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ARTICLE

Executive Function and Psychosocial Adjustment in Adolescent Survivors of Pediatric Brain Tumor

A. Puhr[a], E. Ruud[b], V. Anderson[c], B.J. Due-Tønnessen[d], A.B. Skarbø[e], A. Finset[f], and S. Andersson[g]

[a]Dept. of Pediatric Medicine, Oslo University Hospital & Dept. Of Psychology, University of Oslo, Norway; [b]Dept. of Pediatric Medicine, Oslo University Hospital & Faculty of Medicine, University of Oslo, Norway; [c]Royal Children's Hospital, Melbourne & Depts of Psychology & Paediatrics, University of Melbourne, Melbourne Australia; [d]Dept. of Neurosurgery, Oslo University Hospital, Oslo, Norway; [e]Dept. of Pediatric Neurology, Oslo University Hospital, Oslo, Norway; [f]Faculty of Medicine, University of Oslo, Oslo Norway,; [g]Dept. of Psychology, University of Oslo, Oslo, Norway

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 (EFs), 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 this was most strongly associated to executive dysfunction, compared to psychological symptoms and fatigue. The findings have important implications for long-term follow-ups.

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Introduction

Adolescence is a critical period for the development of executive functions (EFs), 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 to 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 et al., 2016; Brinkman, Recklitis, Michel, Grootenhuis, & Klosky, 2018; Clanton et al., 2011; Husson 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 the 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, &

CONTACT A. Puhr anipuh@ous-hf.no Oslo University Hospital, Seksjon for nevrohabilitering - barn, Barneklinikken, Rikshospitalet, Postboks 4950 Nydalen 0424 Oslo

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, 2000; Rønning, Sundet, Due-Tønnessen, Lundar, & Helseth, 2005). 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 EFs, 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 have 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 now generally acknowledged that the umbrella term 'EF' refers to both cognitive functions and behavioral and social/affective skills. This distinction is often referred to as the "cool" and "hot" EFs. "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" EFs 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" EFs 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 is 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).

Because EF problems are linked to negative long-term outcomes, there is a need to address and assess EFs in the clinic. In light of the diversity of EF skills, different methodological approaches to the clinical assessment of EFs should be employed. While performance-based neuropsychological tests are generally considered as methodologically suitable measures for assessing the "cool" aspects of EFs (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- and informant-report are therefore recommended, also in order 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 is 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) were 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 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 was 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 neuropsychological test data to matched controls and normative data, respectively. However, in order to draw conclusions about the specificity of executive dysfunction on neuropsychological tests, there was also a need to include neuropsychological test measures beyond the EF domain, such as processing speed, IQ, and attention, which are all domains closely interrelated to EF. 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 neuropsychological tests. Also, we explored possible associations between neuropsychological test 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 adaptive functioning is associated to executive dysfunction, 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 data from neuropsychological tests of EF in the PBT subgroup. The third aim was to investigate how self- and parent-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.

Methods

Study Participants

Survivors of PBT fulfilling inclusion criteria, defined as treatment for PBT at ≤16 years, aged 13–17 at the time of recruitment and having completed treatment ≥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- 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 the eligible PBT survivors and their parents/caregivers completed the self- and parent-report forms, respectively. Mean age at the time of survey was 15.7 (SD = 1.37), and 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 neuropsychological retesting. Of 36 invited, 26 (72.2%) underwent retesting. For this subgroup, 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 neuropsychological 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 neuropsychological 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, cranial radiation therapy (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 (i.e., 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- and parent-report forms identical to those of the patient group. Of the 300 controls

Table 1. Clinical characteristics.

	N survey group (*n*= 48)	%	N retested subgroup (*n*= 26)	%
Tumor diagnosis				
Ependymomas and choroid plexus tumors	6	12.5	4	15.4
Astrocytomas	23	47.9	13	50.0
Embryonal tumors	16	33.3	6	23.1
Other gliomas	1	2.1	-	-
Other CNS-tumors	2	4.2	3	11.5
Tumor location				
Supratentorial	14	29.2	7	26.9
Infratentorial	32	66.7	18	69.2
Both	2	4.2	1	3.8
Treatment				
Surgery only	28	58.3	17	65.4
Surgery and chemotherapy	9	18.8	5	19.2
Surgery and CRT[a]	1	2.1	-	-
Surgery, chemotherapy and CRT[a]	10	20.8	4	15.4
Number of surgeries				
One surgery	40	83.3	20	76.9
Two or more surgeries	8	16.7	6	23.1
Postoperative hydrocephalus treatment[b]				
Yes	7	14.6	3	11.5
No	41	85.4	23	88.5
Postoperative seizures				
Yes	6	12.5	3	11.5
No	42	87.5	23	88.5
Hormone replacement treatment[c]				
Yes	12	25.0	6	23.1
No	36	75.0	20	76.9
Psychiatric comorbidity				
Yes	8	15.7	3	11.5
No	43	84.3	23	88.5

[a]CRT = cranial radiation therapy [b] Ventriculoatrial shunt (VA), ventriculperitoneal shunt (VP) or third ventriculostomy (3CVS), [c] Hormone replacement treatment, e.g., growth hormone, cortisol, thyroid stimulating hormone, testosterone and estrogen, and antidiuretic hormone.

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 ($p < .001$). The groups were matched for sex: 55.1% of the survivors and 50.7% of the controls were female (p= .632).

Long-Term Outcome Measures

Self- and Parent-Reports of Cognitive Symptoms, 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 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 Attention Problems subscale 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 the CBCL had high internal consistency for both the survivor and the control group; Cronbach's alpha of = .92 and .94, and .91 and .87, respectively.

PedsQL. The self- and parent-report version of the Pediatric Quality of Life Inventory 4.0 (PedsQL; Varni, Seid, & Kurtin, 2001) measures 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 reflect more problems. Four subscales are generated: Physical, Emotional, Social, and School Functioning, as well as a total score; PedsQL Total. In this study, to define the clinical cutoff for scores on the PedsQL, we use a score of 1 standard deviation (SD) below the control group mean, as recommended by Varni, Burwinkle, Seid, and Skarr (2003). Internal consistency was high; Cronbach's alpha of = .89 and = .75 for the PedsQL parent-report version for the survivor group and the 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 an 18-item questionnaire measuring self-reported problems with fatigue during the last month. The items are scored as with 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 Cognitive Fatigue

subscale may be considered a measure of subjective cognitive complaints rather than a measure of fatigue, as it is comprised of items reflecting everyday cognition. To the best of our knowledge, there are currently no recommended clinical cutoff scores for the PedsQL-MFS. As with the PedsQL, we use a score of 1 SD below the control group mean as the clinical cutoff. The PedsQL-MFS showed high levels of internal consistency; Cronbach's alpha of = .88 for both the survivor and control group.

Neuropsychological Tests

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 EF), by converting all raw scores to T-scores and calculating an average T-score within each domain. A score of 1.5 SD or more below the normative mean was defined as a clinical cutoff.

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

Processing Speed. The Trail Making Test condition 2 (number sequencing) and 3 (letter sequencing), and Color-Word Interference Test condition 1 (color naming) and 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 (total raw score) 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. The Hit Reaction Time Block Change measure (HRT BC) from the Conners' Continuous Performance Test – 3rd Edition (CPT 3; Conners, 2013) was used as a 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 Verbal Fluency condition 1 (letter fluency) and 2 (category 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. The Trail Making Test condition 4 (number-letter switching) and the Color-Word Interference Test condition 4 (inhibition/switching) from the D-KEFS battery were used to assess mental flexibility. The Digit Span Backward (WAIS–IV, WISC – IV) was used to assess working memory. The commissions score from the CPT 3 and the Color-Word Interference Test condition 3 (inhibition) from the D-KEFS battery were used to assess inhibitory control.

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 data from symptom checklists because of non-normally distributed variables. Data from neuropsychological tests were normally distributed, and parametric analyses were performed. Bonferroni corrections for multiple comparisons were employed (i.e., by dividing α by the number of comparisons [Field, 2009, pp. 372–373]). When reporting results, the results surviving Bonferroni corrections will be defined as significant. 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 parent-report differences on the CBCL/YSR and PedsQL. Effect sizes (ESs) for non-parametric statistics are reported as *r*, defining small ESs as *r*= .1 – .3; medium ESs as *r*= .3–.5;

large ESs as $r > .5$ (Field, 2009, p. 57). For neuropsychological test data, ESs are reported as Cohen's d, defining small ESs as $d = .2 - .5$; medium ESs as $d = .5–.8$; large ESs as $d > .8$ (Cohen, 1988). Associations between the YSR/CBCL Total Competence scale and other questionnaire subscales, and between neuropsychological test scores and questionnaire subscales reflecting cognitive symptoms 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. Associations between data from symptom checklists (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 (univariate 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 analyses on associations between tumor types and data from symptom checklists.

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.

Results

Self- and Parent-Reported Cognitive Symptoms, Social/Emotional Adjustment, QoL and Fatigue

Cognitive Symptoms

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. However, all scores in the PBT survivor group were within the normal range (i.e., ±1.5 SD). Following correction for multiple comparisons, only the Working Memory subscale remained significant (new $\alpha = .005$). Parents of PBT survivors reported significantly more problems than parents of controls on the CBCL Attention Problems, and this remained significant after corrections for multiple comparisons (new $\alpha = .004$). On the PedsQL-MFS Cognitive Fatigue, PBT survivors reported significantly more problems than the controls, and this remained significant after corrections for multiple comparisons (new $\alpha = .013$). On the BRIEF, between-group differences on the Working Memory subscale approached medium ES, otherwise all BRIEF subscales showed ESs in the low range. For the between-group differences on the CBCL Attention Problems and the PedsQL-MFS Cognitive Fatigue, there were medium ESs.

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 Social Problems subscale, as well as for the composite scales Internalizing Problems and Total Problems, which all remained significant after corrections for multiple comparisons (new $\alpha = .004$). On the CBCL, between-group differences on the Internalizing Problems composite scale approached medium ES, whereas the between-group differences on the Social Problems subscale and the Total Problems composite scale had medium ESs. However, all scores on the CBCL syndrome scales and composite scales in the PBT survivor group were within the normal range. There were no significant between-group differences on the YSR that survived corrections for multiple comparisons (new $\alpha = .004$).

Table 2. Self- and parent-reported executive functioning, psychological symptoms, and fatigue at ≥2 years after PBT-treatment completion compared to healthy controls.

	PBT survivors (*n*= 48)	Controls (*n*= 73)	Mann-Whitney test	Effect size	Parents of PBT survivors	Parents of controls	Mann-Whitney test	Effect size
	Mean (SD)	Mean (SD)	*p*	*r*	Mean (SD)	Mean (SD)	*p*	*r*
BRIEF scales (*T*-scores)								
Inhibit	-	-	-	-	45.6 (8.01)	45.6 (7.51)	.726	.03
Shift	-	-	-	-	48.2 (11.01)	43.4 (6.99)	.017[2]	−.22
Emotional Control	-	-	-	-	48.3 (9.56)	43.9 (8.23)	.012[2]	−.23
Initiate	-	-	-	-	49.1 (13.44)	45.6 (8.91)	.049	−.18
Working Memory	-	-	-	-	54.1 (14.06)	47.0 (9.34)	.004[1,2]	−.26
Plan/Organize	-	-	-	-	51.2 (11.61)	46.3 (9.22)	.012[2]	−.23
Organization of Materials	-	-	-	-	44.6 (10.95)	44.9 (10.73)	.798	.02
Monitor	-	-	-	-	47.9 (10.49)	44.2 (9.18)	.035[2]	−.19
BRI	-	-	-	-	47.0 (9.19)	43.5 (7.52)	.045[2]	−.18
MI	-	-	-	-	49.1 (13.81)	45.2 (9.59)	.026	−.20
GEC	-	-	-	-	47.9 (12.98)	44.2 (9.07)	.017	−.22
YSR, CBCL subscales (*T*-scores)								
Total Competence	38.5 (11.09)	47.1 (10.97)	<.001[1,2]	.36	38.3 (10.45)	47.5 (9.81)	<.001[1,2]	.40
Anxious/Depressed	55.8 (6.53)	53.9 (7.52)	.120	−.14	56.4 (9.99)	52.0 (3.47)	.095[2]	−.15
Withdrawn/Depressed	55.1 (5.58)	54.4 (7.00)	.301	−.09	57.3 (8.24)	53.5 (4.75)	.008[2]	−.24
Somatic Complaints	54.8 (5.86)	53.6 (6.08)	.088	−.16	60.4 (9.99)	55.0 (5.56)	.005[2]	−.25
Social Problems	55.9 (8.11)	52.7 (4.81)	.019[2]	−.21	56.4 (8.45)	51.4 (3.36)	<.001[1,2]	−.37
Thought Problems	54.1 (5.29)	53.3 (5.95)	.459	−.07	54.6 (7.03)	51.9 (4.03)	.094[2]	−.15
Attention Problems	55.1 (7.64)	52.3 (5.32)	.074[2]	−.16	55.9 (6.22)	52.5 (4.40)	<.001[1,2]	−.35
Rule-Breaking Behavior	52.5 (3.29)	52.7 (4.57)	.321	−.09	52.0 (3.46)	51.4 (2.92)	.149	−.13
Aggressive Behavior	52.7 (4.59)	51.5 (3.92)	.141	−.14	52.3 (4.64)	51.5 (3.92)	.432	−.07
Internalizing Problems	52.4 (9.46)	49.9 (9.76)	.066	−.17	55.2 (12.31)	48.0 (8.91)	.002[1,2]	−.28
Externalizing Problems	47.3 (8.43)	45.0 (8.90)	.088	−.16	45.0 (9.37)	42.5 (8.51)	.117	−.14
Total Problems	49.7 (9.67)	46.5 (9.36)	.079	−.16	50.9 (11.36)	43.5 (9.10)	<.001[1,2]	−.32
PedsQL scales (Likert-scores)								
Physical Functioning	82.8 (19.95)	91.4 (10.07)	.023[2]	.21	79.2 (22.17)	92.7 (11.06)	<.001[1,2]	.34
Emotional Functioning	72.3 (19.68)	82.0 (16.49)	.005[1,2]	.25	74.2 (21.91)	82.9 (14.18)	.044[2]	.18
Social Functioning	81.3 (21.09)	93.0 (10.89)	.001[1,2]	.30	76.4 (24.30)	91.7 (11.58)	.001[1,2]	.29
School Functioning	66.6 (20.81)	82.6 (15.98)	<.001[1,2]	.40	65.6 (22.40)	82.9 (15.52)	<.001[1,2]	.39
Total score	75.7 (17.23)	87.2 (11.25)	<.001[1,2]	.39	73.8 (18.35)	87.6 (8.83)	<.001[1,2]	.39
PedsQL-MFS scales (Likert-scores)								
General Fatigue	71.2 (18.97)	81.7 (16.34)	.001[1,2]	.30	-	-	-	-
Sleep/Rest Fatigue	65.1 (16.77)	67.8 (20.36)	.280	.10	-	-	-	-
Cognitive Fatigue	62.6 (25.43)	80.9 (17.01)	<.001[1,2]	.36	-	-	-	-
Total score	66.2 (17.07)	76.7 (14.78)	.001[1,2]	.31	-	-	-	-

[1]indicate between-group differences that remained significant after Bonferroni corrections for multiple comparisons.
[2]indicate between-group differences that were significant after adjustment for age.

QoL

On the PedsQL, the PBT survivors and their parents generally reported significantly more problems. The differences that remained significant after corrections for multiple comparisons (new α = .010) included the self-report subscales Emotional Functioning, Social Functioning, School Functioning, the Total score, as well as the parent-report subscales Physical Functioning, Social Functioning, School Functioning, and the Total score (Table 2). For these subscales, with the exception of the self-report subscale Emotional Functioning, scores in the PBT survivor group were equal to or below the clinical cutoff of 1 SD below the control group mean, and between-group differences had medium ESs.

Fatigue

PBT survivors reported significantly more problems than the controls on the PedsQL-MFS subscales General Fatigue and the Total score, with medium ESs, and this remained significant after corrections for multiple comparisons (new α = .013). However, scores on the PedsQL-MFS subscales General Fatigue and the Total score were within the normal range.

Self- and Parent-Report Discrepancies in the PBT Survivor Group

Parents of PBT survivors reported significantly more problems on the CBCL Somatic Complaints subscale (self-report mean = 54.8, ± 5.86; parent-report mean = 60.4, ± 9.99; p< .001, r= .63), and this remained significant after corrections for multiple comparisons (new α = .004). No significant discrepancies between parent- and self-reports were found for the PedsQL in the PBT survivor group.

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 medium ESs and scores approaching 1.5 SD below the normative mean, and these differences remained significant after corrections for multiple comparisons (new α = .004).

Associations Between Aspects of Adaptive Functioning and Self- and Parent-Reported EF, Social/Emotional Adjustment, QoL, and Fatigue in the PBT Survivor Group

Following correction for multiple comparisons defining new α-levels, the CBCL Total Competence scale was significantly associated with: the BRIEF subscales Shift (r_s = −.52, p < .001), Initiate (r_s = −.59, p < .001), Working Memory (r_s = −.63, p < .001), and Plan/Organize (r_s = −.59, p < .001), 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). Further, there were significant associations between the CBCL Total Competence scale and the CBCL syndrome scales Withdrawn/Depressed (r_s −.50, p < .001), Social Problems (r_s = −.53, p < .001), Thought

Table 3. Neuropsychological test scores for a subsample of the PBT survivors.

	Mean	SD	Range	ES* *d*	% < 1.5 SD
Estimated current IQ	48.3	10.26	30.0–71.0	.17	7.7
Processing speed	43.5	9.79	25.8–65.0	.66	26.9
Auditory attention span	47.8	11.34	23.5–76.7	.21	19.2
Sustained attention	49.0	7.08	35.0–64.0	.12	3.8
Verbal learning	47.3	16.42	20.0–74.7	.20	19.2
Verbal recall	46.7	17.15	20.0–70.7	.24	34.6
Verbal fluency	48.6	11.15	28.3–80.0	.13	7.7
EF: shift	41.7	12.44	20.0–65.0	.74	38.5
EF: updating	49.2	9.30	30.0–73.3	.08	3.8
EF: inhibition	46.1	8.75	31.0–66.5	.42	7.7

Numbers in bold indicate p < .05. SD = standard deviation.
* Effect size (ES): Cohen's *d* calculated with reference to the normative mean (T = 50, SD = 10)

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). Lastly, there were significant associations between the CBCL Total Competence scale 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 YSR Total Competence scale was significantly associated with: the PedsQL (self-report version) subscales Physical (r_s = .40, p= .006) 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).

Neuropsychological Test Measures of Neurocognitive Function

Data from neuropsychological test measures of neurocognitive function (composite domain T-scores) are presented in Table 3. All mean domain T-scores were within the normal range. However, there was a larger percentage of PBT survivors than expected from the normal distribution performing in the clinically impaired range (i.e., T-scores 1.5 SD below the normative mean), in the cognitive domains processing speed, auditory attention span, verbal learning, verbal recall, and shifting.

Associations Between Neuropsychological Test Data and Self- and Parent-Reports of Cognitive Symptoms

The strongest associations between neuropsychological test measures and self- and parent-reports of cognitive symptoms were for the cognitive domain verbal fluency, which correlated significantly with the CBCL Attention Problems (r_s = –.41, p = .046); the YSR Attention Problems (r_s = –.54, p = .006); the BRIEF subscales Initiate (r_s = –.44, p = .031), Working Memory (r_s = –.43, p = .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

Table 4. Self- and parent-reported executive functioning, psychological symptoms, and fatigue in ICCC-3 tumor type subgroups.

	Ependymomas and choroid plexus tumors (ECPT) (n= 6)		Astrocytomas (A) (n= 23)		Embryonal tumors (ET) (n= 16)		Post hoc tests	Effect size
	Mean	SD	Mean	SD	Mean	SD	p	r
BRIEF BRI	40.2	7.28	46.6	6.98	51.6	11.15	ECPT < ET; p= .006*	–.59
							ECPT < A; p= .042	-.38
BRIEF MI	38.0	2.37	49.6	9.56	53.3	19.64	ECPT < ET; p= .001*	–.68
							ECPT < A; p= .007*	-.50
BRIEF GEC	38.3	4.37	48.1	8.01	52.1	19.06	ECPT < ET; p= .002*	–.66
							ECPT < A; p= .016*	-.45
CBCL Internalizing Problems	46.5	13.68	57.0	13.51	57.4	9.59	-	-
CBCL Externalizing Problems	37.7	5.72	47.0	7.66	46.4	11.50	-	-
CBCL Total Problems	39.5	14.68	52.2	10.06	54.4	10.27	-	-
YSR Internalizing Problems	47.2	9.30	54.3	8.91	53.1	9.34	-	-
YSR Externalizing Problems	39.8	6.01	50.0	8.05	48.0	7.83	ECPT < ET; p= .040	–.44
							ECPT < A; p= .008*	-.49
YSR Total Problems	41.0	6.29	51.7	9.54	51.7	8.24	ECPT < ET; p= .016*	–.51
							ECPT < A; p= .016*	-.45
PedsQL Total – parent report	88.7	11.36	75.0	18.11	65.1	17.67	ECPT > ET; p= .005*	.60
PedsQL Total – self-report	93.2	4.75	78.0	11.84	64.3	20.69	ECPT > ET; p< .001*	.82
							ECPT > A; p= .012*	.47
							A > ET, p= .037	.33
MFS Total	83.6	11.93	66.4	15.53	58.4	16.81	ECPT > ET; p= .004*	.61
							ECPT > A; p= .040	.38

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 remained significant after Bonferroni corrections for multiple comparisons.

= .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 remained significant after corrections for multiple comparisons, defining new α-levels (.004-.013).

Associations Between Aspects of Adaptive Functioning and Neuropsychological Test Measures of EF

The CBCL Total Competence scale was significantly associated with the neurocognitive domain verbal fluency (ρ = .46, p = .027), and the YSR Total Competence scale was significantly associated with auditory attention span (ρ = .44, p = .035) (i.e., good performance on tests of verbal fluency and auditory attention span was associated with positive parent and self-reported adaptive functioning, respectively). However, these associations did not remain significant after corrections for multiple comparisons (new α = .005).

Associations Between Demographic/Medical Variables and Reports on Cognitive Symptoms, Psychological Symptoms, QoL, and Fatigue

Demographic Variables

There were no significant associations between age at time of survey and any of the symptom checklist 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 symptom checklist indices, composite scales or total scores. Tumor type subgroup differences on symptom checklist 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, MI, and GEC and the PedsQL Total, and significantly less problems than parents of survivors of astrocytomas on the BRIEF MI and GEC. Survivors of ependymomas and choroid plexus tumors reported significantly less problems than survivors of embryonal tumors on the YSR Total Problems, the PedsQL Total and the MFS Total, and significantly less problems than survivors of astrocytomas on the YSR Externalizing Problems and the PedsQL Total.

Treatment-Related Variables

There were no significant associations between time since treatment completion and any of the symptom checklist indices, composite scales, or total scores. Treatment type subgroup differences on symptom checklist 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 and GEC and the PedsQL Total. 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.

Discussion

The findings from this study expand on the current PBT literature by investigating PBT survivors in their adolescence specifically. For this age group, there are relatively few studies, despite this critical period for adult adjustment and outcomes. The present cross-sectional study of EF, psychological

Table 5. Self- and parent-reported executive functioning, psychological symptoms, and fatigue in treatment type subgroups.

	Surgery only (SO) (*n*= 28)		Surgery and chemotherapy (SC) (*n*= 9)		Surgery, CRT[1] and chemotherapy (SCC) (*n*= 10)		Post Hoc Tests	Effect size
	Mean	SD	Mean	SD	Mean	SD	*p*	*r*
BRIEF BRI	44.0	6.83	49.2	8.42	52.1	12.56	-	-
BRIEF MI	44.3	12.44	53.8	12.23	57.7	14.70	SO < SCC, *p*= .012*	−.41
BRIEF GEC	43.1	11.19	52.3	10.48	56.1	15.08	SO < SCC, *p*= .015* SO < SC, *p*= .034	−.39 -.35
CBCL Internalizing Problems	54.1	14.30	55.7	9.47	58.4	8.90	-	-
CBCL Externalizing Problems	45.0	8.29	45.1	11.08	44.8	11.92	-	-
CBCL Total Problems	49.2	12.11	52.2	11.30	54.5	9.71	-	-
YSR Internalizing Problems	51.9	9.94	53.9	6.31	52.0	11.25	-	-
YSR Externalizing Problems	48.0	8.44	47.8	9.56	45.2	8.74	-	-
YSR Total Problems	48.9	9.81	51.1	10.82	50.4	9.13	-	-
PEDSQL Total – parent report	78.9	17.70	74.2	17.78	58.7	14.13	SO > SCC, *p*= .002*	.49
PEDSQL Total – self-report	81.8	11.96	73.2	15.51	59.9	23.47	SO > SCC, *p*= .002*	.49
MFS Total	70.4	16.68	64.9	17.46	54.8	16.03	-	-

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 remained significant after Bonferroni corrections for multiple comparisons.

symptoms, behavioral problems and fatigue in adolescent PBT survivors has three main findings. First, the findings indicated that, on average, the PBT survivors in this study are functioning cognitively within the normal range, based on self- and parent-report and neuropsychological test data. However, PBT survivors and their parents reported significantly more problems in the cognitive domain compared to matched controls, including problems with EF, and a larger proportion of PBT survivors than expected from the normal distribution performed in the clinically impaired range (i.e., ≤1.5 SD) in several cognitive domains, with medium and large ESs. Second, PBT survivors and their parents reported significantly more difficulties with aspects of adaptive functioning (i.e., social relationships, school functioning, academic performance, and participation in activities) and QoL than healthy controls and their parents, with scores near clinical cutoff. 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, there were no significant associations between self- or parent-reported aspects of adaptive functioning and QoL and neuropsychological test data surviving Bonferroni correction. 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 symptom checklists, as evidenced by medium to large ESs.

Altogether, the findings show largest between-group differences for both parent- and self-reported cognitive concerns and problems with academic and social functioning, as evidenced by the medium ESs. This was also true for self-reported problems with fatigue and parent-reported difficulties with physical functioning, although self-reports of fatigue were within the normal range (i.e., within 1 SD from the control group mean). Although neurocognitive performance was on average in the normal range, the proportion of PBT survivors performing in the impaired range was larger than expected within the cognitive domains processing speed, auditory attention span, verbal learning, verbal recall, and shifting. These findings confirm the presence of neurocognitive dysfunction in a proportion of adolescent PBT survivors, including difficulties with "cool", or cognitive, aspects of EF. Furthermore, between-group differences on parent-reports of working memory were significant (i.e., a "cool" EF aspect), having a near to medium ES. These findings lend support to studies showing that although PBT survivors, survivors of acute lymphoblastic leukemia, other pediatric acquired brain injury

(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, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Araujo et al., 2017; Krivitzky, Walsh, Fisher, & Berl, 2016; Puhr et al., 2019a; Winter et al., 2014).

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 1.5 SD from the normative mean), and below established clinical cutoff scores based on U.S. norms. However, 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 findings of executive dysfunction on neuropsychological tests (Krivitzky et al., 2016; Wochos, Semerjian, & Walsh, 2014). Interestingly, teacher reports have been found to be more in line with neuropsychological test 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.

No significant correlations between neuropsychological test results and results on symptom checklists survived correction for multiple comparisons, and although parents of PBT survivors reported significantly more problems with working memory, deviations in this EF domain were not supported by the neuropsychological test data. Such discrepancy between 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 et al., 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.

The findings showing a tendency for parents of PBT survivors to endorse few EF problems, despite poor performance on neuropsychological tests of EF, is of importance in a long-term perspective. The complexity and protraction of EF development may also be a likely explanation as to why parents in our study reported few problems in this domain. 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, Northam, & Wrennall, 2019). This harmonizes also with developmental theories suggesting that EFs may emerge hierarchically throughout childhood and adolescence, demonstrating how successful development of some EFs relies on the successful development of other, earlier developing EFs (e.g., Garon, Bryson, & Smith, 2008; Gathercole, Pickering, Ambridge, & Wearing, 2004; Huizinga, Dolan, & Van Der Molen, 2006; Luciana, Conklin, Hooper, & Yarger, 2005; Tillman, Brocki, Sørensen, & Lundervold, 2015). Environmental factors contribute further to the tendency of delays in the onset and increase of impairments, as levels of 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). Accordingly, as adolescents are still living within the supportive, structured system of the home and the school, EF problems may not yet have emerged in the present sample of PBT survivors or that they are not yet observable to parents.

Contrary to earlier findings from studies of survivors of childhood cancers, the findings in this study showed few significantly elevated parent-reported symptoms of psychological distress in PBT survivors, compared to parents of healthy controls. Group differences were mainly evident for parent-reported internalizing problems (i.e., symptoms of withdrawal, depression and somatization). This is in line with findings from other studies showing that, compared to other pABI and CCS populations, PBT survivors may exhibit more internalizing than externalizing problems (Brinkman et al., 2016; Poggi et al., 2005), which 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. Also, 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 (i.e., the PedsQL Emotional Functioning subscale). These findings suggest that in terms of psychological adjustment, PBT survivors do not differ notably from their healthy peers. Further, 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. 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 exceeds 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. Our findings 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 socio-economic 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 et al., 2016, 2018, 2018; De Boer, Verbeek, & Van Dijk, 2006; Frederiksen et al., 2019; Ghaderi et al., 2016, 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 are 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. This is line with a large body of literature that has established a link between impairments in EF and adaptive functioning (e.g., Evans, 2008; Ness et al., 2008; Puhr et al., 2019b; Wolfe, Vannatta, Nelin, & Yeates, 2015; Wolfe et al., 2013). A recent study of young adult, physically well-functioning, PBT survivors, demonstrates how impairments in EF may play a significant role in the development of negative long-term outcomes in social attainment and participation compared to other personal factors (e.g., psychological symptoms) (Puhr et al., 2019b). In light of this, the findings from this study are important, as they indicate that the same pattern may be present 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 into difficulties in transitioning successfully into adulthood and participating in society in a long-term perspective. 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). This is demonstrated by neurocognitive cascade models emphasizing how impairments in cognitive domains such as processing speed, selective attention, working memory and more general EFs may lead to a negative cascading effect on IQ and academic achievement in survivors of

PBT (King, Ailion, Fox, & Hufstetler, 2019; Palmer, 2008; Wolfe et al., 2012). However, although 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 (i.e., "hot" EFs), which are equally important for everyday functioning, working in concert with the "cool"/cognitive aspects of EF. In the present study, reports of "hot" EFs were included, and although parent-reports of EF were within the normal range, poor adaptive functioning was associated with problems in both the "cool" and "hot" EF domains.

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. Combined with symptoms of fatigue, which may also have 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 symptom checklists, 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 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. Also, the subgroup for which neuropsychological test data was collected was small, and these results should therefore be viewed as exploratory. 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. Also, despite attempts to match the PBT survivor group and the healthy control group for age, there was a significant age difference between the groups. However, this difference was taken into account by including analyses adjusting for age.

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, and of including both self-/parent-reports and neuropsychological tests in these assessments. Fortunately, EF are relatively malleable (Zelazo & Carlson, 2012), all the more implicating the importance of improving interventions aimed at preventing further impairments and improving EF skills. Short- and long-term assessments and tailored interventions are 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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Bjørg Eli Eide (Cand. Psychol.), Child Habilitation Services, Haukeland University Hospital, Norway.
Oddmar Steinsvik (Cand. Psychol.), Child Habilitation Services, University Hospital of North Norway, Norway.

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ORCID

A. Puhr http://orcid.org/0000-0002-2763-6784

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