-MFS. The PedsQL-MFS showed high levels of internal consistency; Cronbach’s alpha of =.88 for both the survivor and control group.

2.2.2 Performance-based measures of neurocognitive domains. A battery of well-known neuropsychological tests commonly employed in clinical settings was used to assess neurocognitive functioning in a subset of the PBT survivor group. The tests were grouped into larger neurocognitive domains, i.e. estimated current IQ, processing speed, auditory attention span, sustained attention, verbal learning and recall, verbal fluency and executive functions, by converting all raw scores to T-scores and calculating an average T-scores within each domain. A score of 1.5 standard deviations or more below the normative mean was defined as a clinical cutoff.

Estimated current IQ. The Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were used to estimate current IQ.

Processing speed. The subtests Trail Making Test 2 (TMT 2; number sequencing) and 3 (TMT 3; letter sequencing), and Color-Word Interference Test 1 (CWIT 1; color naming) and 2 (CWIT 2; word reading), from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) were employed in order to assess processing speed.

Auditory attention span. The Digit Span Forward scores from the Wechsler Adult Intelligence Scale –IV (WAIS-IV; Wechsler, 2008) for participants aged >16, and the
Wechsler Intelligence Scale for Children –IV (WISC-IV; Wechsler, 2003) for participants aged <16 was used to assess auditory attention span.

**Sustained attention.** From the Conners’ Continuous Performance Test – Third Version (CPT 3; Conners, 2013), which is a well-known computerized test of different aspects of attention, the Hit Reaction Time Block Change measure (HRT BC) was selected as the measure of sustained attention.

**Verbal learning and recall.** The Children’s Auditory Verbal Learning Test (CAVLT-2; Talley, 1993) was used to assess the two domains verbal learning and recall. For technical reasons, the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) was used for assessing verbal learning and memory in 8 participants.

**Verbal fluency.** The subtest Verbal Fluency from the D-KEFS battery was used to assess verbal fluency, i.e. the ability to rapidly produce words compatible with required criteria.

**EF.** For the assessment of the EF domain “shifting”, we used the subtests Trail Making Test 4 (TMT 4; number-letter switching) and Color-Word Interference Test 4 (CWIT 4; inhibition/switching) from the D-KEFS battery. For the EF domain “working memory”, we used the subtest Digit Span Backward (WAIS–IV, WISC–IV). For the “inhibitory control” domain, we used the commissions score from the CPT 3 and the subtest Color-Word Interference Test 3 (CWIT 3; inhibition) from the D-KEFS battery.

### 2.3 Data analyses

Analyses were performed using the statistical package SPSS for Windows, version 25.0 (SPSS, Inc., Chicago, Illinois). Non-parametric statistics were conducted for questionnaire data due to non-normally distributed variables. Data from performance-based tests were normally distributed, and parametric analyses were performed. Bonferroni corrections for
multiple comparisons were employed. Between-group differences were investigated by Pearson Chi Square and Mann-Whitney $U$ test. Because of the significant age difference between the groups, univariate analyses with age as a covariate were also performed. The Wilcoxon signed-rank test was applied for self- and informant-report differences on the CBCL/YSR and PedsQL questionnaires. Effect sizes (ES) for non-parametric statistics are reported as $r$ defining small ES as $r=.1 - .3$; medium ES as $r=.3–.5$; large ES as $r > .5$ (Field, 2009, p. 57). Associations between the YSR/CBCL Total Competence scale and other questionnaire subscales, and between performance-based test scores and questionnaire subscales reflecting neurocognitive functioning and adaptive functioning (i.e., the BRIEF subscales, the CBCL and YSR subscales Attention and Total Competence, and the PedsQL-MFS Cognitive Fatigue), were investigated by Spearman’s rho ($r_s$) test. One sample T-tests were conducted in order to investigate deviations from the normative average ($T=50$) in performance-based test scores. Associations between questionnaire data (i.e., indices, composite scores and total scores) and a) demographic (sex, age at time of survey), b) tumor-related (age at diagnosis, location [i.e., supra- vs. infratentorial locations], tumor type), and c) treatment-related (time since treatment completion, type of treatment [surgery only vs. surgery combined with chemotherapy vs. surgery combined with CRT and chemotherapy]), were explored by Kruskal-Wallis $H$ test (multivariate analyses). Due to the small number of participants with postoperative hydrocephalus, postoperative seizures, hormone replacement therapy, psychiatric comorbidity, and tumors classified as “other gliomas” and “other CNS-tumors”, these medical late effect variables and tumor types were excluded from the analyses on associations between tumor types and questionnaire data.
2.4 Ethics
The study was conducted in compliance with the Declaration of Helsinki by the World Medical Association Assembly, and was approved by the Regional Committee for Medical Research Ethics in Norway (REC; 2014/379). Written informed consent was obtained after a complete description of the study.

3. Results

3.1 Self- and parent-reported EF, social/emotional adjustment, QoL and fatigue

Neurocognitive functioning. Between group differences on self- and parent-reports are presented in Table 2. On the BRIEF, parents of PBT survivors generally reported more EF problems than parents of controls. The differences that survived correction for multiple comparisons included the Working Memory subscale (corrected $p=.044$, $r = -.26$). Parents of PBT survivors reported more problems than parents of controls on the CBCL Attention Problems, and this difference survived corrections for multiple comparisons (corrected $p<.011$, $r= -.35$). On the PedsQL-MFS Cognitive Fatigue, PBT survivors reported significantly more problems than the controls, and this difference survived corrections for multiple comparisons (corrected $p<.011$, $r= -.36$).

Social/emotional adjustment. As shown in Table 2, significantly more problems were reported by parents of PBT survivors compared to parents of controls on the CBCL subscales Withdrawn/Depressed, Somatic Complaints, Social Problems, as well as for the composite scales Internalizing Problems and Total Problems. The differences that survived corrections for multiple comparisons included the CBCL subscale Social Problems (corrected $p<.012$, $r= -.37$) and the composite scales Internalizing Problems (corrected $p<.012$, $r= -.28$) and Total Problems (corrected $p<.012$, $r= -.32$). PBT survivors reported significantly more problems than the controls on the YSR subscale Social Problems, though this difference did not survive corrections for multiple comparisons.
QoL. On the PedsQL, the PBT survivors and their parents generally reported significantly more problems. The differences that survived corrections for multiple comparisons included the self-report subscales Emotional Functioning (corrected $p=.025$, $r=-.25$), Social Functioning (corrected $p=.005$, $r=-.30$), School Functioning (corrected $p<.005$, $r=-.40$), the total score (corrected $p<.005$, $r=-.39$), as well as the parent-report subscales Physical Functioning (corrected $p<.005$, $r=-.34$), Social Functioning (corrected $p=.005$, $r=-.29$), School Functioning (corrected $p<.005$, $r=-.39$), and the total score (corrected $p<.005$, $r=-.39$).

Fatigue. PBT survivors reported significantly more problems than the controls on the PedsQL-MFS subscales General Fatigue and the total score, (corrected $p=.004$ and .004, $r=.30$ and .31, respectively).

PBT survivor self- and parent-report discrepancies. Parents of PBT survivors reported significantly less problems on the CBCL composite scale Externalizing (self-report mean = 47.3, ± 8.43; parent-report mean =45.0, ± 9.37; $p=.032$) than the PBT survivors themselves, but significantly more problems on the CBCL subscale Somatic Problems (self-report mean = 54.8, ± 5.86; parent-report mean =60.4, ± 9.99; $p<.001$). Only the CBCL the CBCL subscale Somatic Problems (corrected $p<.012$; $r=.63$) survived corrections for multiple comparisons. No significant discrepancies between parent and self-reports were found for the PedsQL in the PBT survivor group.

3.2 Self- and parent-reported aspects of adaptive functioning

As shown in Table 2, PBT survivors and their parents reported significantly more problems than the controls on the YSR and CBCL Total Competence scale, with both differences surviving corrections for multiple comparisons (corrected $p<.012$ and <.012, $r=.36$ and .40, respectively).
Table 2. Self- and parent reported executive functioning, psychological symptoms, and fatigue at ≥ 2 years after PBT-treatment completion compared to healthy controls.

<table>
<thead>
<tr>
<th>BRIEF scales (T-scores)</th>
<th>PBT survivors (n=48)</th>
<th>Controls (n=73)</th>
<th>Mann-Whitney test (uncorrected)</th>
<th>Parents of PBT survivors</th>
<th>Parents of controls</th>
<th>Mann-Whitney test (uncorrected)</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Inhibit</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45.6 (8.01)</td>
<td>45.6 (7.51)</td>
<td>.726 (uncorrected)</td>
<td>.03</td>
</tr>
<tr>
<td>Shift</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48.2 (11.01)</td>
<td>43.4 (6.99)</td>
<td>.017 (uncorrected)</td>
<td>-.22</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48.3 (9.56)</td>
<td>43.9 (8.23)</td>
<td>.012 (uncorrected)</td>
<td>-.23</td>
</tr>
<tr>
<td>Initiate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>49.1 (13.44)</td>
<td>45.6 (8.91)</td>
<td>.049 (uncorrected)</td>
<td>-.18</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>54.1 (14.06)</td>
<td>47.0 (9.34)</td>
<td>.004 (uncorrected)</td>
<td>-.26</td>
</tr>
<tr>
<td>Plan/Organize</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>51.2 (11.61)</td>
<td>46.3 (9.22)</td>
<td>.012 (uncorrected)</td>
<td>-.23</td>
</tr>
<tr>
<td>Organization of Materials</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>44.6 (10.95)</td>
<td>44.9 (10.73)</td>
<td>.798 (uncorrected)</td>
<td>.02</td>
</tr>
<tr>
<td>Monitor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47.9 (10.49)</td>
<td>44.2 (9.18)</td>
<td>.035 (uncorrected)</td>
<td>-.19</td>
</tr>
<tr>
<td>BRI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47.0 (10.49)</td>
<td>43.5 (9.18)</td>
<td>.045 (uncorrected)</td>
<td>-.18</td>
</tr>
<tr>
<td>MI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>49.1 (13.81)</td>
<td>45.2 (9.59)</td>
<td>.026 (uncorrected)</td>
<td>-.20</td>
</tr>
<tr>
<td>GEC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47.9 (12.98)</td>
<td>44.2 (9.07)</td>
<td>.017 (uncorrected)</td>
<td>-.22</td>
</tr>
</tbody>
</table>
### YSR, CBCL subscales (T-scores)

<table>
<thead>
<tr>
<th>Subscale</th>
<th>YSR Mean (SD)</th>
<th>CBCL Mean (SD)</th>
<th>p-value</th>
<th>r</th>
<th>YSR Mean (SD)</th>
<th>CBCL Mean (SD)</th>
<th>p-value</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Competence</td>
<td>38.5 (11.09)</td>
<td>47.1 (10.97)</td>
<td>&lt;.001(^1,^2)</td>
<td>.36</td>
<td>38.3 (10.45)</td>
<td>47.5 (9.81)</td>
<td>&lt;.001(^1,^2)</td>
<td>.40</td>
</tr>
<tr>
<td>Anxious/Depressed</td>
<td>55.8 (6.53)</td>
<td>53.9 (7.52)</td>
<td>.120</td>
<td>-.14</td>
<td>56.4 (9.99)</td>
<td>52.0 (3.47)</td>
<td>.095(^2)</td>
<td>-.15</td>
</tr>
<tr>
<td>Withdrawn/Depressed</td>
<td>55.1 (5.58)</td>
<td>54.4 (7.00)</td>
<td>.301</td>
<td>-.09</td>
<td>57.3 (8.24)</td>
<td>53.5 (4.75)</td>
<td>.008(^2)</td>
<td>-.24</td>
</tr>
<tr>
<td>Somatic Complaints</td>
<td>54.8 (5.86)</td>
<td>53.6 (6.08)</td>
<td>.088</td>
<td>-.16</td>
<td>60.4 (9.99)</td>
<td>55.0 (5.56)</td>
<td>.005(^2)</td>
<td>-.25</td>
</tr>
<tr>
<td>Social Problems</td>
<td>55.9 (8.11)</td>
<td>52.7 (4.81)</td>
<td>.019(^2)</td>
<td>-.21</td>
<td>56.4 (8.45)</td>
<td>51.4 (3.36)</td>
<td>&lt;.001(^1,^2)</td>
<td>-.37</td>
</tr>
<tr>
<td>Thought Problems</td>
<td>54.1 (5.29)</td>
<td>53.3 (5.95)</td>
<td>.459</td>
<td>-.07</td>
<td>54.6 (7.03)</td>
<td>51.9 (4.03)</td>
<td>.094(^2)</td>
<td>-.15</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>55.1 (7.64)</td>
<td>52.3 (5.32)</td>
<td>.074(^2)</td>
<td>-.16</td>
<td>55.9 (6.22)</td>
<td>52.5 (4.40)</td>
<td>&lt;.001(^1,^2)</td>
<td>-.35</td>
</tr>
<tr>
<td>Rule-Breaking Behaviour</td>
<td>52.5 (3.29)</td>
<td>52.7 (4.57)</td>
<td>.321</td>
<td>-.09</td>
<td>52.0 (3.46)</td>
<td>51.4 (2.92)</td>
<td>.149</td>
<td>-.13</td>
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<tr>
<td>Aggressive Behaviour</td>
<td>52.7 (4.59)</td>
<td>51.5 (3.92)</td>
<td>.141</td>
<td>-.14</td>
<td>52.3 (4.64)</td>
<td>51.5 (3.92)</td>
<td>.432</td>
<td>-.07</td>
</tr>
<tr>
<td>Internalizing Problems</td>
<td>52.4 (9.46)</td>
<td>49.9 (9.76)</td>
<td>.066</td>
<td>-.17</td>
<td>55.2 (12.31)</td>
<td>48.0 (8.91)</td>
<td>.002(^1,^2)</td>
<td>-.28</td>
</tr>
<tr>
<td>Externalizing Problems</td>
<td>47.3 (8.43)</td>
<td>45.0 (8.90)</td>
<td>.088</td>
<td>-.16</td>
<td>45.0 (9.37)</td>
<td>42.5 (8.51)</td>
<td>.117</td>
<td>-.14</td>
</tr>
<tr>
<td>Total Problems</td>
<td>49.7 (9.67)</td>
<td>46.5 (9.36)</td>
<td>.079</td>
<td>-.16</td>
<td>50.9 (11.36)</td>
<td>43.5 (9.10)</td>
<td>&lt;.001(^1,^2)</td>
<td>-.32</td>
</tr>
</tbody>
</table>

### PedsQL scales (Likert-scores)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean (SD)</th>
<th>p-value</th>
<th>r</th>
<th>Mean (SD)</th>
<th>p-value</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>82.8 (19.95)</td>
<td>.023(^2)</td>
<td>.21</td>
<td>79.2 (22.17)</td>
<td>&lt;.001(^1,^2)</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>91.4 (10.07)</td>
<td></td>
<td></td>
<td>92.7 (11.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale</td>
<td>Group 1 Mean (SD)</td>
<td>Group 2 Mean (SD)</td>
<td>t-value</td>
<td>df</td>
<td>p-value</td>
<td>Cohen's d</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------</td>
<td>----</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>72.3 (19.68)</td>
<td>82.0 (16.49)</td>
<td>.005</td>
<td>1</td>
<td>.044</td>
<td>.18</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>81.3 (21.09)</td>
<td>93.0 (10.89)</td>
<td>.001</td>
<td>1</td>
<td>.001</td>
<td>.29</td>
</tr>
<tr>
<td>School Functioning</td>
<td>66.6 (20.81)</td>
<td>82.6 (15.98)</td>
<td>&lt;.001</td>
<td>1</td>
<td>&lt;.001</td>
<td>.39</td>
</tr>
<tr>
<td>Total score</td>
<td>75.7 (17.23)</td>
<td>87.2 (11.25)</td>
<td>&lt;.001</td>
<td>1</td>
<td>&lt;.001</td>
<td>.39</td>
</tr>
</tbody>
</table>

**PedsQL-MFS scales (Likert-scores)**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Group 1 Mean (SD)</th>
<th>Group 2 Mean (SD)</th>
<th>t-value</th>
<th>df</th>
<th>p-value</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Fatigue</td>
<td>71.2 (18.97)</td>
<td>81.7 (16.34)</td>
<td>.001</td>
<td>1</td>
<td>.10</td>
<td>-</td>
</tr>
<tr>
<td>Sleep/Rest Fatigue</td>
<td>65.1 (16.77)</td>
<td>67.8 (20.36)</td>
<td>.280</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cognitive Fatigue</td>
<td>62.6 (25.43)</td>
<td>80.9 (17.01)</td>
<td>&lt;.001</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total score</td>
<td>66.2 (17.07)</td>
<td>76.7 (14.78)</td>
<td>.001</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 indicate between group differences that survived corrections for multiple comparisons.
2 indicate between group differences that were significant after adjustment for age.
Associations between aspects of adaptive functioning and self- and parent-reported EF, social/emotional adjustment, and fatigue. The CBCL Total Competence scale was significantly associated with: the BRIEF subscales Shift ($r_s = -.52, p < .001$), Emotional Control ($r_s = -.41, p = .006$), Initiate ($r_s = -.59, p < .001$), Working Memory ($r_s = -.63, p < .001$), Plan/Organize ($r_s = -.59, p < .001$), and Monitor ($r_s = -.39, p = .008$), as well as the indices BRI ($r_s = -.49, p = .001$) and MI ($r_s = -.56, p < .001$), and the GEC ($r_s = -.57, p < .001$); the CBCL syndrome scales Withdrawn/Depressed ($r_s = -.50, p < .001$), Social Problems ($r_s = -.53, p < .001$), Thought Problems ($r_s = -.32, p = .003$), and Attention Problems ($r_s = -.61, p < .001$), as well as the CBCL composite scores Internalizing Problems ($r_s = -.45, p = .002$) and Total Problems ($r_s = -.56, p < .001$); and the PedsQL (parent-report version) subscales Physical Functioning ($r_s = .61, p < .001$), Social ($r_s = .58, p < .001$), and School Functioning ($r_s = .45, p = .002$), as well as the PedsQL Total ($r_s = .57, p < .001$). The associations between the CBCL Total Competence scale and the BRIEF subscales Emotional Control and Monitor did not survive corrections for multiple comparisons.

The YSR Total Competence scale was significantly associated with: the PedsQL (self-report version) subscales Physical ($r_s = .40, p = .006$) and Social Functioning ($r_s = .32, p = .034$), and the PedsQL Total ($r_s = .33, p = .026$); and the PedsQL-MFS subscales Sleep/Rest Fatigue ($r_s = .42, p = .005$) and Cognitive Fatigue ($r_s = .40, p = .007$), as well as the PedsQL-MFS Total ($r_s = .45, p = .002$). The associations between the YSR Total Competence scale and the PedsQL subscale Social Functioning and PedsQL Total did not survive corrections for multiple comparisons.

3.3. Performance-based measures of neurocognitive function
Data from performance-based measures of neurocognitive function (composite domain T-scores) are presented in Table 3. One-sample T-test showed no significant deviations from the
normative mean (T=50) on estimated IQ, but significantly below normative mean on measures of processing speed and two of three EF domains; shifting and inhibitory control. There was a larger percentage of PBT survivors than expected from the normal distribution performing clinically impaired, i.e., T-scores 1.5 standard deviation below the normative mean, in the cognitive domains processing speed, auditory attention span, verbal learning, verbal recall, and shifting.

Table 3 Performance-based measures of neurocognitive domains reported as T-scores; one sample t-test and percentage ≤ 1.5 standard deviation under the mean

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
<th>p</th>
<th>One sample t-test % &lt; 1.5 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated current IQ</td>
<td>48.3</td>
<td>10.26</td>
<td>- .828</td>
<td>.415</td>
<td>7.7</td>
</tr>
<tr>
<td>Processing speed</td>
<td>43.5</td>
<td>9.79</td>
<td>-3.373</td>
<td>.002</td>
<td>26.9</td>
</tr>
<tr>
<td>Auditory attention span</td>
<td>47.8</td>
<td>11.34</td>
<td>- .991</td>
<td>.331</td>
<td>19.2</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>49.0</td>
<td>7.08</td>
<td>- .693</td>
<td>.495</td>
<td>3.8</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>47.3</td>
<td>16.42</td>
<td>- .849</td>
<td>.404</td>
<td>19.2</td>
</tr>
<tr>
<td>Verbal recall</td>
<td>46.7</td>
<td>17.15</td>
<td>- .972</td>
<td>.340</td>
<td>34.6</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>48.6</td>
<td>11.15</td>
<td>- .645</td>
<td>.525</td>
<td>7.7</td>
</tr>
<tr>
<td>EF: shift</td>
<td>41.7</td>
<td>12.44</td>
<td>-3.417</td>
<td><strong>.002</strong></td>
<td>38.5</td>
</tr>
<tr>
<td>EF: updating</td>
<td>49.2</td>
<td>9.30</td>
<td>- .422</td>
<td>.677</td>
<td>3.8</td>
</tr>
<tr>
<td>EF: inhibition</td>
<td>46.1</td>
<td>8.75</td>
<td>-2.302</td>
<td><strong>.030</strong></td>
<td>7.7</td>
</tr>
</tbody>
</table>

Numbers in bold indicate p < .05. SD = standard deviation.

**Associations between performance-based measures and self- and parent-reports of neurocognitive functioning.** The strongest associations between performance-based measures and self- and parent-reports of neurocognitive functioning were for the cognitive domain verbal fluency, which correlated significantly with the CBCL Attention ($r_s = -.41$, $p = .046$); the YSR Attention ($r_s = -.54$, $p = .006$); the BRIEF subscales Initiate ($r_s = -.44$, $p = .031$), Working Memory ($r_s = -.43$, .037), Plan/Organize ($r_s = -.51$, $p = .011$), and the GEC ($r_s = -.45$, $p = .028$); and the MFS Cognitive Fatigue ($r_s = .49$, $p = .018$). The association between verbal fluency and the BRIEF MI was near significant ($r_s = -.40$, $p = .052$), as was the association
between the neurocognitive domain speed and the BRIEF Inhibit ($r_s = -.39, p=.057$). However, neither of these correlations survived corrections for multiple comparisons.

**Associations between aspects of adaptive functioning and performance-based measures of EF.** The CBCL Total Competence scale was significantly associated with the neurocognitive domain verbal fluency ($\rho=.46, p=.027$), and the YSR Total Competence scale was significantly associated with Auditory Attention Span ($\rho=.44, p=.035$), i.e., good performance on tests of verbal fluency and auditory attention span were associated with positive parent and self-reported adaptive functioning, respectively. However, these associations did not survive corrections for multiple comparisons.

### 3.4 Associations between demographic/medical variables and reports on EF, psychological symptoms, and fatigue

**Demographic variables.** There were no significant associations between age at time of survey and any of the questionnaire indices, composite scales or total scores. Male PBT survivors reported significantly more problems than female PBT survivors on the BRIEF MI index (female mean = 45.3, ± 13.94; male mean = 53.6, ± 12.53; $p=.031; r=.31$).

**Tumor-related variables.** There were no significant associations between age at diagnosis and location (i.e., supra- vs. infratentorial locations) and any of the questionnaire indices, composite scales or total scores. Tumor type subgroup differences on questionnaire indices, composite scales and total scores are presented in Table 4. Parents of survivors of ependymomas and choroid plexus tumors reported significantly less problems than parents of survivors of embryonal tumors on the BRIEF BRI (corrected $p=.017, r=-.59$), MI (corrected $p=.004, r=-.68$) and GEC (corrected $p=.006, r=-.66$) and the PedsQL Total (corrected $p=.015, r=.60$). Significantly less problems were reported by parents of survivors of ependymomas and choroid plexus tumors than parents of survivors of astrocytomas on the
BRIEF MI (corrected $p=.022$, $r=-.50$) and GEC (corrected $p=.047$, $r=-.45$). Survivors of ependymomas and choroid plexus tumors reported significantly less problems than survivors of embryonal tumors on the YSR Total Problems (corrected $p=.049$, $r=-.51$), the PedsQL Total (corrected $p<.001$, $r=.82$) and the MFS Total (corrected $p=.012$, $r=.61$). Survivors of ependymomas and choroid plexus tumors reported significantly less problems than survivors of astrocytomas on the YSR Externalizing Problems (corrected $p=.047$, $r=-.45$) and the PedsQL Total (corrected $p=.035$, $r=.47$).

**Treatment-related variables.** There were no significant associations between time since treatment completion and any of the questionnaire indices, composite scales, or total scores. Treatment type subgroup differences on questionnaire indices, composite scales and total scores are presented in Table 5. Parents of PBT survivors treated with surgery combined with CRT and chemotherapy reported significantly more problems than parents of PBT survivors treated with surgery only on the BRIEF MI (corrected $p=.035$, $r=-.41$) and GEC (corrected $p=.046$, $r=-.39$) and the PedsQL Total (corrected $p=.007$, $r=.49$). PBT survivors treated with surgery combined with CRT and chemotherapy reported significantly more problems on the PedsQL Total than PBT survivors treated with surgery only (corrected $p=.007$, $r=.49$).
Table 4. **Self- and parent reported executive functioning, psychological symptoms, and fatigue in ICCC-3 tumor type subgroups**

<table>
<thead>
<tr>
<th></th>
<th>Ependymomas and choroid plexus tumors (ECPT) (n=6)</th>
<th>Astrocytomas (A) (n=23)</th>
<th>Embryonal tumors (ET) (n=16)</th>
<th>Post hoc tests</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>BRIEF BRI</td>
<td>40.2</td>
<td>7.28</td>
<td>46.6</td>
<td>6.98</td>
<td>51.6</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BRIEF MI</td>
<td>38.0</td>
<td>2.37</td>
<td>49.6</td>
<td>9.56</td>
<td>53.3</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>38.3</td>
<td>4.37</td>
<td>48.1</td>
<td>8.01</td>
<td>52.1</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CBCL Internalizing Problems</td>
<td>46.5</td>
<td>13.68</td>
<td>57.0</td>
<td>13.51</td>
<td>57.4</td>
</tr>
<tr>
<td>CBCL Externalizing Problems</td>
<td>37.7</td>
<td>5.72</td>
<td>47.0</td>
<td>7.66</td>
<td>46.4</td>
</tr>
<tr>
<td>CBCL Total Problems</td>
<td>39.5</td>
<td>14.68</td>
<td>52.2</td>
<td>10.06</td>
<td>54.4</td>
</tr>
<tr>
<td>YSR Internalizing Problems</td>
<td>47.2</td>
<td>9.30</td>
<td>54.3</td>
<td>8.91</td>
<td>53.1</td>
</tr>
<tr>
<td>YSR Externalizing Problems</td>
<td>39.8</td>
<td>6.01</td>
<td>50.0</td>
<td>8.05</td>
<td>48.0</td>
</tr>
<tr>
<td>YSR Total Problems</td>
<td>41.0</td>
<td>6.29</td>
<td>51.7</td>
<td>9.54</td>
<td>51.7</td>
</tr>
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<tr>
<td>PedSQL Total - parent report</td>
<td>88.7</td>
<td>11.36</td>
<td>75.0</td>
<td>18.11</td>
<td>65.1</td>
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<tr>
<td>PedSQL Total - self-report</td>
<td>93.2</td>
<td>4.75</td>
<td>78.0</td>
<td>11.84</td>
<td>64.3</td>
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</tr>
</tbody>
</table>

Note: - indicates between subgroup differences that did not reach statistical significance, and for which p-values and effect size r therefore could not be obtained.

*indicates between subgroup differences that survived Bonferroni corrections for multiple comparisons.
Table 5 Self- and parent reported executive functioning, psychological symptoms, and fatigue in treatment type subgroups

<table>
<thead>
<tr>
<th></th>
<th>Surgery only (SO) (n=28)</th>
<th>Surgery and chemotherapy (SC) (n=9)</th>
<th>Surgery, CRT(^1) and chemotherapy (SCC) (n=10)</th>
<th>Post Hoc Tests</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>BRIEF BRI</td>
<td>44.0</td>
<td>6.83</td>
<td>49.2</td>
<td>8.42</td>
<td>52.1</td>
</tr>
<tr>
<td>BRIEF MI</td>
<td>44.3</td>
<td>12.44</td>
<td>53.8</td>
<td>12.23</td>
<td>57.7</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>43.1</td>
<td>11.19</td>
<td>52.3</td>
<td>10.48</td>
<td>56.1</td>
</tr>
<tr>
<td>CBCL Internalizing Problems</td>
<td>54.1</td>
<td>14.30</td>
<td>55.7</td>
<td>9.47</td>
<td>58.4</td>
</tr>
<tr>
<td>CBCL Externalizing Problems</td>
<td>45.0</td>
<td>8.29</td>
<td>45.1</td>
<td>11.08</td>
<td>44.8</td>
</tr>
<tr>
<td>CBCL Total Problems</td>
<td>49.2</td>
<td>12.11</td>
<td>52.2</td>
<td>11.30</td>
<td>54.5</td>
</tr>
<tr>
<td>YSR Internalizing Problems</td>
<td>51.9</td>
<td>9.94</td>
<td>53.9</td>
<td>6.31</td>
<td>52.0</td>
</tr>
<tr>
<td>YSR Externalizing Problems</td>
<td>48.0</td>
<td>8.44</td>
<td>47.8</td>
<td>9.56</td>
<td>45.2</td>
</tr>
<tr>
<td>YSR Total Problems</td>
<td>48.9</td>
<td>9.81</td>
<td>51.1</td>
<td>10.82</td>
<td>50.4</td>
</tr>
<tr>
<td>PEDSQL Total - parent report</td>
<td>78.9</td>
<td>17.70</td>
<td>74.2</td>
<td>17.78</td>
<td>58.7</td>
</tr>
<tr>
<td>PEDSQL Total - self-report</td>
<td>81.8</td>
<td>11.96</td>
<td>73.2</td>
<td>15.51</td>
<td>59.9</td>
</tr>
<tr>
<td>MFS Total</td>
<td>70.4</td>
<td>16.68</td>
<td>64.9</td>
<td>17.46</td>
<td>54.8</td>
</tr>
</tbody>
</table>

Note: - indicates those between subgroup differences that did not reach statistical significance, and for which p-values and effect size r therefore could not be obtained.
\(^1\)CRT=cranial radiation therapy
* indicates between subgroup differences that survived Bonferroni corrections for multiple comparisons.
3. Discussion

The present cross-sectional study of EF, psychological symptoms, behavioral problems and fatigue in adolescent PBT survivors has four main findings. First, we found significantly elevated rates of neurocognitive impairment, including executive dysfunction, both in PBT survivors’ parent-reports of EF compared to matched controls, as well as on performance-based tests of EF compared to normative data. Second, PBT survivors and their parents reported significantly more difficulties with aspects of adaptive functioning and QoL (i.e., social relationships, school functioning, academic performance, and participation in activities) than healthy controls and their parents, and these difficulties were most strongly related to parent-reported problems with executive dysfunction, internalizing symptoms of withdrawal/depression and thought problems, and physical functioning, as well as to self-reported problems with EF, physical functioning and sleep/need for rest. Also, corrected for multiple comparisons, there were no significant associations between self- or parent-reported aspects of adaptive functioning and QoL, and performance-based data. Third, we found that being male, having sustained an embryonal tumor or an astrocytoma, and having undergone surgery combined with CRT and chemotherapy, was significantly associated with higher rates of parent and self-reported problems on the various questionnaires.

The findings altogether show that, along with problems with physical functioning and fatigue, the largest differences between the adolescent PBT survivor group and the healthy control group were for parent and self-reported neurocognitive concerns and problems with academic and social functioning, as evidenced by the medium effect sizes. Neurocognitive weaknesses were also evident on performance-based tasks, showing significant deviations from the normative mean within the processing speed domain, and within two out of three EF domains; shift and inhibitory control. These findings confirm the presence of neurocognitive dysfunction, including difficulties with “cool”, or cognitive, aspects of EF, in this group of
adolescent PBT survivors. Furthermore, between-group differences on parent-reports of working memory were significant, i.e., a “cool” EF aspect, having a near to medium ES.

Although parents of PBT survivors reported significantly more EF difficulties than parents of healthy controls, the PBT survivor mean scores are well within the normal range by clinical standards, i.e., within one standard deviation from the normative mean. However, several studies have shown that mean scores in healthy Norwegian and non-U.S. samples on both the BRIEF and BRIEF- Adult Version (BRIEF-A; Roth et al., 2005) are significantly below the U.S. normative mean of T = 50 (Grane, Endestad, Pinto, & Solbakk, 2014; Hovik et al., 2017; Løvstad et al., 2012; Løvstad et al., 2016; Sølsnes, Skranes, Brubakk, & Løhaugen, 2014). The appropriateness of using the U.S. norms in a Norwegian setting is therefore questioned. Furthermore, a tendency of low levels of parental endorsement of problems of EF in survivors of PBT has been demonstrated in previous studies, even in the presence of performance-based findings of executive dysfunction (Krivitzky, Walsh, Fisher, & Berl, 2016; Wochos, Semerjian, & Walsh, 2014). Interestingly, teacher reports have been found to be more in line with performance-based findings (Wochos et al., 2014). Low levels of parental endorsement of EF difficulties may be explained by a possible rater bias in parents, such as psychological defense mechanisms and adjusting to the needs/challenges of their medically fragile child, and/or differences across home and school settings in EF demands. Similar to the parent-reports of EF, mean scores for parent-reported psychological and emotional problems on a culturally acceptable questionnaire (Ivanova et al., 2007; Nøvik, 1999) were well within the normal range, indicating that, as a group, PBT survivors are psychologically relatively well-functioning, with the exception of difficulties within the EF domain.

No significant correlations between performance-based results and results on questionnaires survived correction for multiple comparisons, and although parents of PBT
survivors reported significantly more problems with working memory, significant deviations in this EF domain were not found in the performance-based data. The discrepancy between the findings from these two methodological approaches is in line with previous studies, and confirms the notion that they most likely tap separate, but associated, constructs within the EF domain, and that functioning varies in different settings that place different or higher demands on cognitive functioning (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; de Vries et al., 2017; McCurdy et al., 2016). For this reason, the two approaches simply cannot replace one another without potentially losing valuable information.

In addition to confirming previous studies noting neurocognitive impairment in PBT survivors, the findings from this study expand on current knowledge by investigating neurocognitive impairment in PBT survivors in their adolescence specifically. For this age group, there are relatively few studies, despite this critical period for adult adjustment and outcomes. Furthermore, the findings expand on the knowledge as to the nuances within the neurocognitive profile, by showing that adolescent PBT survivors seemingly struggle more with the “cool”/cognitive aspects of EF relative to the “hot”/behavioral aspects. This finding lends support to studies showing that although PBT survivors, survivors of acute lymphoblastic leukemia, other pABI populations (i.e., traumatic brain injury, arterial ischemic stroke), and congenital brain disorder populations (i.e., ADHD, autism spectrum disorder) may have executive dysfunction in common, there seems to exist a distinctive cognitive/executive profile in PBT survivors different from that of the other populations (Anderson et al., 2002; Araujo et al., 2017; Krivitzky et al., 2016; Puhr et al., 2019a; Winter et al., 2014).

Contrary to earlier findings from studies of survivors of childhood cancers noting an increased risk of psychological problems in PBT survivors compared to other CCS populations and the general population, the findings in this study showed few significantly
elevated parent-reported symptoms of psychological distress in PBT survivors, compared to parents of healthy peers. Group differences were mainly evident for parent-reported internalizing problems, i.e., symptoms of withdrawal, depression and somatization, a finding which is in line with findings from other studies showing that, compared to other pABI and adolescent CCS populations, PBT survivors may exhibit more internalizing than externalizing problems (Brinkman, Li, et al., 2016; Poggi et al., 2005), a distinction that may further be comparable to the findings from this and previous studies indicating more problems with cognitive than behavioral aspects of EF. However, the group differences for parent-reported internalizing problems yielded small ESs, and PBT survivors’ and healthy controls’ own reports did not differ significantly on measures of psychological distress, other than for a single subscale screening emotional symptoms. These findings suggest that in terms of psychological adjustment, PBT survivors do not differ notably from their healthy peers. Also, contrary to findings in pediatric populations (Jurbergs et al., 2008; Lund et al., 2011), there were no significant discrepancies between parent and self-reports of psychological distress, physical functioning or aspects of adaptive functioning and QoL within the PBT survivor group other than PBT survivor parents reporting more symptoms of somatization than the PBT survivors themselves. Thus, in light of this, parents and their adolescents in the PBT survivor group seemed to be in agreement in this study. However, on the whole, the number of group differences on parent-reports exceed the number of group differences found between PBT survivors’ and the healthy controls’ self-reports. Altogether, these findings seem somewhat conflicting as to whether or not parent and self-reports are in alignment, and can therefore neither lend support to studies showing more parent-reported mental health problems and lower QoL compared to child-reported, nor to studies showing the opposite.

The largest group differences in this study were for problems with aspects of adaptive functioning and QoL, i.e., problems with academic achievement and social functioning, with
PBT survivors and their parents reporting significantly more difficulties than healthy controls and their parents. This finding confirms conclusions from previous studies in pediatric and adult populations, demonstrating that PBT survivors are at heightened risk of experiencing social difficulties (e.g., poor peer acceptance, isolation, and diminished leadership roles), lower academic/educational achievement, and poor socioeconomic attainment (e.g., being engaged in regular employment or training and being financially independent), both in comparison to other CCS populations, and to the general population (Boman, Lindblad, & Hjern, 2010; Brinkman, Krasin, et al., 2016; Brinkman, Ness, et al., 2018; Brinkman, Recklitis, et al., 2018; de Boer, Verbeek, & van Dijk, 2006; Frederiksen et al., 2019; Ghaderi et al., 2016; Ghaderi et al., 2013; Mader, Michel, & Roser, 2017; Ness et al., 2008).

Not surprisingly, parent and self-reported problems of physical functioning and self-reported symptoms of fatigue were strongly related to problems with aspects of adaptive functioning and QoL, and is in accordance with previous studies (Boonstra et al., 2017; Brand et al., 2016; Ness et al., 2005). Fatigue is one of the most distressing and debilitating late effects after childhood cancer, hampering the individual’s possibilities of participating in social and educational settings, even in the absence of other impairments. However, as hypothesized, neurocognitive complaints, including executive dysfunction, exhibited the strongest correlations to problems with adaptive functioning, demonstrating the particular importance of these functions with respect to participating in society. More specifically, problems with attention, working memory, mental shifting, and initiation were reported to stand in the way of successful academic functioning and social participation. Certain psychological symptoms were also significantly related to problems with adaptive functioning, but to a lesser degree, as demonstrated by smaller ESs. Several studies have established a link between impairments in EF and adaptive functioning (Evans, 2008; Ness et al., 2008; Wolfe, Vannatta, Nelin, & Yeates, 2015; Wolfe et al., 2013). For example, a recent
study demonstrates how impairments in EF, although subtle, may play an especially significant role in the development of these negative long-term outcomes compared to other personal factors (Puhr et al., 2019b). The findings from this study are important, as they indicate that the same pattern is present also at an earlier time point, i.e., in adolescence, although future outcomes in our survivors remain to be seen.

There are several ways in which executive dysfunction may hamper scholastic and social functioning in adolescence, potentially translating/accumulating in a long-term perspective into difficulties transitioning successfully into adulthood and participating in society. In order to succeed in academic/educational settings, intact EF is paramount (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009; Duckworth & Seligman, 2005; Jacobson, Williford, & Pianta, 2011; Poon, 2018; Treble-Barna et al., 2017). For example, children with impaired working memory have difficulties retaining crucial information long enough to perform adequate mental operations or store the information, leading to insufficient learning. Poor organizational skills, impaired cognitive flexibility, difficulties initiating new tasks and deploying effective strategies for reading/studying, interfere with academic/educational efficiency.

The link between intact EF and the development of social competence and interpersonal skills has for some time been noted in the child neuropsychology literature (Beauchamp & Anderson, 2010), with findings demonstrating an association between executive dysfunction and impaired social functioning across different pediatric brain injury populations, including PBT survivors (Muscara, Catroppa, & Anderson, 2008; Sirois et al., 2017; Willard, Allen, Hardy, & Bonner, 2015; Wolfe et al., 2013). For example, again considering working memory, impairments in this area have been associated with social difficulties, such as peer rejection, poor overall social competence, and impaired conflict
resolution skills in normally developing children (McQuade, Murray-Close, Shoulberg, & Hoza, 2013).

Altogether, executive dysfunction in PBT survivors may play a pivotal role for long-term outcomes. Further, in a developmental perspective, although neurocognitive impairments may initially be discreet upon treatment completion, a tendency to “grow into deficit” has been noted in pABI populations (Anderson, Northam, & Wrennall, 2019). Subtle EF impairments present immediately after injury to brain networks may be followed by a delayed onset and increase of impairments, as difficulty levels and cognitive demands increase with time (Anderson, Jacobs, & Harvey, 2008; de Vries et al., 2017). Combined with symptoms of fatigue, which also may a negative impact on neurocognitive functioning (Clanton et al., 2011), the challenges are compounded further. Continued experiences of social and academic failure, may well discourage an adolescent from pursuing educational and vocational goals.

As expected from previous findings in the PBT literature, certain tumor- and treatment-related risk factors were identified in this study; having sustained an embryonal tumor or an astrocytoma, and having undergone with surgery combined with CRT and chemotherapy, was significantly associated with overall higher rates of parent and self-reported problems on most questionnaires, with the exception of psychological problems, for which there were few significant associations. Although these findings should be viewed as explorative due to the small number of cases in some of the subgroups, they are nonetheless in line with previous studies showing a considerably increased risk of negative outcomes after complex treatment regimens (i.e., including CRT and/or chemotherapy, in addition to surgery) (Bell et al., 2018; Brinkman, Recklitis, et al., 2018; Turner et al., 2009).

This study has several important limitations that need to be addressed, including a cross-sectional design and the small number of participants in the PBT survivor group for subgroup analyses of tumor- and treatment-related factors. Data on coping styles, family
factors (e.g., parental responsiveness, health and socioeconomic status, impact of serious
disease on family interactions), and social support were not collected, although these are all
factors that may have contributed to the observed differences (Kupst & Patenaude, 2016;
Ryan et al., 2016; Van Schoors et al., 2017). However, the response rate was relatively high
(53.3%) compared to previous studies in the child brain injury and CCS literature, ensuring an
adequate level of representativeness of this particular PBT population, and increasing
possibilities of generalization of the findings.

Despite study limitations, the findings provide important insights into the difficulties
experienced by adolescent PBT survivors, for which there traditionally has been limited
knowledge. The findings have clinical implications, as they demonstrate the importance of
assessing neurocognitive impairment in the critical phase that adolescence and young
adulthood presents. Fortunately, EF are relatively malleable (Zelazo & Carlson, 2012), all the
more implicating the importance of improving efficient interventions aimed at preventing
further impairments and improving EF skills. Short- and long-term assessments and tailored
interventions are as such essential in order to optimize PBT survivors’ chances of succeeding
in the transition to adulthood and participating in society, and to improve social equity in
survivors in a lifetime perspective.

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