Sad, shattered or slow? Fatigue after childhood cancer.

Irestorm, Elin

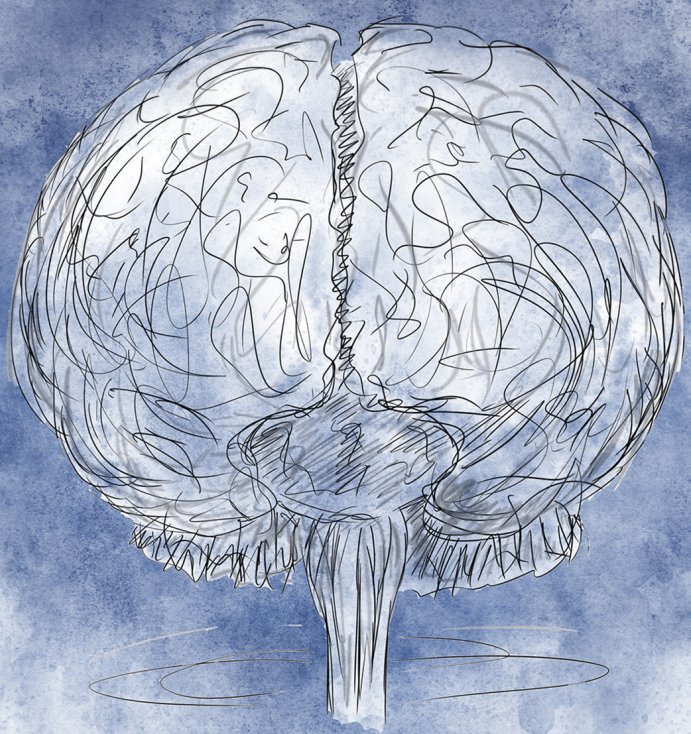
2021

Document Version:
Publisher's PDF, also known as Version of record

Sad, shattered or slow?

Fatigue after childhood cancer

ELIN IRESTORM
DEPARTMENT OF PAEDIATRICS | FACULTY OF MEDICINE | LUND UNIVERSITY



Sad, shattered or slow?

Fatigue in survivors of childhood cancer

Elin Irestorm

LUND
UNIVERSITY

DOCTORAL THESIS

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at D1539a Belfragesalen, Lund University,
on March 19th, 2021, at 9.00 a.m.

Faculty opponent
Professor Ann-Charlotte Smedler
Stockholm University, Sweden

Organization LUND UNIVERSITY	Document name
	Date of issue: 19 March, 2021
Author(s)	Sponsoring organization

Title and subtitle Sad, shattered or slow?
Fatigue in survivors of childhood cancer

Abstract

Systematic assessments of cognition, fatigue, and mental health in survivors of childhood cancer can serve two different purposes. One is to enable research about development over time and medical predictors of cognitive deficits. The other is to identify individual patients in need of rehabilitation or interventions. The overall aim of this doctoral thesis was to contribute to the ongoing development of systematic neuropsychological follow-up protocols for survivors of childhood cancer. The included studies investigated whether cognitive deficits were present already at diagnosis in children with brain tumours, the overlap between cognitive fatigue and symptoms of depression, and the association between fatigue and cognitive impairment.

The results showed that a pre-treatment assessment was feasible for the majority of cases, and that some aspects of cognition were affected already at baseline. Assessment of fatigue at follow-up revealed that cognitive fatigue was the fatigue domain most affected in survivors, but also that survivors of brain tumours suffered more from fatigue than survivors of acute lymphoblastic leukaemia. The results also indicated that cognitive fatigue should not be assessed on its own, but that depressive symptoms and cognitive processing speed should be considered as well. A decrease in cognitive processing speed from the pre-treatment assessment to the follow-up was also associated with experiencing more cognitive fatigue.

Overall, the results suggest that additional studies are warranted to further examine the relationship between baseline and long-term cognitive deficits. Regarding fatigue, more research is needed concerning the development over time, to see if it decreases or if there instead is a risk of increasing symptoms. Future studies should also focus on finding medical predictors and developing a biopsychosocial model of fatigue in survivors of childhood cancer.

Key words		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language: Eng
ISSN and key title 1652-8220		**ISBN** 978-91-8021-023-2
Recipient's notes	Number of pages: 90	Price
	Security classification	

Signature  Date 2021-02-08

Sad, shattered or slow?

Fatigue in survivors of childhood cancer

Elin Irestorm

LUND
UNIVERSITY

Cover illustration Johan Sarfelt Nilsson

Author photo Jörgen Lundh, StudioMix, 2021

Faculty of Medicine
Department of Paediatrics

ISBN 978-91-8021-023-2
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2021

Media-Tryck is an environmentally certified and ISO 14001:2015 certified provider of printed material. Read more about our environmental work at www.mediatryck.lu.se

MADE IN SWEDEN

To Marcus

Whenever I count my blessings, I count you twice

Contents

Abstract

Systematic assessments of cognition, fatigue, and mental health in survivors of childhood cancer can serve two different purposes. One is to enable research about development over time and medical predictors of cognitive deficits. The other is to identify individual patients in need of rehabilitation or interventions. The overall aim of this doctoral thesis was to contribute to the ongoing development of systematic neuropsychological follow-up protocols for survivors of childhood cancer. The included studies investigated whether cognitive deficits were present already at diagnosis in children with brain tumours, the overlap between cognitive fatigue and symptoms of depression, and the association between fatigue and cognitive impairment.

The results showed that a pre-treatment assessment was feasible for the majority of cases, and that some aspects of cognition were affected already at baseline. Assessment of fatigue at follow-up revealed that cognitive fatigue was the fatigue domain most affected in survivors, but also that survivors of brain tumours suffered more from fatigue than survivors of acute lymphoblastic leukaemia. The results also indicated that cognitive fatigue should not be assessed on its own, but that depressive symptoms and cognitive processing speed should be considered as well. A decrease in cognitive processing speed from the pre-treatment assessment to the follow-up was also associated with experiencing more cognitive fatigue.

Overall, the results suggest that additional studies are warranted to further examine the relationship between baseline and long-term cognitive deficits. Regarding fatigue, more research is needed concerning the development over time, to see if it decreases or if there instead is a risk of increasing symptoms. Future studies should also focus on finding medical predictors and developing a biopsychosocial model of fatigue in survivors of childhood cancer.

Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Irestorm, E., Perrin, S., Tonning Olsson, I. Pretreatment Cognition in Patients Diagnosed with Pediatric Brain Tumors. *Pediatric Neurology 2018*, *79*: 28-33.

II. Irestorm, E., Tonning Olsson, I., Johansson, B., Øra, I. Cognitive fatigue in relation to depressive symptoms after treatment for childhood cancer. *BMC Psychology, 2020*, 8:31.

III. Irestorm, E., Linge, H., Øra, I., Tonning Olsson, I. Cognitive fatigue and information processing after paediatric brain tumours. *Journal of International Neuropsychological Society, 2021, 1-10*

"It has been said, 'time heals all wounds.' I do not agree. The wounds remain. In time, the mind, protecting its sanity, covers them with scar tissue and the pain lessens. But it is never gone."

Rose Fitzgerald Kennedy

Abbreviations and definitions

ADHD	Attention Deficit Hyperactivity Disorder
ALL	Acute Lymphoblastic Leukaemia
BRIEF	Behaviour Rating Inventory of Executive Function
BYI	Beck Youth Inventories
CBT	Cognitive Behavioural Therapy
CCSS	Childhood Cancer Survivorship Study
CNS	Central Nervous System
CPT	Continuous Performance Test
CRF	Cancer-Related Fatigue
D-KEFS	Delis–Kaplan Executive Function System
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed.
ICC	Intraclass Correlation Coefficient
ICD-10	International Classification of Diseases, 10th ed.
IQ	Intelligence Quotient
MFS	Multidimensional Fatigue Scale
NEPSY	A Developmental NEuroPSYchological Assessment
NF1	Neurofibromatosis type 1
PBTs	Paediatric Brain Tumours
PedsQL™	Pediatric Quality of Life
TMT	Trail-Making Test
Wechsler scales	Intelligence Scales for preschoolers (WPPSI), children (WISC), and Adults (WAIS)

Acknowledgements

As this is a quantitative thesis, I estimate the amount of time I enjoyed my PhD studies to be approximately 98.5%. (Had it been a qualitative thesis, I would have said that I had the time of my life.) Most of the time, it was a sheer pleasure. I was allowed to focus on something I really found interesting and to acquire so much new knowledge, but an equally important part of this experience was the aid and backup I received. I would like to express my sincere gratitude to everyone who helped me during the past four years. Many people have contributed in one way or another; but there are some who deserve special appreciation.

To my main supervisor **Ingrid Øra,** for resolutely being enthusiastic, supportive, engaged, and encouraging, no matter the situation or the challenge faced. But most of all, for your unrivaled courage and your willingness to take me on as a PhD student without ever having worked with me or even met me before.

To my assistant supervisor **Helena Linge**, for all the inspiration and insight provided, and for exhibiting excellent leadership skills (you really did deserve an award for that). But perhaps most of all for providing Zoom-company during the pandemic coffee breaks.

To my assistant supervisor **Ingrid Tonning-Olsson**, for inviting me to visit you at St Jude and stay with you in Memphis. And above else – for staying in touch and carrying on our collaboration even for the years when we were 7600 kilometres apart.

To **HaideMarie Axberg-Roos**, for giving me time off to finish my thesis, despite the constant staff shortage, and for navigating the maze of contradicting rules and regulations for clinical PhD students together with me.

To **Pia Tham**, for your endless supply of biscuits and for being an infinite source of knowledge**.** I have yet to encounter a problem you cannot solve or a question you do not have the answer to.

To tumour contact nurse **Johanna Mårtensson** and her predecessor **Charlotte Castor,** for always being at the top of their game and making sure our survivors get the best possible care.

To **Thomas Wiebe**, for talking me into this, for helping me get my very first research grant, and for recommending me a supervisor.

To **Klara Thorstensson,** for making the task of correcting questionnaires and calculating scores endurable.

To consultant statisticians **Axel Ström** and **Anna Åkesson,** for detecting flaws in my logic and providing new angles.

To the wonderful and highly efficient **Maria Söderqvist** and **Anette Gunder Nilsson,** for always being so helpful and amiable.

To **Johan Sarfelt Nilsson**, for the beautiful cover illustration and for always being up for discussing video games.

To my friends and personal cheerleaders **Tiina "Hilkamo" Nilsson, Emma Englund,** and **Hanna Järnehage**, for exhibiting relentless belief in me and expressing tireless interest. To **Pasi Kurvinen** and **Awi Rozenberg**, for sending me pictures of cats whenever I needed it. And to **Anders Ruuth** and **Maria Pedersen**, for still being there, after all these years. I am fortunate to have you in my life.

To mischievous mastermind **Zelda Irestorm**, for keeping me company while writing my thesis, and for constantly reminding me that a sedentary working day is bad for the health and that it is important to get up regularly. I also thank you for not messing up any more SPSS calculations than absolutely necessary.

To my soulmate and guiding light **Marcus Irestorm,** for providing unconditional support and unfaltering patience in every imaginable situation. You carried me through these years and cheered me over the finishing line. While I'm immensely proud of all the work I did and all the effort I put into this, I can also honestly say that nothing of this would have been possible without you. In this and in every adventure, you are my legendary comrade-in-arms – the Luigi to my Mario, the moogle to my chocobo, and yes, the Ben to my Leslie.

Last, but not least… To every survivor of childhood cancer who confirmed that my research mattered, and that I was on the right track. You have provided me with so much insight and have been my main motivation to write this thesis.

Funding

The work presented in this thesis was supported financially by grants from the Swedish Childhood Cancer Foundation, the Jonas Foundation, and The Skåne University Hospital Psychology Research and Development Grant. The open access fees for studies II and III were covered by Lund University.

Preface

My thesis, like that of most clinical PhD students, originates in an urge to improve the care of my patients and a desire to learn more about the diagnoses I work with. When I enrolled in the psychologist programme at Lund University, I realised early on that neuropsychology was something that I would specialise in. After I acquired my licence to practise as a clinician, I started working at a department of neurology, where I assessed cognition in adults with acquired brain injuries. The concept of cognitive fatigue was something that was well known, and I felt confident in my own ability both to assess this sequela and to offer psychoeducational interventions. In early 2015, halfway through my specialisation in clinical neuropsychology, I started working at the department of neuropaediatrics in Lund. Here, I met survivors of childhood cancer who complained about the same impairment so well known amongst adult neurology patients, and suddenly I was at loss about what to do. The major challenges were to assess the impact of fatigue on cognition (or possibly the other way around), the overlap with depression and how to differentiate between the two phenomena, and what educational adjustments to recommend in order to help these patients manage school days and teaching situations. The above-mentioned areas were (and still are, but to a lesser extent now) what I struggled most with as a clinician, and in order to learn more I started to read the available research. However, I soon realised that very little had been published on the subject and I only managed to find a handful of relevant studies. This left me frustrated and concerned, and my inability to ease my patients' suffering made me feel inadequate and incompetent. As a result, I wrote down a list of everything I thought I needed to learn in order to be remotely satisfied with my own knowledge. This list would later develop into my first draft of the research plan that was the origin of this thesis. During the time I have spent on my own research, a few more studies have been published. Defending my thesis will not be the last step on the journey towards the so highly sought-after "subject expertise", but hopefully some of the things I have learned along the way will benefit both myself and my colleagues – and in the end be useful in the follow-up care of childhood cancer survivors.

Introduction

Background

Approximately 300 children are diagnosed with cancer in Sweden every year, with leukaemia and central nervous system (CNS) tumours being the most common paediatric cancer diagnoses [1]. Cancer is the most common cause of death in Swedish children below the age of 15 [2], but the 5-year survival rate is now around 80% for CNS tumours and around 90% for acute lymphoblastic leukaemia (ALL) [3].

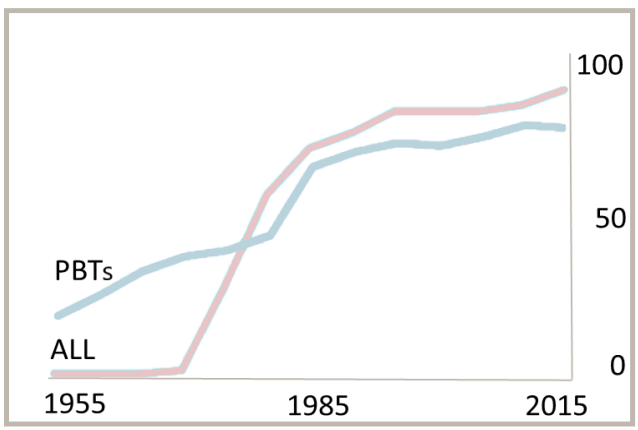


Figure 1. Swedish survival rates for acute lymphoblastic leukaemia (ALL) and paediatric brain tumours (PBTs) 1955–2015, percentage [3].

As survival rates have increased, so has the population of childhood cancer survivors. This is as much a political challenge as it is an issue for childhood cancer centres. These survivors are now a part of our society and face an educational system that is not adapted to their disabilities and a labour market that offers fewer and fewer opportunities for those without higher education [4]. Getting these survivors through school is not necessarily sufficient to prepare them for an independent life, but in today's society it is without a doubt the most important first step. In Sweden, advancement from lower secondary education to upper secondary education is dependent on grades (where it is

especially important for the students to pass the "core" subjects Swedish, English, and mathematics). In the general population, 92% are entitled to move on to upper secondary education, whereas the corresponding rate for survivors of paediatric brain tumours (PBTs) is 76%. [5] Almost a quarter of the survivors are hence unable to make this transition. Swedish studies have revealed that both survivors of CNS tumours and survivors of ALL are at risk of negative socioeconomic effects, attaining lower education levels and exhibiting lower employment rates than healthy controls [6,7]. A recent review on social and socioeconomic outcome amongst childhood cancers survivors concluded that the health implications of adverse socioeconomic outcomes can vary depending on different healthcare regulations and legislation in different regions [8]. At the same time, the late effects after treatment for childhood cancer may alter the psychosocial trajectory of survivors and affect them across their entire life course [9].

The health care system has to identify late complications after childhood cancer, so that survivors may be offered treatment or rehabilitation when possible, and other adjustments when necessary. The psychological aspects of the long-term sequelae require systematic assessments and follow-up protocols for these survivors.

Systematic psychological assessments of survivors

Cancer is one of the first areas where clinical paediatric psychologists established themselves, and psychological research has been conducted in paediatric cancer settings since the 1970s [10]. Neuropsychological screenings are recommended in order to detect cognitive deficits, especially for survivors of PBTs [10-16], and it is also recommended that follow-up of survivors of paediatric cancers should include assessments of depression and anxiety [14,17]. While most protocols do not yet contain measurements of fatigue, there is an increased demand for including it in follow-up protocols for survivors of both paediatric and adult cancer [15,16,18,19]. Fatigue has consistently been found to be one of the most prevalent and distressing symptoms in childhood cancer survivors [17,20,21], but despite this it is frequently overlooked as a long-term sequela to paediatric cancer diagnosis and treatment [20,22].

The current Nordic protocol

The national Swedish care programme for long-term follow-up after childhood cancer ("Nationellt vårdprogram för långtidsuppföljning efter barncancer") was updated in 2019 and provides guidelines for most types of sequelae [23]. This care programme also includes recommendations for a neuropsychological core battery (Table 1), which is based on the Nordic protocol and has many similarities to the European guidelines [16].

Table 1. Swedish guidelines for follow-up after treatment for paediatric brain tumours, cognitive tests [23]

Domain	Core Battery	Alternative
Motoric speed	>5 years Grooved Pegboard	>3 years NEPSY II: Visuo-motor precision
Processing speed	>4 years Wechsler Coding >4 years Wechsler Symbol Search	
Verbal skills	>2:6 years Wechsler Vocabulary >2:6 years Wechsler Similarities	
Fluid intelligence	>2:6 years Wechsler Matrix >2:6 years Wechsler Block Design	
Working memory	<6 years Numbers (Children's Memory Scale) >6 years Wechsler Digit Span	>3 years NEPSY-II Sentence Repetition
Visual-motor integration	Beery Visual-Motor Integration	
Sustained attention	>8 years Conner's CPT III	
Executive functions	>8 years D-KEFS TMT >8 years D-KEFS Tower 5–8 years NEPSY II: Inhibition	

Table 2. Swedish guidelines for follow-up after treatment for paediatric brain tumours, questionnaires [23]

Area	Core Battery	Alternative
Quality of life	>2 years PedsQL General module	Strengths and Difficulties Questionnaire
Psychosocial		Development and Well-being Assessment (given high scores on the Strengths and Difficulties Questionnaire)
Executive functioning	>2 years BRIEF parent-proxy report >11 years BRIEF self-report	

Regarding psychological assessments, these guidelines recommend that age-appropriate psychosocial support should be offered continuously after end of treatment. Neuropsychological assessments should be conducted 1–2 years after diagnosis for survivors diagnosed with PBTs or a cancer diagnosis that required cranial radiotherapy and/or treatment with a chemotherapy known to cause cognitive sequelae. Depending on the results and prognosis, these assessments should be repeated when necessary (for example when preparing for educational transitions). One cognitive domain that is not included in the protocol is long-term memory. Neither visual nor verbal long-term memory is part of the screening. In this respect, the Swedish guidelines differ from those found in Limond et al. [16]. St Jude Life is an American research study with long-term childhood cancer survivors, and the neuropsychological protocol for these studies also includes tests of long-term memory [24-27].

Cooperation between healthcare and educational systems

School liaison programmes, which include cooperation between schools, hospitals and parents, have been reported to improve the educational progress in survivors of PBTs

[28,29]. A study that aimed to coordinate the neurocognitive, psychosocial, and educational follow-up of children treated for PBTs in two different Swedish healthcare regions concluded that these follow-up programmes must be structured and coordinated and well anchored in the healthcare organisation [30].

A Danish study was recently published on school results in ninth grade during 2001–2014. The study included 1320 childhood cancer survivors. In this study, survivors of CNS tumours, neuroblastoma, lymphoma, leukaemia, other malignant neoplasm, and germ-cell tumours were the most affected. Diagnosis at a young age was a predictor of low grades for survivors of CNS tumours and leukaemia, but was not associated with school results for other diagnoses. As expected, survivors of CNS tumours were the most affected, with only 73% of this group receiving grades in the ninth grade. The study did not find lower grades for survivors of other cancer types [31]. The results regarding grades in ninth class and graduation from lower secondary school for survivors of PBTs are in line with those reported from Sweden [5] and Finland [32], which is not surprising considering the many similarities between the neighbouring school systems.

Cognitive late effects

Risk factors for cognitive sequelae

Cognitive impairments are common in long-term survivors of paediatric cancers, with up to 40% of survivors being affected [33]. Cognitive deficits can result in poor academic and occupational outcome, affecting the socioeconomic status of the survivors. Not surprisingly, survivors of PBTs have worse neuropsychological outcome than other childhood cancer diagnoses [34-36], with several studies reporting cognitive long-term effects in over 80% of survivors [37,38]. Severe cognitive deficits (usually defined as results more than 2 standard deviations below the age-adjusted average) has been reported in 20-30% of these survivors [39]. Treatment with radiotherapy is the most documented risk factor [36,38-40], but younger age at diagnosis has also been reported as a predictor of cognitive impairments [38,41-44]. The latter is in line with research on acquired brain injury due to other aetiologies than PBTs, where research has shown that the age at insult predicts outcome, with children below 2 years of age sustaining the worst impairments in all cognitive domains [45].

While survivors of ALL generally have higher functioning at a group level than survivors of PBTs, long-term cognitive effects is a documented outcome in this group as well. Survivors exposed to radiotherapy are at particular risk of long-term effects, with research indicating a dose-response effect [46,47]. Systematic reviews and meta-analyses of cognitive deficits after treatment for ALL have concluded that although children

treated with radiotherapy suffer the worst deficits, children treated with chemotherapy alone are also affected [48,49]. The direct effect of chemotherapy exposure has been found to be the best predictor of cognitive deficits, both at the end of treatment and at long-term follow-up [24].

Cognitive domains affected

Reduced processing speed has been reported in survivors of both PBTs and ALL [35,50]. In survivors of PBTs, this is the most well-documented late cognitive effect after diagnosis and treatment, with the mean processing speed index for the study populations reported to be 1–1.5 SD below the age-adjusted mean [38,40,41,51,52]. Cognitive processing speed is included as an index in all Wechsler intelligence scales. It also contributes to full-scale intelligence quotient (IQ), which is a composite score based on 4–5 different indexes [53-55]. The subtests contributing to the processing speed index in the Wechsler scales are not measures of simple reaction times or simple visual discrimination, but a cognitive decision making or learning component is always involved [56,57]. Processing speed is heavily dependent on white matter [58-61], and radiotherapy causes white matter damage [40,62]. It is therefore not surprising that the major risk factor for this cognitive deficit is radiotherapy (especially cranial radiation), in survivors of both PBTs and ALL [38-40,50,63].

However, processing speed is not the only cognitive domain affected. Survivors of PBTs usually perform significantly lower than controls or age-adjusted norms on most neuropsychological tests. Attention, working memory, long-term memory, executive functions, and full-scale IQ are domains typically investigated in such studies [33,38,39,41,52]. The same results are also reported when academic abilities, such as reading or mathematical skills, are tested [33,39,52,64]. A recent Swedish study comparing comprehension and speed in both reading and mathematics found that while comprehension skills did not differ significantly from age-equivalent norms, the speed did for both reading and mathematics. The same study also reported that time since diagnosis increased the risk of a poor performance, indicating that school results could decline with time [65]. However, not all cognitive domains are equally affected. Verbal intelligence, verbal reasoning, and vocabulary are areas that are less likely to be affected than non-verbal skills [38,64,66]. Fewer studies have been conducted regarding neuropsychological outcome after treatment for ALL than PBTs, but the available results imply that this group is also at risk of cognitive deficits. In addition to reduced processing speed, impairments have been reported regarding working memory, full-scale IQ, executive functions, and attention [46,48,49,63,67].

One area that has received increased attention as survival rates have improved is that of social perception. A Childhood Cancer Survivorship Study (CCSS) report on 665 adolescent survivors of CNS tumours found that only 53.4% were socially well-adjusted, whereas 30.4% had poor peer relationships and 16.2% had social deficits.

Treatment with cranial radiotherapy was a strong predictor, and the risk of having social adjustment deficits or poor peer relationships increased with the radiation dose [68]. A review on social adjustment and social interaction of survivors of PBTs concluded that survivors generally show problems when compared to controls [69]. Social skills can be negatively affected by different cognitive disabilities. A recent study using eye-tracking technology found that adolescent survivors of PBTs responded more similar in youths diagnosed with autism than healthy controls in tasks measuring social attention [70]. Executive dysfunction has been linked to social dysfunction in survivors of PBTs [71-73]. Several studies have found attention problems to be an underlying contributor to social deficits in survivors of both ALL and PBTs [74-76]. It has also been hypothesised that the non-verbal deficits usually found in the latter group could cause problems with social perception [64]. Another possible cause is that these survivors can express problems with facial recognition [77,78], which could further complicate social interactions. Survivors of PBTs, especially females, also tend to underestimate their own social difficulties [79].

Emerging research areas

For natural reasons, when it comes to neuropsychological research, cognition after PBTs is the most well-documented field. The demand has also increased for research on neuropsychological outcomes after treatment with contemporary protocols for ALL. When it comes to cognitive late effects after other childhood cancer diagnosis, fewer studies have been conducted. In recent years, however, this area has received more and more attention and three large St Jude Life studies have been published. The first reported neurocognitive outcomes and academic skills in survivors of non-Hodgkin lymphoma. These survivors had intelligence and attention within normal limits, but impaired memory, executive function, processing speed, and academic skills [80]. The second investigated the same outcomes in long-term survivors of Wilms tumour. This group of survivors demonstrated deficits regarding verbal reasoning, executive functions, long-term memory, attention, and academic skills [25]. The third study investigated neurocognitive and psychosocial consequences for survivors of soft-tissue sarcoma, and concluded that these survivors are at risk of negative outcomes in both areas [26].

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is a neurocutaneous syndrome, a genetically driven syndrome that increases the likelihood of both tumours and cognitive impairments [81]. Because of this, patients with NF1 are often excluded from studies on cognition after PBTs [72,82,83], as it is difficult to determine whether the cognitive deficits are

part of the syndrome or caused by the treatment. Nearly 80% of all patients with NF1 exhibit cognitive deficits and behavioural problems [84,85].

A recent review on cognitive and behavioural disorders in children with NF1 concluded that the group is characterised by alterations in language, reading, visuospatial skills, motor function, executive function, attention, behaviour, emotion, and social skills [85]. Attention deficit hyperactivity disorder (ADHD) has been reported in 40–50% of the patient group [81,85]. While executive dysfunction is an essential clinical feature of ADHD, executive problems are also present in children with NF1 without a comorbid diagnosis of ADHD [86,87]. Full-scale IQ has ranged between 86 and 91 [81,88,89], which is significantly lower than the normative mean of 100 (SD 15). However, a recent study on genotypes on NF1 reported that while mean full-scale IQ in a sample of 495 children with NF1 was 87.8, there was a large difference between different genotype groups [90]. The group with the lowest mean full-scale IQ (72.8) and the smallest SD (9.9) was the genotype chromosomal microdeletion.

Depression and anxiety in survivors of childhood cancer

Children and adolescents

While it has been recommended that follow-up of survivors of paediatric cancers should include depression and anxiety [14,17], few studies have been published on the subject. The majority of the research is focused either on a paediatric population with ongoing treatment or on adult survivors of childhood cancer instead of children and teenagers. Many studies also look at either general psychological adjustment or depression/anxiety as the same concept, and not as separate constructs. The complex interaction between cancer and psychological symptoms also causes a challenge when diagnosing children undergoing treatment for cancer. Dejong & Fombonne [91] discuss the methodological problems that arise when investigating depression in a cancer population, where exclusion of somatic symptoms can lead to a high rate of false negatives, while inclusion can result in the opposite. Other methodological problems include the exclusion of CNS tumours, limited sample sizes, and low statistical power.

A recent review by Mertens & Gilleland Marchak [92] emphasises the need for further research on mental health in adolescent survivors of cancer. In one study, Swedish children on and off cancer treatments were compared regarding self-esteem, depression, and anxiety [93]. Children on treatment did not report significantly higher levels of depression and anxiety than healthy children, while children off treatment did for both measures. In this study, 17% of children off treatment reported high levels of depression. The authors concluded that the period after the treatment has ceased is characterised by a higher risk of psychosocial problems than the treatment period itself.

Another Swedish study, looking at adolescents undergoing treatment, found that paediatric oncology staff could reasonably identify patients with anxiety but not with depression [94]. A review on updates in paediatric psycho-oncology concluded that it is easier to diagnose anxiety than depression in children and adolescents undergoing cancer treatment, but also that there also are more available treatment options for anxiety [11]. If anxiety is easier both to detect and to treat than depression, this implicates that patients suffering from anxiety are more likely to receive treatment than those suffering from depression.

The CCSS is an American multicentre project with sibling controls. In one CCSS study on behavioural and social outcomes in adolescent survivors of childhood cancer, the authors reported that survivors were 1.5 times more likely to have symptoms of depression/anxiety than sibling controls. Survivors treated for CNS tumours or leukaemia were at increased risk compared to survivors of other cancer diagnoses. Female gender, treatment with cranial radiotherapy, or disfigurements were the strongest predictors of mental distress in this study [95]. Another CCSS study found that internalising symptoms (i.e. depression, anxiety, social withdrawal, peer conflict) were present amongst 31% of adolescent survivors treated with cranial radiotherapy, compared to 16% of survivors who had not received this treatment [96].

Adult survivors of childhood cancer

There is more available research regarding mental status in adult survivors of childhood cancers. Survivors of both PBTs and ALL have consistently been found to express more problems with depression as adults than sibling controls in CCSS reports [97-99]. Studies regarding anxiety report more mixed results, with some finding increased anxiety amongst survivors [97] and others reporting no difference [99].

A recent review by Sha et al. [100] provides a compilation of psychiatric consequences in adult survivors of PBTs. The incidence of depression amongst survivors was over 19%, and survivors of PBTs were 2.6 times more likely to develop depression compared to sibling counterparts. Anxiety incidence was also over 19%. Findings are similar compared to studies on adolescents regarding female gender being a risk factor for depression [97-100], and most studies additionally report treatment with cranial radiotherapy as a risk factor [97,98,100]. Being diagnosed with cancer during childhood or adolescence was similarly a risk factor for suicide in a Norwegian cohort study. Compared to the reference group, survivors of CNS tumours had a hazard ratio for suicide of 3.9 and the average for all cancer types was 2.5 [101]. Regarding suicidal ideation, a CCSS report with 9126 survivors of childhood cancer reported increased suicidal ideation for survivors compared to sibling controls, with survivors of CNS tumours and survivors treated with radiation towards the head/brain having the highest risk [102].

Fatigue

While the classic definition of fatigue is an "extreme and persistent tiredness, weakness or exhaustion" [103], the term is still complicated as there is no clear definition of when it should be considered a disability. In a similar manner, there is no agreement on whether it should be based on the patients' subjective experience or on objective measurements. Kluger, Krupp & Enoka [104] have proposed a unified taxonomy, where *fatigue* describes the patient's perception and *fatigability* the actual performance. Wylie & Flashman [105] argue that fatigue should be further divided into 6 different dimensions. Their model is based on traumatic brain injuries, and for cancer patients only two dimensions have been clearly established: physical fatigue and cognitive/mental fatigue [106]. However, this division is not present in the International Classification of Diseases, 10th edition (ICD-10).

Fatigue in cancer populations

Cancer-related fatigue (CRF) is a type of fatigue associated with either cancer or cancer treatment, and has consistently been found to be one of the most prevalent and distressing symptoms in childhood cancer survivors [17,20,21]. In the ICD-10, CRF is included in R53.0 under the term neoplastic (malignant)-related fatigue [107]. There are four diagnostic criteria:

A) 1. At least a 2-week period within the preceding month during which significant fatigue was experienced each day, along with the experience of at least 5 of 10 fatigue-symptoms (A2-11).
   2. General weakness/heavy limbs.
   3. Diminished concentration/attention.
   4. Decreased motivation/interests.
   5. Insomnia or hypersomnia.
   6. Nonrestorative sleep.
   7. Struggle to overcome inactivity.
   8. Emotional reactivity to feeling fatigued.
   9. Difficulties completing daily tasks.
   10. Problems with short-term memory.
   11. Post-exertional malaise.

B) The fatigue results in significant distress or impairment.

C) The fatigue is a consequence of cancer or cancer therapy.

D) The fatigue is not primarily a consequence of a major depressive disorder.

The diagnosis CRF is complicated by two factors: The first is the overlap with depression, and the second the unidimensional construct.

Donovan et al. [108] conducted a systematic review on the diagnostic criteria of cancer-related fatigue in order to describe the prevalence, reliability, and validity of each criterion. They found that there was a large variability regarding how criterion D was applied, and little evidence to support the number of symptoms selected for criterion A. The symptoms with the highest prevalence were general weakness/heavy libs, insomnia or hypersomnia, and unrefreshing sleep. The same 3 criteria were also found to have both the highest sensitivity and the lowest specificity in a study on the screening properties of diagnostic criteria for CRF [109].

The American National Comprehensive Cancer Network has published consensus clinical practice guidelines in oncology [110], where CRF is defined as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer-treatment that is not proportional to recent activity and interferes with usual functioning". Both this description and the diagnostic criteria hence define CRF as a unidimensional concept. A Cochrane review of 18 studies, with 14,573 participants, on severe fatigue after treatment for childhood cancer reported that severe fatigue ranged from 0% (bone cancer) to 61% (heterogeneous sample) [111]. However, the outcome measure in this study was severe fatigue rather than CRF (due to inclusion criteria), and one limitation with the review was that many studies used unidimensional rather than multidimensional instruments, which affected the outcome.

Amongst cancer populations, most fatigue research is conducted on women treated for breast cancer [110]. Although CRF usually decreases during the first year after end of treatment in this group, 20–30% of breast cancer survivors experience persistent fatigue that may last for more than 10 years after end of treatment [112]. In studies with mixed cancer groups, breast cancer is usually the largest group, and this might exaggerate the effect of gender on fatigue [113]. A study on 111 women treated with surgery, followed by whole breast radiotherapy, found a strong correlation between inflammatory markers, stress, sleep, depression, and fatigue. However, statistical analysis revealed that depression was a mediator for both stress and sleep, and that only depressive symptoms and inflammation were independent risk factors for fatigue [114]. Research has shown a correlation between inflammatory markers and fatigue in adult cancer survivors [115]. Inflammation has emerged as a key biological pathway for CRF, and relationships between inflammatory markers and fatigue have been reported before, during, and particularly after treatment. Amongst breast cancer survivors with persistent post-treatment fatigue, alterations in the pro-inflammatory cytokine network (including elevations in inflammatory markers and increased intracellular cytokine production) have been well-documented and replicated in larger samples of survivors of this type of

cancer [116]. Additionally, it has been suggested that systemic inflammation may cause neurocognitive impairments in survivors of paediatric ALL [49,117].

During treatment for breast cancer, both chemotherapy and radiotherapy are known to increase fatigue [118-121]. However, several studies have reported that the therapy scheme had no influence on fatigue scores at follow-up [113,118,122]. The relationship between different treatment protocols and fatigue is less apparent than that between treatment and cognition. A study on chronic fatigue in adult survivors of childhood ALL and lymphoma reported that neither radiotherapy nor chemotherapy predicted fatigue scores [123]. At the same time, a study on fatigue in adult survivors of PBTs reported that the group treated with surgery only was less likely to exhibit severe fatigue in adulthood than those who had received a combination of surgery, chemotherapy, and radiotherapy [124].

The National Cancer Institute has published recommendations for high-priority research on CRF in children and adults, and these identify a need for longitudinal studies to uncover the biopsychosocial mechanisms of CRF [125]. These recommendations summarise two crucial research gaps: 1) the course of fatigue over time, and 2) medical, psychological and social variables related to fatigue.

Overlapping symptoms between depression and fatigue

Several studies have reported a strong correlation between fatigue and depression [126-129], but a meta-analysis of CRF also concluded that there was a large variability in research regarding how criterion D was applied when including participants [108]. Depression has been seen to be the strongest predictor of fatigue in breast cancer survivors [114,130], and is also closely linked to fatigue in adult survivors of childhood cancer [131]. One study of adult survivors of childhood ALL and lymphoma reported that level of depressive symptoms was the strongest predictor of persisting fatigue that did not decrease with time since treatment [123]. The diagnostic criteria of CRF should hence be compared to those for F.32 Depressive episode in ICD-10 [132]:

A) A duration of at least 2 weeks.

B) At least 2 of the following symptoms for a mild or moderate episode, and 3 for a severe episode: Depressed mood, loss of interest and enjoyment, reduced energy leading to increased fatigability and diminished activity.

C) At least 2 of the following symptoms for a mild episode, and 4 for a moderate or severe episode: Reduced concentration and activation, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic view of the future, ideas or acts of self-harm or suicide, disturbed sleep (hypersomnia or insomnia), increased or decreased appetite.

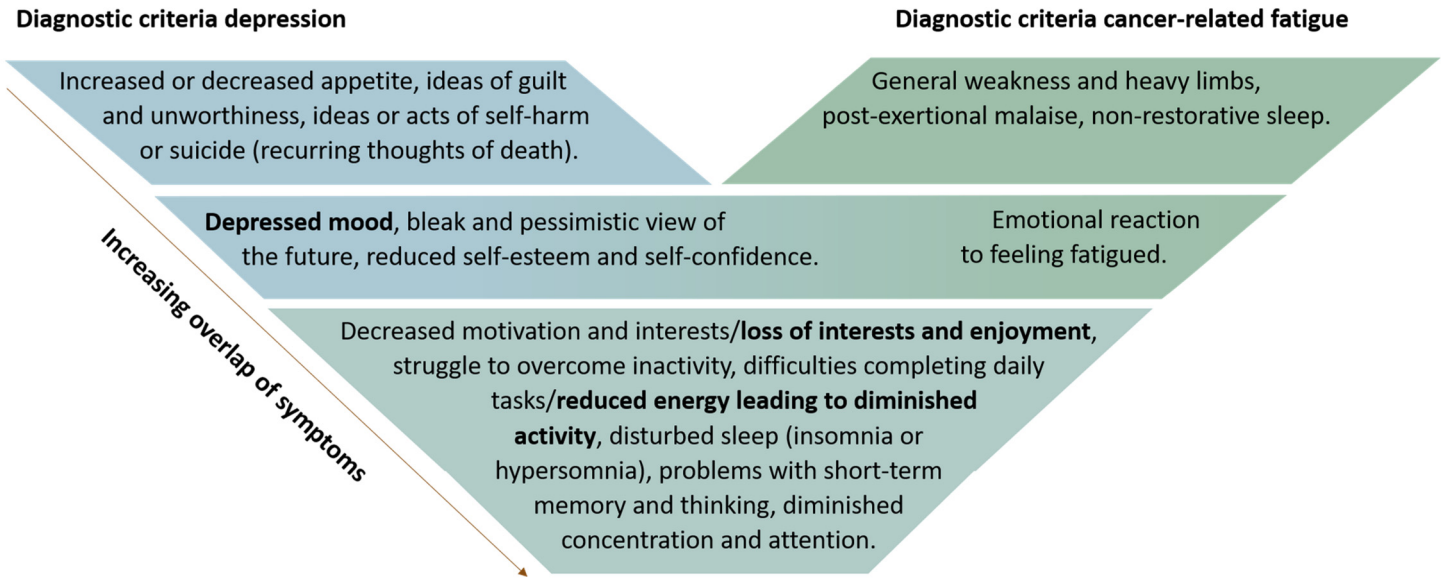


Figure 2. Overlapping diagnstic symptoms of depression and cancer-related fatigue. Compulsory symptoms for depression are indicated in bold.

A comparison between the ICD-10 diagnostic criteria for CRF and depression is illustrated in Figure 2. The compulsory key symptoms for depression all have an overlap with CRF, and since none of the diagnoses requires more than half of the possible symptoms this can make differential diagnosis difficult.

Many clinical psychologists in Sweden rely on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) when diagnosing patients. It is therefore relevant to look at diagnostic criteria for depression (296.20–296.36, depending on type and severity) in DSM-5 [133]. There are only minor differences between the two nosologies. DSM-5 requires at least 5 symptoms for a diagnosis, but there are only 2 key symptoms (depressed mood, and loss of interest and enjoyment) out of which only 1 is necessary for a diagnosis. This could make the potential overlap with CRF larger, but DSM-5 also has several exclusion criteria, and one of them is that the symptoms should not be attributable to a known medical condition. This has a specific purpose in DSM-5, as depressive symptoms caused by a medical condition are coded as 293.83 (depressive disorder due to a known medical condition). This is similar to F06.31 (known physiological condition with depressive features) and F06.32 (known physiological condition with major depressive-like episode) in ICD-10 [107]. However, this does not automatically make the differential diagnosis easier. What determines when a patient, with a known history of cancer and cancer treatment in the past, who is expressing the above-mentioned symptoms, should be diagnosed with CRF and when depression is a more appropriate diagnosis? (Both at the same time is not an option, due to the exclusion criteria included in CRF.) This distinction is important in ensuring that the correct therapeutic strategies are offered, and to avoid unsatisfactory outcomes. Misdiagnosis could potentially lead to either delayed treatment, complete inaction from the health care providers, or non-specifically targeted interventions.

Cognitive fatigue

The second type of critique against CRF is that it is a unidimensional diagnosis. As only 5 out of 10 symptoms are necessary to fulfil criteria A, and half of these symptoms are cognitive and half of them physical, it is possible for patients to exhibit CRF with entirely different symptom constellations. Research has also clearly established that CRF consists of two separate dimensions: physical fatigue and cognitive/mental fatigue [106]. Cognitive fatigue (without the presence of physical fatigue) is reported in both adult and paediatric patient populations and is associated with acquired brain injuries, inflammatory disease, infections, and degenerative neurological disorders [134-140]. Research on cognitive fatigue in breast cancer patients also indicates that cognitive fatigue has different predictors than physical fatigue. In a study of 255 breast cancer survivors, poor sleep quality was the strongest predictor of cognitive fatigue at the 12-month follow-up [122]. Another study on 459 breast cancer survivors found that high

cognitive function before treatment strongly reduced the risk of cognitive fatigue at the follow-up 2 years after surgery [118].

Figure 3. For patients suffering from cognitive fatigue, prolonged cognitive tasks can cause mental exhaustion. © John Holcroft/Ikon Images (reproduced with permission)

Regarding symptoms, cognitive fatigue manifests as mental exhaustion caused by sensory stimulation and/or prolonged cognitive tasks [134,141,142]. Sensitivity to sound (and in some patient groups also sensitivity to light), as well as a specific diurnal pattern are also clinical features of this sequela. The diurnal pattern is characterised by performance decreasing continuously throughout the day [143-145]. The cognitive symptoms associated with cognitive fatigue are especially a decreased processing speed [143,146,147], but also impairments in attention, memory, and executive functions

[49,148-152]. Just as with fatigue, the similarities between cognitive fatigue and depression pose a problem for both clinicians and researchers, but previous studies demonstrate that depression and cognitive fatigue are separate constructs [127,144]. The auditory and visual hypersensitivity described in cognitive fatigue serves to distinguish, but the most striking difference is the diurnal pattern. The diurnal pattern in depression is the direct opposite of that in cognitive fatigue, as mood and energy increase during the day in people with depression [153-155].

Aetiology of cognitive fatigue

In children and adolescent suffering from cognitive fatigue due to acquired brain damage, injuries with greater severity have been reported to be associated with higher levels of fatigue and worse outcomes in some studies [156], but not in others [157,158]. Age at onset has been reported as a predictor in some studies [159], while others have found no effect for age [157,158]. A Dutch study on acquired brain injuries in children and adolescents found that participants reported more cognitive fatigue after non-traumatic brain injuries (where brain tumours are included) than after traumatic brain injuries, which could be caused by the additional impact of chemotherapy and radiotherapy in survivors of PBTs [159].

Research on aetiology indicates that cognitive fatigue is caused by a neuroinflammation in the astrocytes [105,160,161], and in the cancer population inflammatory cytokines also seem to be a key factor [162]. Even though most chemotherapeutic molecules do not pass the blood–brain barrier, they may still cause toxicity in the brain indirectly through proinflammatory cytokine pathways. Proinflammatory cytokines impair astroglial glutamate uptake, and increased levels of proinflammatory cytokines have been reported in disorders associated with cognitive fatigue [160,163].

Considering the link between cognitive fatigue and neuroinflammation, this sequela might also be the result of complex interactions between many underlying mechanisms. One example is the bidirectional link between inflammation and depression [164]. Another is the pathway between neuroinflammation and obesity, and the role it plays in cognitive decline [165]. Both adult [166] and adolescent [9] survivors of childhood cancer are at increased risk of excessive weight, and many different treatment and lifestyle factors contribute to this. Treatment with radiotherapy is a factor that is associated with increased risk of both obesity [167-169] and neuroinflammation [170]. Because of this, complex underlying mechanisms could cause the symptoms associated with both depression and cognitive fatigue in this patient group, and more research is needed regarding biomarkers such as proinflammatory cytokines and other risk factors.

Treatment of cognitive fatigue and cognitive fatigability

The distinction between cognitive fatigue and cognitive fatigability is especially important when it comes to evaluating the effects of different interventions. A review

by Walker et al. [171] focused on interventions for cognitive fatigability in neurological disorders, and the authors reported that studies on interventions for cognitive fatigue are much more common than studies on interventions for cognitive fatigability. Some studies combine measures of fatigue and fatigability, such as the research on methylphenidate as a possible treatment for adults after traumatic brain injury [147]. A longitudinal follow-up of the same patients, after 5.5 years of treatment, also reported that the effect was found to be stable over the years. A comparison was made between those who had continued and those who had discontinued the treatment, and withdrawal was reported to produce a pronounced and significant deterioration in both objective and subjective measures [172]. A Cochrane review on the management of fatigue in adults with primary brain tumours reported no difference between modafinil and placebo for either subjective or objective measures of cognitive fatigue [173]. The different results might be due to the different aetiologies of the two diagnoses, or due to the different therapeutic mechanisms of the two medications.

Regardless of outcome measure, these types of studies are usually conducted on an adult population. To date, only one study has been published on children and adolescents. The population consisted of survivors of PBTs undergoing physical training as an intervention, and the authors reported that exercise significantly reduced cognitive fatigue, but not physical fatigue [174]. For adults, pharmacological treatments such as monoaminergic stabilisers [175] and methylphenidate [147,172,176] have been evaluated as treatments for cognitive fatigue after stroke and traumatic brain injury. When it comes to psychological interventions, mindfulness has been reported to decrease cognitive fatigue in adults after stroke or traumatic brain injury [177,178].

Lifestyle factors

The cognitive symptoms associated with cognitive fatigue can also be caused by a suboptimal lifestyle. Lack of sleep and insufficient exercise can cause mental exhaustion, memory problems, and attention problems. A government report on lifestyle factors amongst Swedish school children concluded that both insufficient exercise and sleep problems are common in this age group. Sleep problems are prevalent in 30% of children and adolescents, which is twice as much as in 1985. At the same time, a minority of Swedish school children (40% of boys and 30% of girls) get the minimum amount of weekly exercise recommended by the World Health Organization [179].

Exercise

Exercise intolerance (the ability to complete physical tasks) has been reported in survivors of ALL [180], and an association between exercise intolerance and

neurocognitive outcomes has also been demonstrated in this group of survivors [181]. This association is not surprising, since it has been demonstrated that improved exercise capacity positively impacts certain cognitive domains. Several neuropsychological studies on adult cancer survivors have found physical activity to be associated with processing speed, memory, executive functioning, and attention [182-186]. These findings are in line with research on healthy populations, where increased exercise has been found to improve cognition. Amongst different cognitive domains, executive functions seem to benefit most from frequent exercise [186-191]. However, a gender difference has also been reported, and in a study by Stern et al. [188] aerobic exercise improved both executive function and processing speed in men, whereas the same effect was not seen in women. At the same time, female elite football players outperformed the healthy controls on the measures of processing speed in a study on cognitive ageing in contact sports [192]. Thus, there seem to be an association between processing speed and aerobic activity in both genders. Regarding school results, several Swedish studies have concluded that physical interventions improve learning outcomes [193,194].

In adults, physical activity is also associated with a decreased risk of depression. This has been reported in both observational [195,196] and intervention studies [197-199]. This is not only the case for the general population, but is also well-document in adult cancer survivors [200]. However, this is an understudied area in the paediatric population. Meta-reviews on exercise in prevention and treatment of depression in children and adolescents have concluded that the same assumptions cannot be made for the younger population due to a low number of studies [201,202]. One recent meta-review compared the effect of exercise on cognition and on different aspects of mental health (including depression), and found that while there is strong evidence for a causal association between physical activity and cognitive functioning in children and adolescents, there is only partial evidence for an association with depression [203].

Regarding the effect of exercise on fatigue, an intervention study on children and adolescents with cancer reported that a 6-week walking exercise regime (with at least five sessions a week) significantly reduced both cognitive fatigue and general fatigue, but not sleep/rest fatigue [174]. In a Dutch study on fatigue and physical activity after treatment for childhood cancer, both measures were assessed at baseline, and at 4 months and 12 months. Most PedsQL™ MFS scores improved from baseline to 12 months, and so did physical activity (measured with an accelerometer). More physically active children experienced less fatigue, and the associations were not influenced by diagnosis, type of treatment, time since diagnoses, percentage of body fati, or BMI score at baseline [204].

For adults, there is much more available research regarding the impact of exercise on fatigue, and reviews and meta-analyses have concluded that physical training (especially aerobic training) can reduce fatigue both during and after treatment [205-207]. The effect of exercise is strongest for moderate to vigorous intensity, whereas low-intensity

training is unlikely to reduce fatigue [200]. In line with the recommendations regarding using multidimensional fatigue scales in clinical practice [19,110], the same concern was raised regarding research in a Cochrane review [206]. As some intervention studies used unidimensional instruments and others multidimensional, this made it difficult to compare the effect of exercise on different types of fatigue. The current American guidelines for most adult cancer survivors (certain risk groups are excluded) recommend at least 150 minutes of moderate intensity aerobic activity each week [205]. There is insufficient evidence for a linear dose response, and increasing the aerobic exercise beyond 150 minutes per week does not result in decreased fatigue [200].

Sleep

Inadequate sleep is defined as short and/or disrupted sleep patterns, and reports regarding lifestyle factors amongst Swedish children and adolescents have revealed unsatisfactory levels of sleep [208-210]. As sleep behaviour is related to both working memory performance [211,212] and attention [213,214] in children and adolescents, this is an important lifestyle factor to consider when assessing survivors with these symptoms. A review on functional outcomes of inadequate sleep in adolescents by Shochat et al. [215] summarises the role of sleep in several areas of health and development. Not only does inadequate sleep affect cognition and school performance, it also increases the risk of obesity, depressive symptoms, and fatigue. A meta-analysis of the dose-response relationship between sleep and obesity found that with every 1 hour/day increase in sleep duration, the risk of overweight/obesity was reduced by 21% [216]. While the recommended duration of sleep for teenagers is 8 hours/night, the average duration for Swedish teenagers is 7.28 hours and 26% sleep less than 6 hours [208].

Research on sleep, inflammation, fatigue, and neurocognitive outcomes in adult survivors of childhood ALL found a gender difference regarding the relationship between these outcomes. More consistent associations were found between inflammatory biomarkers and neurocognitive outcomes in female survivors compared with male survivors, and neurocognitive function in female survivors also appeared more susceptible to the effects of sleep disturbances and fatigue [117]. In a German study of 255 breast cancer survivors, poor sleep quality was the strongest predictor of cognitive fatigue both during therapy and at the 12-month follow-up [122].

The use of questionnaires in clinical practice

Direct and indirect measures

Questionnaires – both self-reports and parent-proxy reports – are indirect measures of cognitive status, whereas neuropsychological tests are direct measures. Many larger studies – for example CCSS – use either self-report or parent-proxy reports when researching neurocognitive outcomes in survivors of childhood cancer [36,217-219]. While this is both less expensive and less time-consuming than neuropsychological testing, agreement between direct and indirect measures is usually low. A comparison of executive ratings and performance on executive tests in a sample of brain tumour patients revealed no clear associations between the reported executive functions and the test performance [220]. A review that examined the association between performance-based and rating measures of executive function in 20 studies (13 child and 7 adult samples) concluded that direct and indirect measures capture different underlying cognitive constructs [221]. Discrepancies in direct and indirect cognitive measures have been reported in many different clinical groups [222-225], and it is often concluded that direct and indirect measures are complementary and that comprehensive assessments require both.

One problem that often occurs when using research questionnaires in clinical practice is the lack of a published cut-off. This dilemma was addressed in a recent Cochrane review on severe fatigue after treatment for childhood cancer. For those questionnaires that did not have a published cut-off, the criterion for severe fatigue was defined as a score above or below two standard deviations of the mean from a healthy reference group [111]. Another method is to use the 10th percentile of the control group as a cut-off, as established for self-rating questionnaires used by both CCSS and other cancer research projects [131,226,227]. This cut-off is also used in questionnaires like the Behaviour Rating Inventory of Executive Function (BRIEF) and Beck Youth Inventories (BYI) [228,229].

While fatigability is an objective performance, fatigue is the patient's perception [104]. As the impact of fatigue is individual and a subjective experience, it is recommended to use self-reports for the assessment of fatigue in cancer patients [110,162]. Self-report instruments commonly used in studies on fatigue in survivors of childhood cancer are listed in Table 3.

Table 3. Self-report instruments used in studies on fatigue in survivors of childhood cancer [111,230].

Instrument	Ages	Dimensions	Proxy versions
PedsQL™ Multidimensional Fatigue Scale	2–4 5–7 8–12 13–18 19–25 Adults	3 (general, sleep, cognitive)	Parent
The (Childhood Cancer) Fatigue Scale	7–12 13–18	1	Parent and staff
PROMIS® fatigue subscale	8–17 Adults	1	Parent
Short Form-36 vitality subscale	All*	1**	No
EORTC-QLQ symptom scale fatigue	All*	3 (physical, emotional, cognitive)	No
(Chalder) Fatigue Questionnaire	All*	2 (physical, mental)	No
FACIT-Fatigue Scale	All*	1	No
Revised-Piper Fatigue Scale	All*	4 (affective, behavioural, sensory, cognitive)	No
The Brief Fatigue Inventory	All*	1	No
The Multidimensional Fatigue Inventory	All*	5 (general, physical, mental, motivation, activity)	No

*No specific version for children and/or adolescents.

** The scale is multidimensional, but only 1 subscale covers fatigue.

Single-item screening measures for fatigue in survivors of PBTs have been reported to have low accuracy compared to in-depth multidimensional scales [231]. Additionally, multidimensional instruments are recommended in order to facilitate discrimination between depression and fatigue [19,110], but also for evaluating the impact of interventions [206]. The *Pediatric Quality of Life Multidimensional Fatigue Scale* (PedsQL™ MFS) is one such multidimensional instrument.

Reviews of existing fatigue instruments for children and adolescents have concluded that PedsQL™ MFS has strong evidence of reliability [230] and that its psychometric properties make it suitable for incorporation in clinical research [18]. The inclusion of PedsQL™ MFS is also recommended in the European follow-up guidelines for survivors of PBTs, for children both above and below 5 years of age [15,16]. An alternative to PedsQL™ MFS is the Fatigue Scale, which in earlier publications was called the Childhood Cancer Fatigue Scale [232]. This instrument has specific versions for children and adolescents, and offers both parent- and staff-proxy versions. PedsQL™ MFS and the Fatigue Scale have equally strong measurement properties, with similar attributes regarding internal consistency and responsiveness [18,230]. However, the Fatigue Scale is neither multidimensional nor (currently) available in a

Swedish translation. Since PROMIS® is the most recently developed fatigue instrument for children, the measurement properties have not yet been thoroughly evaluated [230].

Self-reports vs. proxy reports

Many instruments for children – including PedsQL™ MFS – allow for the use of both self-reports and proxy reports. Parent-proxy means that the parent rates the child's problems. Usually, the two different forms contain the same items and may therefore give the impression that they can be used interchangeably. But choosing whether to rely on self-reports or parent-proxy reports is a delicate matter in both clinical practice and research. Due to low agreement, it is recommended that children and parent report instruments should not be compared directly [230]. When assessing children and adolescents, it is sometimes possible to use teacher-proxy reports instead of (or as a complement to) parent-proxy reports. Correlations between test performance and questionnaires have been found to be much higher for teacher reports than parent reports, regarding both adaptive skills and executive functions [233,234]. Low interrater reliability between parent and child reports has been described in several studies using PedsQL™ MFS [158,235,236]. A study on children and adolescents coping with cancer also reported that the percentage of patients with elevated symptoms of depression/anxiety was twice as high in the self-reports than in the parent-proxy reports [237]. These results are thought-provoking, and highlight the need for further discussions regarding the guidelines for assessment protocols.

Aims and objectives

Main objectives of this work

Studies of cognitive sequelae in survivors of childhood cancer almost exclusively focus on long-term cognitive impairments after treatment and do not take pre-treatment cognitive status into account. Cognition at baseline is important to consider when evaluating the effects of different kinds of treatment, but most studies on treatment-related sequalae do not include a pre-treatment neuropsychological testing. Another field of limited research is cognitive fatigue as a result of disease or treatment, and its relationship to cognition and mental health. Additions to the body of knowledge in these areas do not only have scientific value, but also clinical relevance. As the population of survivors steadily increases, so does the demand on society, employment agencies, schools, and hospitals. While many different institutions are responsible for offering these survivors support, the health care system has an especially prominent role when it comes to identifying survivors in need of rehabilitation. In order to do so efficiently, structured protocols must be developed and implemented. While it is essential for the survivors that all possible long-term deficits are assessed and evaluated, it is equally important not to include too many variables as it would make the follow-up assessment excessively time-consuming and mentally exhausting for the patient. The hospitals and health care system need cost-effective protocols, but must at the same time be able to rely on the screenings to properly identify individuals with additional needs.

The main objectives of the work presented in this doctoral thesis were to investigate whether cognitive deficits were present already at diagnosis in children with brain tumours, and whether the development of such deficits over time was linked to cognitive fatigue. The overall goals of the studies presented here were to contribute to the ongoing development of systematic neuropsychological follow-up protocols for survivors at risk of cognitive deficits or mental distress as sequalae after childhood cancers.

Brief descriptions of the studies and aims

Pre-treatment cognition

In study I, the objective was to extend our knowledge of cognitive impairment at baseline and associated risk factors for the same. In this study, results were analysed from a large sample of children and adolescents diagnosed with PBTs who underwent a pre-treatment neuropsychological assessment.

Cognitive fatigue in relation to depressive symptoms

In study II, the aims were to investigate the prevalence of cognitive fatigue in survivors of childhood cancer, the overlap between cognitive fatigue and depressive symptoms, and some psychometric properties of the MFS. The study compared survivors of PBTs and ALL with a sample of healthy controls.

Associations between cognitive fatigue and cognitive abilities

Previous studies have investigated the association between cognition and cognitive fatigue in adults. Study III was carried out to examine whether the same cognitive domains are affected in children and adolescents as in adults suffering from cognitive fatigue. The study compared self-rated measures of fatigue with neuropsychological test results in survivors of PBTs aged 8–18 years.

Method

Design

All three studies in this thesis were observational and used quantitative methods, but data collection and patient population differed. Table 4 gives an overview of the participants and the design in the different studies. The Statistical Package for the Social Sciences (software versions 23–26), was used to record, structure, and analyse study data.

Table 4. Study overview

Study	Population	Design	Data collection
I	101 children and adolescents at diagnosis, before treatment for PBTs	Cross-sectional	Neuropsychological assessment at baseline
II	30 survivors of PBTs, 30 survivors of ALL, and 60 healthy controls	Cross-sectional	Self-report and parent-proxy questionnaires
III	45 survivors of PBTs	Cross-sectional, longitudinal	Neuropsychological assessment at baseline and follow-up, questionnaires

Abbreviations: PBTs: Survivors of paediatric brain tumours; ALL: Survivors of acute lymphoblastic leukaemia.

Participants and study setting

Patients in all three studies were children and adolescents living in the Southern Hospital Region in Sweden. Skåne University Hospital in Lund is the childhood cancer centre for this region, which has a population of 1.8 million people. Participants in study I were patients diagnosed with a PBT, who had undergone a pre-treatment neuropsychological assessment (regardless of age at assessment). In study II, the participants were survivors of PBTs or ALL who had received treatment at Skåne University Hospital, were participating in the follow-up programme there, and were 8–18 years old at the time of assessment. Children and adolescents from Lund and the surrounding municipalities were recruited for the control group in study II. In study III, the participants were survivors of PBTs who had received a neuropsychological follow-up testing, and were 8–18 years old at the time of assessment.

Ethical approvals and considerations

Two different ethical approvals were acquired for the studies included in this thesis. Data for study I and III were collected as part of a larger clinical project (*CogCan: cognition after childhood cancer*). The aim of this project is to identify PBT survivors with cognitive impairments, to evaluate the relationship between the treatments received, and to engage the child and the family with rehabilitative services. Neuropsychological variables gathered during the testing are registered in a database approved by the Regional Ethics Board in Lund (No 500/2007). As this database only includes survivors of PBTs and revolves around neuropsychological assessments, a second ethical approval was therefore needed for study II (No 2017/851).

Part of the requirements for getting the ethical approval for study II was to present a plan for following up those patients who scored elevated or very elevated symptoms of either depression or anxiety on the BYI. This was of particular importance as there was a substantial staff shortage of psychologists when data for this study were collected, and this affected the department of paediatric oncology (where survivors of ALL received follow-up) more than the department of paediatric neurology (where survivors of PBTs received follow-up). Detecting survivors in need of psychological treatment could therefore potentially expose an under-staffed department to extra stress and a higher workload. It could also cause resources to be relocated from one department to another, meaning that other patient groups would get less psychological support than they would have if the study had not been conducted. In comparison, not assessing these survivors in the first place could also be considered unethical. Hence, the ethical considerations of that study went beyond just applying for approval from the Regional Ethics Board.

Statistical analysis

Study I

Study I was a cross-sectional registry study. Included in the project were patients diagnosed with a PBTs at Skåne University Hospital between 1 January 2006 and 31 December 2015. The inclusion criterion was to have undergone a neuropsychological assessment at baseline, before the start of treatment (surgery, radiotherapy, or chemotherapy). Exclusion criteria were a diagnosis of a neurocutaneous syndrome (NF1 or tuberous sclerosis) or a previous diagnosis of PBTs. A total of 161 patients were diagnosed with a PBT for the first time during this time period, of whom 31 had neurocutaneous syndromes. Twenty-nine of the eligible patients had not undergone a pre-treatment assessment, leaving 101 study participants. A pre-treatment assessment had hence been conducted for 78% of all study participants. (If patients with

neurocutaneous syndromes had been included in this analysis the total number would have been 82%.)

Six different cognitive measures were included in the statistical analysis: Full-scale IQ, performance IQ, verbal IQ, processing speed, working memory, and visual attention. Scores on the cognitive measures were assessed for normality and outliers. Six clinical variables were included in the analysis: age at diagnosis, gender, tumour size, increased intracranial pressure as onset symptom, epilepsy as onset symptom, and tumour location (supratentorial or infratentorial). A series of stepwise linear regressions was carried out, where the six clinical variables were backwardly regressed in each of the six cognitive variables separately. Variables were removed when $p>0.05$. Comparisons between the 101 study participants and the 29 excluded patients were made with Student's t-test for continuous variables and χ^2 for categorical variables.

Study II

Data for study II were collected 2017–2019. Survivors of PBTs and ALL, who were aged between 8 and 18 years and who completed the treatment between 2 and 6 years ago, were eligible to participate. Exclusion criteria were non-proficiency in Swedish, a diagnosis of intellectual disability, or a diagnosis of Down syndrome. A total of 65 survivors were eligible, but three families declined to participate and a further two were excluded due to relapse after inclusion, leaving 60 survivors in the study. A control group of 60 healthy children, 8–18 years of age, was included for comparison. Parent-proxy and self-report version of the PedsQL™ MFS were administered to the participants. The children and adolescents also completed Beck Youth Inventories (BYI). Both the depression and anxiety subscales of BYI were administered, but only the depression subscale was used in the analysis.

As several of the parent-proxy scales violated assumptions of parametric tests, the non-parametric Kruskal-Wallis was used to analyse group differences. The Mann-Whitney U test was used for post hoc analysis of the significant differences, and effect sizes were calculated for the pairwise tests. Parent-child concordance was examined with intraclass correlation coefficient (ICC), and Cronbach's alpha was used for internal consistency reliability. Gender differences were investigated with the Mann-Whitney U test. A general linear model (factorial ANOVA) was used to analyse the effect of diagnosis and symptoms of depression on the PedsQL™ self-rated cognitive fatigue subscale. Diagnosis included three levels (controls, survivors of ALL, survivors of PBTs), and depression included three levels (average symptoms, elevated symptoms, highly elevated symptoms).

Study III

Data for study III were collected 2017–2020. Survivors of PBTs who came for a neuropsychological assessment (either 2 or 5 years after diagnosis) during that time period were included in the study. A total of 56 survivors in the age group had follow-up testing during that time period. Survivors were excluded if they had a diagnosis of either autism or intellectual disability before being treated for PBTs, if they were candidates for epilepsy surgery, if their sequalae prevented participation, or if they were currently undergoing treatment for relapse. A total of 45 survivors were eligible for inclusion. A pre-treatment assessment had been conducted with 37 of the 45 included patients (82%). In order to investigate the relationship between cognition and fatigue, results from the self-rate version of the PedsQL™ MFS were compared with results from 9 different neuropsychological tests (2 measures of processing speed, 4 measures of attention, 2 measures of executive function, and 1 measure of working memory). Regression analysis, adjusted for treatment with radiotherapy and age at onset, was used to investigate the associations between 9 cognitive variables and 3 different measures of fatigue. All scores were transformed to Z-scores, and the scales for the Conners Continuous Performance Test (CPT-3) were converted, so that a higher score on all scales meant a better result. With the false discovery rate set at 0.05, the Benjamini–Hochberg procedure was used to correct for multiple comparisons. Cognitive variables with a significant association with fatigue were also exploratively assessed through graphs and visual analysis. The difference in test scores between the pre-treatment testing and the follow-up was examined in this analysis.

Results

Comparisons between the three studies

While the 3 studies had different aims and methods, there were some similarities between the findings. In study I, 78% of all patients diagnosed with a PBT had undergone a pre-treatment neuropsychological assessment, but these numbers were based on the exclusion of patients with neurocutaneous syndromes. When these patients were included, 82% had been tested at baseline. Only a few patients were included in both study I and III, but 82% of the participants in study III had also received an assessment at diagnosis. Hence, these pre-treatment assessments were not possible for all patients, but feasible in the majority of cases. Another similarity between study I and III was that the average age at diagnosis of a PBT was 9.4 years in both studies, and that there was a slight overrepresentation of males (54.5% in study I and 53.3% in study III). The somewhat higher incidence in males in Sweden has previously been described by Lannering et al., together with equal survival rates for males and females [238], and the same results were therefore expected at follow-up.

The PedsQL™ MFS was used in both study II and III, and for survivors of PBTs the scores – both regarding distribution, mean, and SD – for the 3 different subscales were similar in the two studies. Hence, increasing the sample by 50% did not affect the results on a group level. The mean score for the cognitive fatigue subscale was lower than for the other two fatigue subscales, indicating that the impact of fatigue differed between different categories.

Study I

Overall, cognitive performance was relatively intact at baseline. The results were close to norm means for most variables, but impairments were found in memory and cognitive processing speed. Male gender, older age, epilepsy, increased intracranial pressure, and larger tumours were all associated with lower cognitive function at the time of diagnosis. No demographic or clinical variable predicted perceptual IQ, but for the remaining cognitive variables the models could predict lower cognitive function.

However, explained variance was very modest for most cognitive variables except attention. Patients with epilepsy as onset symptom also had significantly smaller tumours than patients with other onset symptoms, and tumour size masked the effect of epilepsy on cognition at baseline.

The main conclusions were that pre-treatment neuropsychologic assessments, with some adjustments, can be carried out with children and adolescents diagnosed with PBTs, but also that the relationship between baseline and longer-term cognitive deficits requires further examination. The study was the largest published so far on the subject of pre-treatment cognition, contributing one third of the total patient material in all studies, and the findings regarding clinical predictors were consistent with previous research. The result that pre-treatment processing speed was reduced (especially in boys) was a new finding, and these impairments may partly explain the longer-term deficits that commonly occur in survivors of PBTs.

Study II

When using the 10th percentile of the control group as a cut-off, 70% of PBTs survivors and 30% of ALL survivors scored below this limit for cognitive fatigue. Very elevated symptoms of depression were reported by 27% of the PBT survivors and 20% of ALL survivors. Survivors of PBTs reported significantly more fatigue than healthy controls on all fatigue subscales. Both diagnosis and depression level were significant predictors of cognitive fatigue, but diagnosis was the stronger of these two. While survivors of PBTs expressed more symptoms of depression than both survivors of ALL and the healthy controls, there was no evidence for an interaction effect.

The study also evaluated some psychometric properties of the PedsQL™ MFS. While children consistently rated greater problems than parents (resulting in lower mean scores for the self-reported values than the parent-proxy values), the differences were smaller for the cancer survivors than for the controls. Parent-child concordance was better for survivors than for controls. Similarly, intraclass correlations were poor for the controls, but moderate to good for the survivors. With the exception of the self-rated sleep fatigue subscale, all other subscales showed satisfactory reliability, with Cronbach's alpha exceeding 0.70 for the total sample of survivors and controls.

Both the depression and anxiety subscales of BYI were administered to all participants, but as anxiety has no symptom overlap with cognitive fatigue only the results for depressive symptoms were included in the statistical analysis. The results for both subscales are therefore presented in Table 5.

Table 5. Results from the Beck Youth Inventories

	PBTs	ALL	Controls
	n (%)	n (%)	n (%)
Symptoms of anxiety			
total	30 (100)	30 (100)	60 (100)
average	20 (66.7)	21 (70.0)	45 (75.0)
elevated	3 (10.0)	4 (13.1)	11 (18.3)
highly elevated	7 (23.3)	5 (16.7)	4 (6.7)
Symptoms of depression			
total	30 (100)	30 (100)	60 (100)
average	18 (60.0)	21 (70.0)	46 (76.7)
elevated	4 (13.3)	3 (10.0)	7 (11.7)
highly elevated	8 (26.7)	6 (20.0)	7 (11.7)

Abbreviations: PBTs: Survivors of paediatric brain tumours; ALL: Survivors of acute lymphoblastic leukaemia.
Swedish norms: percentile 0–74 average, percentile 75–89 elevated, above percentile 90 very elevated.

Study III

The mean results for the survivors were lower than the normative means for cognitive processing speed, working memory, and cognitive flexibility. The results for the fatigue subscales were very similar to those in study II, regarding both scores and the pattern. Of the 3 different fatigue subscales, cognitive fatigue had the lowest mean score (indicating lower quality of life and more problems). Significant associations were found for measures of cognitive processing speed and the cognitive fatigue self-rate subscale, with slower processing speed associated with poorer results for cognitive fatigue. No associations were found for the other cognitive domains or the other fatigue subscales. In this respect, the results differ from those reported in adults, where associations between cognitive fatigue and executive functions, working memory, and attention have been reported.

The explorative analysis revealed that all survivors with impaired processing speed also scored substantial problems with cognitive fatigue. The survivors experiencing the least cognitive fatigue also had the best processing speed. While some survivors expressed problems with cognitive fatigue without having an impairment in processing speed, the opposite was not prevalent in any survivors. The change in processing speed between baseline and follow-up was also plotted against the score in cognitive fatigue, and revealed that survivors with the largest decrease in processing speed from baseline to follow-up also experienced the most cognitive fatigue.

As in study I, processing speed was impaired already at baseline. When the patients were split into two groups – radiated and non-radiated – this revealed an interesting pattern. While the total group average was lower than the normative mean, there was a striking difference between the two groups. The group that would receive radiotherapy

after the assessment was more impaired than the group that would not receive this treatment. In the manuscript, the results from the two groups were not separated but combined into one variable. As this division adds information to the results from study I, it is demonstrated in Figure 4.

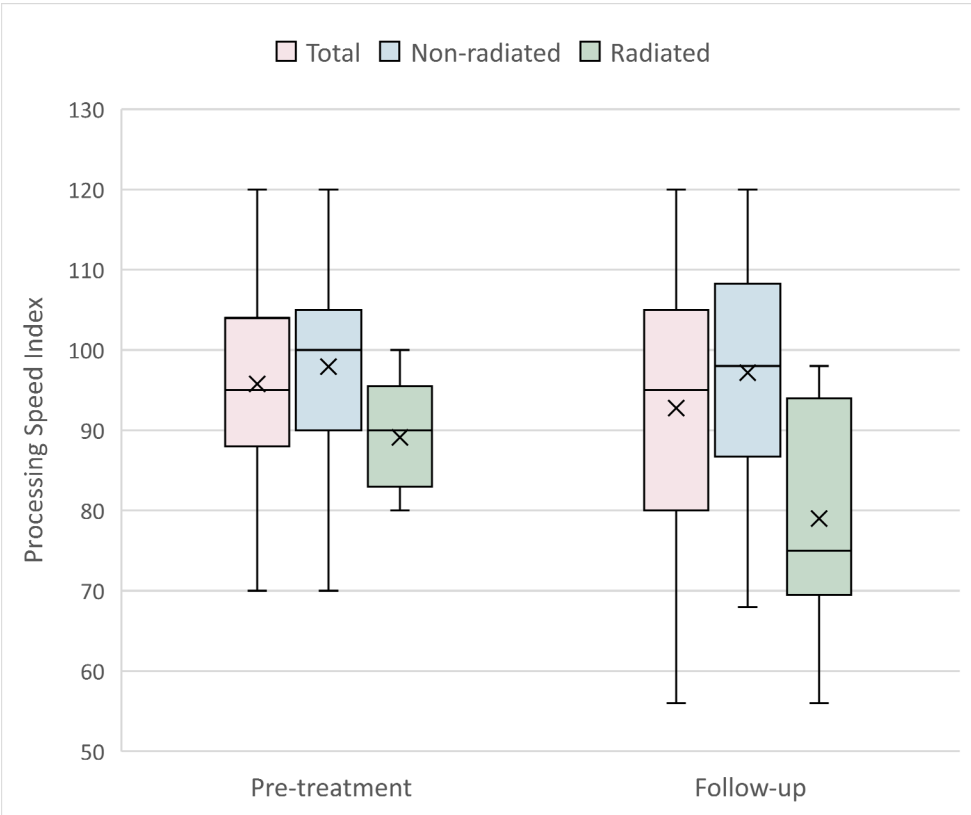


Figure 4. There was a large difference in processing speed (M 100, SD 15) between the two treatment groups at both the baseline assessment and the follow-up assessment (n 37).

Discussion

Improving psychological follow-up protocols

In a review of recommendations for neuropsychological follow-up protocols of childhood cancer survivors, Annette et al. [239] discuss both which survivors to assess and when those assessments should be conducted. They conclude that there are two groups of survivors that should be considered: 1) children diagnosed with brain tumours, and 2) children with other types of cancers that received CNS-directed therapies (mainly survivors of ALL). Regarding the timing of the assessment, they recommended that the intervals should be 2–3 years (or until change was identified). When deciding on psychological follow-up protocols, there are two additional aspects to consider. When the assessments should be conducted and which survivors to include are only the first step, while the second consists of defining which domains to focus on and which instruments to use for this. The challenge is to find a balance and a protocol that focuses on the right aspects, while being efficient regarding both time and economy, and tolerable for the patients.

When it comes to points in time for the assessments, the results from both studies I and III show that pre-treatment assessments are feasible with the majority of patients diagnosed with PBTs. Pre-treatment assessments can – if implemented – contribute to research regarding the development of long term-deficits since they make it possible to investigate comparisons between baseline impairments and sequelae caused by the treatment. Merchant et al. [240] concluded that the long-term effects of radiotherapy may be exaggerated when the baseline function of the patients is not assessed. Establishing a baseline is hence important for longitudinal research, and Ris et al. [241] list the advantages and disadvantages of different approaches. The major weakness with the pre-treatment assessment is the small window of opportunity and, as demonstrated in studies I and III, this will not be possible with all patients. Conducting the "baseline" assessment post-surgery, but before the start of radiotherapy or chemotherapy, will allow for a larger window but means that post-surgical effects can influence the results. Other commonly used methods are proxy

Figure 5. The 5-year survival for paediatric brain tumours is currently 80% in Sweden, and 80% of those who survive have long-term deficits as a consequence after the tumour and/or the treatment. The psychological assessment protocols should identify survivors suffering from cognitive deficits, mental ailments, behavioural problems, and/or fatigue.

estimations (based on prediction formulas, taking for example socioeconomic status, parental education, and parental occupation into consideration) or relative change (where the mean of a group of survivors is compared to the normative mean). The latter two methods are based on a "normality assumption", i.e. that development follows the average trajectory up to the point of symptom onset, and that normality assumption has been questioned [83].

An observed change in performance on neurocognitive tests could be caused by a practice effect, but can also reflect tumour- or treatment-related decline, altered developmental trajectory, or recovery due to either intervention or spontaneous reasons [242]. Statistical methods for determining whether the observed changes are reliable and clinically meaningful are described by Duff [242] and were further adapted to assess change in survivors of PBTs by Duda et al. [243]. Knowledge about the stability of test scores and howto interpret observed change is important when deciding on the retest interval. It is necessary to test often enough to detect a possible decline, but also not to conduct them too often. This is both in order to avoid having the patients undergo unnecessary testing sessions, but also due to the test-retest effect, which could potentially mask a cognitive regression or stagnation. The short-term stability of the different Wechsler scales is reported in the technical manuals for each test [56,57]. It is worth mentioning that the reliability for the processing speed indexes is lower than for other composite scores for the Wechsler intelligence scales for both children and adults. While reliability for the other composite scores is based on split-half reliabilities, it is based on test-retest reliabilities for the processing speed indexes (which tend to be lower) [57,56].

In clinical practice, the retest-interval is usually longer than that used when the test was standardised, but long-term stability is sometimes investigated in studies. One example of this is that Watkins & Smith investigated the long-term stability of the fourth edition of the Wechsler Intelligence Scale for Children, by comparing different studies that had reported retest scores. Of the different indexes, processing speed had the most variability in test-retest stability [244]. When non-clinical participants were retested within weeks, the processing speed index (M 100, SD 15) increased with by 7.1 points on average, with the largest difference being 9.9 points for 6–7-year-olds [245]. When non-clinical participants were retested within a year, the average increase in processing speed index was 2.3 points. When 344 children eligible for special education were retested 2–3 years after the first testing, the processing scores instead decreased by 2.1 points [244]. This could mean that only typically developing children benefit from the test-retest effect, or it could instead indicate that the effect fades with time. The large increase in scores is not specific for the Wechsler processing speed tests. The National Institutes of Health Toolbox also includes a processing speed test, and when 537 participants from the normative sample were retested after a week the mean increase in processing speed was 5.5 scale scores (M10, SD 3), with age groups between 7 and 19 years increasing more than the average [246]. This illustrates the importance of being

familiar with the psychometric properties of a test when evaluating differences in performance between two assessments.

While there are obvious challenges with repeated assessments, research has shown that IQ has a tendency to decline in survivors of PBTs over time [44,247]. It is therefore necessary to include more than one assessment in the follow-up protocols in order to detect such a deterioration. Preferably, they should have at least 2–3 years between them. A shorter interval would make it harder to detect a stagnation or regression, and could allow for a potential practice effect to mask slighter deficits. Regarding the decline in IQ, King et al. [248] developed a neurodevelopmental model of cognitive long-term outcomes in survivors of PBTs. They found support for a model where processing speed was significantly associated with attention span and working memory. All three domains had unique relationships with IQ, but processing speed was concluded to be the central cognitive ability that disrupted other core cognitive skills (the Wechsler abbreviated scale of intelligence was used in this study, as this measure of IQ avoids timed measures and therefore limits the impact of processing speed measures). Reduced processing speed is especially common after radiotherapy, but survivors of ALL and PBTs who did not receive this treatment can also exhibit this deficit [35,38-40,50,63]. This, together with the results from studies I and III, supports the inclusion of processing speed tests in protocols, both at baseline and at follow-up.

The choice of instruments obviously relies on the included domains, but also on which survivors are assessed. The results from study III did not indicate the kinds of attention problems that the instrument CPT-3 was developed to identify [249]. A meta-analysis by de Ruiter et al. [250] on the neurocognitive consequences of paediatric brain tumours investigated studies where the CPT and CPT-2 had been administrated, and reported that the only variable where survivors performed worse than the norms was that they committed more errors of omission. In contrast to these results, the participants in study III did not differ from the norms regarding errors of omission. At the same time, 24% had impaired scores for hit reaction time – which was not found in the meta-analysis. While different versions of the CPT were used, it is also possible that these results are a consequence of a population-based sample (as opposed to the studies included in the meta-analysis, which looked at specific tumour pathologies). This test has a long administration time, and it could therefore be debated whether it is efficient to include in a screening protocol. The CPT-3 was developed to facilitate diagnosing of ADHD. As the prevalence of ADHD in patients with NF1 has been reported to be 40–50% [81,85], survivors with a neurocutaneous disorder might need different types of follow-ups compared to other survivors. Another group that might need a more extensive protocol is survivors treated with radiotherapy, as this treatment has been shown to increase the risk of both fatigue [124] and mental distress [95-98,100]. While it might be easy to criticise the exclusion of long-term memory in the contemporary follow-up protocol for survivors of PBTs, it must also be considered that there currently is a lack of such tests for the age group 13–16 years in Sweden (meaning

that there is either no Swedish translation at all, or a translation but no norms with satisfactory psychometric properties). This makes it difficult to demand an inclusion of that cognitive domain. Two areas that are easier to discuss are those of fatigue and depression.

Assessment of fatigue

While multidimensional fatigue scales facilitate the assessment of fatigue and make it easier for clinicians to distinguish between cognitive fatigue and depression, the cognitive deficits associated with cognitive fatigue must also be considered. If the instruments are too long and all-embracing, patients suffering from impaired working memory or reduced processing speed might have problems answering the questions, and the implementation of such questionnaires could therefore become counterproductive. Another important consideration is whether to use parent-proxy or self-report questionnaires. In the European guidelines for follow-up after PBTs the PedsQL™ MFS is included, but there is no recommendation regarding which version to implement [16]. Parents under-reporting children's fatigue is a phenomenon that has been demonstrated in several studies applying the MFS [158,236,251]. Considering the poor parent-child concordance in study II as well as previous studies utilising the MFS [158,235,236], the best solution ought to be to use both versions of the instruments. This is something that should be clarified in the protocols.

While studies II and III both clearly showed that cognitive fatigue was the most affected fatigue dimension, CRF is still a unidimensional diagnosis. Neuropsychologists might be more interested in cognitive fatigue, due to the natural connection to cognition, but the diagnostic criteria must be considered. As with fatigue, the concept of cognitive fatigue has been criticised for being used interchangeably to describe a symptom, a consequence, and a cause [252]. Hence, cognitive fatigue should only be used to express difficulties that are not included in or accounted for through more established models of explanation. Even though studies II and III are both in line with previous research demonstrating that fatigue consists of separate dimension, many of the deficits included in cognitive fatigue are better described by other diagnoses/disabilities.

Depression and anxiety

As seen in Table 5, survivors reported elevated symptoms of both depression and anxiety compared to both the control group and the national norms. Even though the study sample was too small to conduct a statistical analysis or draw any major conclusions from these results, other studies have reported similar numbers [95,253]. A CCSS publication on adolescent survivors reported that mental distress was present in as many as 31% of survivors of childhood cancer, with survivors treated with cranial radiotherapy being more affected than other survivors [96]. Other CCSS papers on

mental health in adolescent survivors have also reported treatment with cranial radiotherapy to be a risk factor [95]. The need for assessing mental health, depression, and anxiety has been highlighted regarding both clinical practice [14,17] and research [92]. Results from previous studies indicate that the risk of developing depression and anxiety is higher after the treatment has been completed [93], which makes this an issue for the follow-up protocols rather than at the ward.

How the assessment should be conducted is also a relevant issue. While a clinical interview by an experienced psychologist will be more precise than just self-rated symptoms, it is also far more time-consuming. A questionnaire will be more effective, and in a study by Liptak et al. [253] where BYI was administered to survivors of brain tumours, 90% reported no associated distress and 98% found the items easy to understand. However, agreement with clinician report was low and the authors concluded self-reports should not be used as a "stand-alone" assessment. Like fatigue scales, these symptoms can be evaluated with both self-rate and parent-proxy questionnaires, but the use of parent-proxy scales can be just as complicated when screening for mental distress as when screening for fatigue. A study on children and adolescents with cancer reported that elevated symptoms of depression/anxiety were twice as common in the self-reports as in the parent-proxy reports [237]. This is in line with previous research on the subject of parent-child concordance, which reported lower agreement for internalising than externalising problems [254]. It is possible that this phenomenon is generalisable to fatigue as well (which can be considered more of an internalising than externalising problem), and could thus explain that parents consistently scored fewer problems than the survivors in study II – even for the groups with acceptable ICC.

The Swedish National Board of Health and Welfare (Socialstyrelsen) documents the prevalence of psychiatric diagnoses in the population. In 2017, approximately 10 percent of citizens under the age of 18 (three times as many girls as boys) had received treatment through a psychiatric clinic (primary health care excluded), and the diagnosed cases of depression in children and adolescents had tripled since 2006 [255]. This does not automatically indicate that mental illness has increased, as it could be a consequence of more people seeking psychiatric help. A report from the Swedish Public Health Agency (Folkhälsomyndigheten) on health in the age group 11–15 years stated that self-rated psychological symptoms had doubled from 1985 to 2018. Twice as many girls as boys reported these symptoms. If children and adolescents in general are experiencing more psychological distress and are in need of treatment for depression, this will very likely affect survivors of childhood cancer as the reason for the increase in the general population will be relevant for this group as well. The gender differences in these two reports are especially interesting when considering that female gender has been found to be a risk factor for depression in survivors of childhood cancer [95,97-100]. The guidelines from the Swedish National Board of Health and Welfare recommend cognitive behavioural therapy (CBT) as first-line treatment for mild and

moderate depression in children and adolescents. Regarding anxiety disorders, CBT is recommended as first-line treatments for obsessive-compulsory disorder and post-traumatic stress disorder, while a combination of CBT and pharmacological treatment is recommended for social phobia, separation anxiety, and for generalised anxiety disorder [256]. Interventions based on CBT have also shown promise in reducing psychological distress in adolescent survivors of childhood cancer [257,258]. A few studies have also investigated how to tailor CBT and adapt it to the specific needs of this population [259,260]. These patients should hence be referred to the appropriate health care provider, but in order to do so they must be properly identified.

Management of cognitive fatigue

There are two reasons for assessing cognition and cognitive fatigue in survivors of childhood cancer, and for developing follow-up protocols for them. The first is for research, and the other for clinical management. The studies in this thesis were part of the *CogCan project*, and one purpose of that project was to identify those survivors in need of treatment and rehabilitative services. When identifying survivors with different types of long-term deficits, it is also important that there is a routine for managing these deficits within the health-care system. Merely researching the different types of sequelae is not enough for these survivors and the families; clinical implications and school liaisons must also be considered.

Clinical implications

The lack of established cut-off scores for research questionnaires is a problem that must be overcome before implementing such questionnaires in clinical practice. In study II, we decided to use the 10th percentile of the control group as a cut-off. If we had instead used the cut-off for "severe fatigue" utilised by van Deuren et al. [111], which is 2 SD below the mean of the healthy controls, the threshold for the MFS cognitive fatigue subscale would have been 46 instead of 55. This would have slightly changed the results, as 50% of the survivors of PBTs and 30% of the survivors of ALL would have scored below the cut-off. Hence, for survivors of ALL the same patients would have been considered suffering from cognitive fatigue. While clinical judgement is obviously more important than blindly looking at a cut-off score, there is hardly any point in asking the patients to fill out a questionnaire if you do not know what constitutes a "poor" result. Hence, this is something to consider when using an instrument in clinical practice. One solution could be to utilise two different cut-offs (like the BYI) and use the 10th percentile as the threshold for "fatigue" and the 2nd percentile (in a normal distribution, 2SD below the mean corresponds to percentile 2.28) for "severe fatigue".

As with the BYI, this would result in 3 groups where the scores correspond to either average, elevated, or very elevated symptoms.

Figure 6. Clinical management of long-term deficits in survivors of childhood cancers should not only focus on one type of symptoms, but rather on how they overlap, affect, and interact with each other.

The impact of fatigue on neurocognitive outcomes in adult survivors of childhood cancer has been reported to be independent of the effects of both cranial radiotherapy and chemotherapy [34]. Cognition in long-term survivors of childhood cancers therefore seems to be vulnerable to the effects of fatigue. Even though the potential impact of different treatment protocols is yet to be clarified [123,124], it is evident that these survivors should be carefully monitored. The relationship between cognitive fatigue, cognitive deficits, depressive symptoms, and sleep deprivation means that all four areas should be covered in a systematic neuropsychological assessment. This is illustrated in Figure 6. Not taking all of these into account when investigating the patients' symptoms means that a possible cause could easily be missed, potentially leading to incorrect treatment or insufficient educational adjustments.

A pharmacological treatment option might seem desirable, but the effectiveness of such therapies has not yet been established in children and adolescents. It is worth noting that methylphenidate has been reported to improve both cognitive fatigue and cognitive processing speed in adults [147,172]. However, exercise has been found to result in improvement in the same two areas, even though the improvement in processing speed is weaker than the improvement in fatigue [174,188,189]. Exercise

has not been proven to have an effect on sleep fatigue in children and adolescents [174], and this indicates that sleep problems ought to be monitored separately. Psychological interventions have been used to treat cognitive fatigue in adults [177,178], and CBT is commonly recommended as first-line treatment for insomnia in adults [261]. Only a limited number of studies have been conducted on children and adolescents, but the results show promising effects for this age group too [262]. The role of psychologists within paediatric oncology is therefore not limited to neuropsychological assessments.

Educational adjustments and school liaison programmes

The compulsory education in Sweden spans over 10 years, from the "pre-school class", year 0, until the end of year 9. However, while upper secondary education (which consists of an additional 3–4 years, depending on the programme) is voluntary, access to the job market almost always requires it [4]. Recent research has shown that survivors of PBTs are less likely than adolescents in general to make the transition to upper secondary education. While the 92% share of the general population is entitled to make this transition, only 76% of survivors of PBTs are able to do so [5]. This is a decrease from earlier studies. Boman et al. [7] reported that the corresponding numbers were 91.2% for the general population and 84.5% for survivors of CNS tumours in 2002. It is possible that this decrease was caused by the increase in survival rates [3], as it is likely that more impaired children are now surviving, but it can also be due to a change of grading system. The current grade system (used in years 6–9) has been criticised for requiring a high capacity for critical thinking and abstract reasoning [263], thus making it virtually impossible for children with low IQ to pass a subject regardless of how hard they study. As low IQ is a well-known long-term deficit in survivors of PBTs [38,39,42,52], they might have to look for other ways into the job market in order to earn their living and provide for themselves. However, as the first 10 years of school are compulsory, educational adjustments must be made for these survivors as far as it is feasible. The goal might not be to pass all subjects, but rather to learn as much as possible within their individual capacity and make the school days bearable. A thorough neuropsychological assessment, where the survivor's strengths and deficits are clarified and described, could serve as the decision basis for such adjustments. As there is currently no well-accepted treatment or evidence-based method for managing cognitive fatigue in children and adolescents, cooperation between the health care system and the schools is necessary when it comes to survivors of PBTs. School liaison programmes have been developed in Sweden in order to provide a structured and coordinated follow-up [30], but are currently not implemented in all regions. Cooperation between schools, hospitals, and parents has been reported to improve the educational progress in survivors of PBTs [28,29]. Even though there is some indication that fatigue can decrease with time after end of treatment for PBTs [124], full-scale IQ is at the same time known to decline over time in these survivors [44,247]. Therefore, this

cooperation must not be restricted to a single event, but continue as long as the survivors are attending school.

A study on family factors and academic achievement in survivors of PBTS reported that survivors from families with poorer family resources had lower school results, and that these associations remained after controlling for age at diagnosis, time since treatment, and type of treatment [264]. These results indicate that educational resources might not be sufficient to help these survivors, and that they might benefit from interventions to enhance family functioning.

Limitations

The three studies had different study designs, and therefore different weaknesses and limitations. Since study I was a register-based study, where data were collected from the patients' medical records retrospectively, the researchers had little control over test selection and data recorded. In addition to this, the percentage of patients with epilepsy in the study group was slightly higher than that in prior studies, which may have led to an overestimation of epilepsy as a risk factor for baseline cognitive impairment.

A minor limitation for study II was an overrepresentation of male participants amongst the survivors of ALL. More boys than girls are diagnosed, with a ratio of 1.1 for CNS tumours and 1.3 for ALL, which can be compared to the ratio being 1.05 in the general Swedish child population [1]. Previous Swedish studies have reported a higher incidence of males in both paediatric ALL and PBTs [238,265], but the sex distribution in this study was more skewed towards males for survivors of ALL than expected. However, in line with previous research [266] we found no gender differences regarding response patterns. It is therefore unlikely that the gender distribution affected the results. Of more pressing concern was the relatively small sample sizes, which were shared limitations in studies II and III, as the study cohorts were too small to allow for comparisons between treatment modalities. Since Sweden is a small country with 6 different childhood cancers centres, no individual hospital will have enough patients to investigate the impact of different types of treatment on fatigue as an outcome, even if all eligible survivors agree to participate. This sort of study will therefore have to be conducted as a multi-centre study. A larger sample would also enable research of the development of fatigue over time, since results from the 2- and 5-year follow-ups could be compared with each other.

The results from study III should also be interpreted in the light of the results from study II. In study II, we concluded that self-rate and parent-proxy versions of questionnaires cannot be used interchangeably and should be considered different types of information sources, with both adding valuable information from separate perspectives. While both versions were collected for all patients in study III, for practical

reasons we had to settle on using one of the two types for the statistical analysis. As concluded in study III, this obviously meant that some information might have been lost and there is a possibility that using the other version would have rendered different results.

Another possible limitation that must be considered for study III is that the structures of most neuropsychological tests are not random. Instead, they are frequently based on an increasing level of difficulty, where every item will be more complicated and challenging than the previous one. They are arranged this way so that test subjects with cognitive deficits will not have to face a large number of "impossible" tasks, and the better score a test subject gets the longer the test session will become. Möller et al. [142] discuss how this structure might punish people suffering from cognitive fatigue, as exhaustion – rather than a lack of understanding or skill – might be what stops them from reaching the more advanced items. At the same time, the one test where the participants in study III did not perform more poorly than the standardised norms was CPT-3. This test was administered last in every test session, where the survivors ought to have been most depleted. Hence, it is unlikely that this had an impact on group level, but it is something that should be taken into consideration with individual patients.

Conclusions

Systematic assessments of cognition, fatigue, and mental health in survivors of childhood cancer can serve two different purposes. One is to enable research on development over time and medical predictors of cognitive deficits. The other is to identify and help individual patients in need of treatment, rehabilitation, and educational adjustments or interventions. A uniform national protocol would not only enable multicentre studies, but also ensure equal care for all survivors, regardless of the centre to which they belong. When settling on follow-up protocols, there are 4 different aspects to consider: **who**, **when**, **what**, and **how**. Who should get these assessments, when should they be conducted, what areas/domains should be included, and how should they be measured?

The national Swedish care programme for long-term follow-up after childhood cancer recommends that neuropsychological assessments should be offered to survivors diagnosed with either PBTs or cancer diagnoses that required cranial radiotherapy and/or treatment with a chemotherapy known to cause cognitive sequelae [23]. These are almost identical to international recommendations, stating that survivors diagnosed with PTBs or having received CNS-directed therapies should be included in the protocols [239]. The results from the studies in this thesis support these recommendations, but results from previous research indicate that survivors with an additional diagnosis of NF1 might need a different protocol (focusing on the deficits associated with the aetiology).

As for when the assessments should be scheduled, this could require more flexibility. For research purposes, it is best if these assessments are conducted at the same intervals for all patients. However, as not all patients are diagnosed at the same age, the need for follow-ups due to school transitions might collide with a protocol that is too strict, and school liaisons are important to consider when planning these. In study III, a quarter of the survivors had been treated for relapse, and such an event will of course also have an impact on the interval. The protocol should not only focus on follow-up, but also on a baseline testing. These have a scientific purpose – as it improves the research on the impact of different types of treatments and other medical predictors – but they can also be seen as part of the survivor's individual care plan. While statistical methods such as proxy estimation or relative change [241] can contribute an estimated baseline for longitudinal studies, the individual patient will not benefit from them. A pre-treatment

assessment could help the survivors understand the changes they go through and how the sequalae affect them, but also provide information that is important when deciding on educational adjustments. In both study I and study III, we showed that pre-treatment assessments are feasible with the majority of patients. Regarding processing speed, the results from study I can also be re-evaluated in the light of Figure 4, which demonstrates that the two groups (radiated vs. non-radiated) differed from each other regarding the baseline mean for processing speed. In study I, we did not use treatment as a variable as we did not consider this to be a baseline variable. However, as seen in Figure 4, there is a striking difference between the two groups. While radiotherapy is well known to cause impairments in processing speed [38-40], this group was already more impaired before they had received that treatment. There must hence be an additional factor or previously unknown variable that contributes to this impairment. These results further demonstrate why baseline assessments are so important when researching longitudinal changes, as they implicate that the impact of radiotherapy might be smaller than previously assumed.

As for what domains to include, the results from studies II and III indicate that cognitive fatigue is the fatigue domain most affected in survivors. This is worrying, as cognitive fatigue has been reported to be frequently overlooked as a long-term sequela to paediatric cancer diagnosis and treatment [20,22]. A multidimensional instrument will include cognitive fatigue as well as other types of fatigue, and this is reasonable as previous research has shown that fatigue can be one of the most prevalent and distressing symptoms in childhood cancer survivors [20,267,268]. The results from studies II and III indicate that cognitive fatigue should not be assessed on its own, but that depressive symptoms and cognitive processing speed should be taken into account as well. This is in line with previous research, demonstrating an overlap between cognitive fatigue and both processing speed and depressive symptoms. The association between processing speed and cognitive fatigue had not been previously demonstrated in children and adolescents, but has been reported in several studies on adults [143,146,147,269]. Regarding depression, previous studies demonstrate that depression and cognitive fatigue are separate constructs [144,127], despite having overlapping symptoms. However, there is also a strong correlation between fatigue and depression [126-129], and depression is a strong predictor of fatigue in survivors of both childhood and adult cancer [130,131]. Even though there is much to indicate neuroinflammation and inflammatory cytokines as a probable cause of cognitive fatigue [105,115,160-163], the underlying mechanisms are complex and lifestyle factors cannot be ignored. Currently, there are not enough studies to conclude that exercise has the same positive effect on fatigue and depression in children and adolescents as in adults, but a strong causal association between physical activity and cognitive functioning has been reported [203]. Several neuropsychological studies on adult cancer survivors have also reported physical activity to be associated with better cognitive performance [182-186]. It is therefore reasonable to include lifestyle factors

as variables when assessing the impact of long-term sequelae in survivors of childhood cancers. The unpublished data from study II – presented in Table 5 – revealed that fewer survivors suffered from elevated symptoms of anxiety than depression, but the percentages scoring above the cut-offs were high enough to argue that anxiety should not be overlooked when assessing mental distress. The need to include both depression and anxiety in these assessments was also accentuated by the authors of a review on the psychiatric aspects of paediatric cancer [14].

How to measure the extent of potential sequelae is the final question. It has been suggested that fatigue should be based on the patient's experience [104]. Since this makes the impact and symptom severity individual and subjective, it is recommended to use self-reports for the assessment of fatigue in cancer patients [110,162]. For children and adolescents, there is additionally often a possibility to use parent-proxy reports. However, despite identical items and scales, a parent-proxy report is not automatically a replacement for a self-report. In study II, we reported a poor parent-child concordance as well as a tendency for parents to under-report the survivors' fatigue. Both phenomena have been demonstrated in previous studies using the MFS [158,235,236,251]. As the different versions hence cannot be used interchangeably, the best solution ought to be to use both and consider them as different sources of information.

Suggestions for future research

It is evident that there currently is a research gap regarding mental health – especially depression – in child and adolescent survivors of childhood cancer. This type of research is mostly conducted on adult long-term survivors and the results are therefore not necessarily relevant in a paediatric setting. More research is also needed concerning the treatment of such disorders, and how to adapt it to the specific needs of the patient group. While this was not the main focus of the thesis, the overlap between fatigue and depression means that research on depression in this group of survivors will add to the body of knowledge regarding fatigue. It is hence important to discuss these two topics in relation to each other, and consider the biopsychosocial model recommended by the National Cancer Institute as high-priority research [125].

Additionally, three important areas for future research were identified in studies I–III:

1) The relationship between baseline and long-term cognitive deficits requires further examination. One necessary step in order to do so is to implement pre-treatment neuropsychological testing in the research protocols.
2) Future studies should focus on finding medical predictors of fatigue in survivors of ALL, and investigate the effect of surgery, radiotherapy, and

chemotherapeutic agents, to further clarify the contribution of treatment modality to cognitive fatigue.

3) More research is needed regarding the development of fatigue over time, to see if it decreases or if there instead is a risk of increasing symptoms. Longitudinal studies are also necessary to uncover the biopsychosocial mechanism of CRF.

In order to enable the above, fatigue must be included in the follow-up protocols. If this research is to be conducted in Sweden, which has a large number of childhood cancer centres for its population, a uniform protocol must be agreed upon, and a database established for registering these variables.

Svensk sammanfattning

Begrepp

En del av introduktionen i denna avhandling och två av delstudierna kretsar kring begreppet *fatigue*. En direktöversättning från engelska skulle vara *trötthet*, men i medicinska sammanhang innebär fatigue en mer omfattande kraftlöshet och hastigare uttröttbarhet än vad man menar i vardagligt tal. Därför används som regel fatigue även på svenska inom sjukvården. På engelska skiljer man också mellan *fatigue* (den subjektiva upplevelsen) och *fatigability* (det som är objektivt mätbart). Svenskan saknar dock en motsvarighet till begreppet *fatigability*. Här används istället fatigue om både den subjektiva och objektiva definitionen. Det gör att man då måste förtydliga om man menar subjektiv eller objektiv fatigue för att undvika begreppsförvirring. Av de olika typer av fatigue som finns så är det framförallt den som kallas för *cognitive fatigue* eller *mental fatigue* som är av intresse ur ett neuropsykologiskt perspektiv. På svenska brukar det översättas med hjärntrötthet, mental trötthet eller kognitiv fatigue. Jag upplever att barn och ungdomar har lättare för att ta till sig uttrycket hjärntrötthet än de andra två, varpå det är detta jag använder i min kliniska vardag. I denna sammanfattning väljer jag dock att använda direktöversättningen kognitiv fatigue, för att det lättare ska gå att referera till de olika studierna.

Ett annat begrepp som skiljer sig åt mellan svenska och engelska är den baslinjemätning som gjordes i studie I. En sådan baslinjemätning kallas på svenska för preoperativ bedömning, även om behandlingen blir en annan än operation. På engelska kallas det istället *pretreatment assessment*, vilket förtydligar att det inkluderar alla typer av behandlingar.

Bakgrund

I takt med att allt fler överlever barncancer så ökar också kravet på omhändertagandet av överlevarna. En stor del av dessa får kognitiva seneffekter – i synnerhet de som har behandlats för en hjärntumör eller får en behandling som påverkar centrala nervsystemet. Dessa överlevare får svårigheter med kunskapsinhämtning och

pedagogisk utveckling och riskerar att inte kunna få en gymnasieexamen, vilket påverkar deras möjligheter att etablera sig på arbetsmarknaden och att försörja sig själva. Dessa seneffekter kräver ett samarbete mellan sjukvård och skola så att överlevarna ska kunna få pedagogiska anpassningar som underlättar deras skolgång. Som underlag för extra anpassningar och stöd behövs en neuropsykologisk utredning, som fastställer vilka styrkor och svagheter överlevarna har. De psykologiska uppföljningarna kan också fungera som ett sätt att fånga upp överlevare som lider av psykisk ohälsa, så att de kan erbjudas behandling för denna, och kan även användas vid forskning om olika typer av seneffeker. För att försäkra sig om att alla patienter får likvärdig vård och att forskningen får användbara variabler behöver dock de psykologiska uppföljningsprotokollen vara strukturerade och etablerade. I Sverige finns ett nationellt vårdprogram för långtidsuppföljning efter barncancer, men riktlinjerna för neuropsykologiska utredningar är där otillräckliga på flera punkter. Bland annat ingår varken psykisk ohälsa eller fatigue i riktlinjerna. Vissa barncanceröverlevare (i synnerhet de som har behandlats för hjärntumör eller har fått strålning mot hjärnan) har en ökad risk för både depression och kognitiv fatigue. Symptomöverlappningen mellan depression och kognitiv fatigue är stor, vilket gör att det differentialdiagnostiskt finns en risk för sammanblandning, samtidigt som depression också är en av de starkaste prediktorerna för fatigue. Det finns således stora risker med att bedöma fatigue utan att också ta psykisk ohälsa i beaktande.

Syfte med avhandlingen och delstudierna

Det övergripande syftet med denna avhandling var att bidra till arbetet med att etablera och förbättra strukturerade psykologiska uppföljningsprotokoll för barncanceröverlevare, vilket skulle gynna både det kliniska omhändertagandet av barncanceröverlevare och forskningen.

De tre ingående delstudierna var alla kvantitativa och data bearbetades statistiskt. Mycket av forskningen kring kognition och cancer kretsar kring seneffekter efter specifika behandlingar. För att kunna utvärdera detta behöver man dock veta vilken kognitiv nivå barnen och ungdomarna låg på innan behandlingen startade – den så kallade baslinjen. Väldigt lite forskning finns dock kring eventuell kognitiv påverkan vid diagnos. Syftet med studie I var därför att kartlägga om en sådan påverkan fanns innan patienterna påbörjade behandling för en hjärntumör. I studie II var syftet att undersöka prevalens av kognitiv fatigue hos barn och ungdomar som behandlats för hjärntumör respektive akut lymfatisk leukemi, samt överlappningen med symptom på depression. I denna delstudie utvärderades också de psykometriska egenskaperna för självskattningsformuläret *multidimensional fatigue scale* (MFS). I studie III var syftet att analysera sambandet mellan olika sorters fatigue och kognitiva nedsättningar hos barn och ungdomar som behandlats för hjärntumör. Medan både studie I och II var

tvärsnittsstudier så ingick även longitidunella data i studie III, där även den kognitiva utvecklingen sedan diagnos ingick i analysen.

Resultat

Resultaten från studie I visade att kognitiv funktion var relativt intakt vid den preoperativa bedömningen, men på gruppnivå var resultaten lägre än normgruppens för arbetsminne och processhastighet. Manligt kön, högre ålder, tumörstorlek, epilepsi och förhöjt intrakraniellt tryck predicerade lägre kognitiv funktion. Förklaringsvärdet för de flesta modeller var dock lågt. Däremot var en av slutsatserna från studien att preoperativa bedömningar är möjliga för majoriteten av patienter.

Resultaten från studie II var att en majoritet av de som behandlats för hjärntumör upplevde (subjektiv) kognitiv fatigue vid uppföljningen, och att även en del av de som behandlats för akut lymfatisk leukemi hade denna seneffekt. Symptom på depression var vanligt i båda grupperna, och förhöjda symptom på depression var också en prediktor för kognitiv fatigue. Typ av diagnos var dock en starkare prediktor. Vad gällde de psykometriska egenskaperna hos MFS så var intern reliabilitet tillfredsställande för alla delskalor utom en. Däremot var interbedömarreliabiliteten (samstämmigheten mellan föräldra- och barnskattningar) varierande. Genomgående så skattade föräldrarna också att barnen hade mindre svårigheter än vad barnen själva uppgav att de hade.

Resultaten från studie III var att kognitiv fatigue var den enda av delskalorna i MFS som hade en signifikant association med någon kognitiv domän, nämligen ett starkt samband med processhastighet. Även i denna studie hade en majoritet av deltagarna kunnat genomgå en preoperativ bedömning och förändringarna från den preoperativa bedömningen till uppföljningen ingick i en explorativ analys. De patienter som hade tappat mest i processhastighet efter att ha genomgått behandling för hjärntumör var också de som rapporterade mest kognitiv fatigue.

Slutsatser

Resultaten från studie I och III visar att en preoperativ neuropsykologisk bedömning är möjlig för de flesta patienter. Sådana preoperativa bedömningar är värdefulla när man ska undersöka eventuella kognitiva seneffekter och den kognitiva utvecklingen på sikt. Om fatigue ska ingå som ett område i uppföljningsprotokollet så rekommenderas ett multidimensionellt formulär, eftersom resultaten från studie II och III visar på stora skillnader mellan olika typer av fatigue. Det behöver också klargöras om det är föräldra- eller självskattningarna som ska användas, eftersom resultaten från dessa skiljer sig

mycket åt och de inte är utbytbara. Vad gäller kognitiv fatigue så kan detta inte screenas ensamt, utan överlappningen med både depressiva symptom och sänkt kognitiv processhastighet måste tas i beaktande.

References

1. Gustafsson, G., Kogner, P., & Heyman, M. (2013). Childhood cancer incidence and survival in Sweden 1984-2010, Report from the Swedish Childhood Cancer Registry.
2. Socialstyrelsen (2018). Cancer i siffror 2018.
3. Barncancerfonden (2019). Barncancerrapporten 2019.
4. Arbetsförmedlingen (2016). Perspektiv På Ungdomsarbetslösheten 2016.: Swedish Public Employment Service.
5. Lonnerblad, M., Van't Hooft, I., Blomgren, K., & Berglund, E. (2020). A nationwide, population-based study of school grades, delayed graduation, and qualification for school years 10-12, in children with brain tumors in Sweden. *Pediatr Blood Cancer, 67*(2), e28014, doi:10.1002/pbc.28014.
6. Holmqvist, A. S., Wiebe, T., Hjorth, L., Lindgren, A., Ora, I., & Moell, C. (2010). Young age at diagnosis is a risk factor for negative late socio-economic effects after acute lymphoblastic leukemia in childhood. *Pediatr Blood Cancer, 55*(4), 698-707, doi:10.1002/pbc.22670.
7. Boman, K. K., Lindblad, F., & Hjern, A. (2010). Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. *Cancer, 116*(5), 1385-1391, doi:10.1002/cncr.24840.
8. Lund, L. W., Schmiegelow, K., Rechnitzer, C., & Johansen, C. (2011). A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions. *Pediatr Blood Cancer, 56*(4), 532-543, doi:10.1002/pbc.22883.
9. Brinkman, T. M., Recklitis, C. J., Michel, G., Grootenhuis, M. A., & Klosky, J. L. (2018). Psychological Symptoms, Social Outcomes, Socioeconomic Attainment, and Health Behaviors Among Survivors of Childhood Cancer: Current State of the Literature. *J Clin Oncol, 36*(21), 2190-2197, doi:10.1200/JCO.2017.76.5552.
10. Kazak, A. E., & Noll, R. B. (2015). The integration of psychology in pediatric oncology research and practice: collaboration to improve care and outcomes for children and families. *Am Psychol, 70*(2), 146-158, doi:10.1037/a0035695.
11. Mavrides, N., & Pao, M. (2014). Updates in paediatric psycho-oncology. *Int Rev Psychiatry, 26*(1), 63-73, doi:10.3109/09540261.2013.870537.
12. Ris, M. D., Beebe, D. W., Armstrong, F. D., Fontanesi, J., Holmes, E., Sanford, R. A., et al. (2008). Cognitive and adaptive outcome in extracerebellar low-

grade brain tumors in children: a report from the Children's Oncology Group. *J Clin Oncol, 26*(29), 4765-4770, doi:10.1200/JCO.2008.17.1371.
13. Walsh, K. S., Noll, R. B., Annett, R. D., Patel, S. K., Patenaude, A. F., & Embry, L. (2016). Standard of Care for Neuropsychological Monitoring in Pediatric Neuro-Oncology: Lessons From the Children's Oncology Group (COG). *Pediatr Blood Cancer, 63*(2), 191-195, doi:10.1002/pbc.25759.
14. Kurtz, B. P., & Abrams, A. N. (2010). Psychiatric aspects of pediatric cancer. *Child Adolesc Psychiatr Clin N Am, 19*(2), 401-421, x-xi, doi:10.1016/j.chc.2010.01.009.
15. Limond, J., Thomas, S., Bull, K. S., Calaminus, G., Lemiere, J., Traunwieser, T., et al. (2020). Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years. *Eur J Paediatr Neurol, 25*, 59-67, doi:10.1016/j.ejpn.2019.10.002.
16. Limond, J. A., Bull, K. S., Calaminus, G., Kennedy, C. R., Spoudeas, H. A., Chevignard, M. P., et al. (2015). Quality of survival assessment in European childhood brain tumour trials, for children aged 5 years and over. *Eur J Paediatr Neurol, 19*(2), 202-210, doi:10.1016/j.ejpn.2014.12.003.
17. Kanellopoulos, A., Hamre, H. M., Dahl, A. A., Fossa, S. D., & Ruud, E. (2013). Factors associated with poor quality of life in survivors of childhood acute lymphoblastic leukemia and lymphoma. *Pediatr Blood Cancer, 60*(5), 849-855, doi:10.1002/pbc.24375.
18. Tomlinson, D., Hinds, P. S., Ethier, M. C., Ness, K. K., Zupanec, S., & Sung, L. (2013). Psychometric properties of instruments used to measure fatigue in children and adolescents with cancer: a systematic review. *J Pain Symptom Manage, 45*(1), 83-91, doi:10.1016/j.jpainsymman.2012.02.010.
19. Berger, A. M., Mitchell, S. A., Jacobsen, P. B., & Pirl, W. F. (2015). Screening, evaluation, and management of cancer-related fatigue: Ready for implementation to practice? *CA Cancer J Clin, 65*(3), 190-211, doi:10.3322/caac.21268.
20. Spathis, A., Booth, S., Grove, S., Hatcher, H., Kuhn, I., & Barclay, S. (2015). Teenage and Young Adult Cancer-Related Fatigue Is Prevalent, Distressing, and Neglected: It Is Time to Intervene. A Systematic Literature Review and Narrative Synthesis. *Journal of Adolescent and Young Adult Oncology, 4*(1), 3-17, doi:10.1089/jayao.2014.0023.
21. Meeske, K., Patel, S., Palmer, S. N., Nelson, M. B., & Parow, A. M. (2007). Factors associated with health-related quality of life in pediatric cancer survivors. *Pediatr Blood Cancer, 49*(3), 298-305, doi:10.1002/pbc.20923.
22. Walter, L. M., Nixon, G. M., Davey, M. J., Downie, P. A., & Horne, R. S. (2015). Sleep and fatigue in pediatric oncology: A review of the literature. *Sleep Med Rev, 24*, 71-82, doi:10.1016/j.smrv.2015.01.001.
23. Regionala Cancercentrum i Samverkan (2019). Långtidsuppföljning efter barncancer - nationellt vårdprogram. (2.1 ed.).
24. Liu, W., Cheung, Y. T., Conklin, H. M., Jacola, L. M., Srivastava, D., Nolan, V. G., et al. (2018). Evolution of neurocognitive function in long-term survivors

of childhood acute lymphoblastic leukemia treated with chemotherapy only. *J Cancer Surviv, 12*(3), 398-406, doi:10.1007/s11764-018-0679-7.
25. Tonning Olsson, I., Brinkman, T. M., Hyun, G., Banerjee, P., Mulrooney, D. A., Huang, I. C., et al. (2019). Neurocognitive outcomes in long-term survivors of Wilms tumor: a report from the St. Jude Lifetime Cohort. *J Cancer Surviv, 13*(4), 570-579, doi:10.1007/s11764-019-00776-8.
26. Tonning Olsson, I., Brinkman, T. M., Wang, M., Ehrhardt, M. J., Banerjee, P., Mulrooney, D. A., et al. (2020). Neurocognitive and psychosocial outcomes in adult survivors of childhood soft-tissue sarcoma: A report from the St. Jude Lifetime Cohort. *Cancer, 126*(7), 1576-1584, doi:10.1002/cncr.32694.
27. Brinkman, T. M., Merchant, T. E., Li, Z., Brennan, R., Wilson, M., Hoehn, M. E., et al. (2015). Cognitive function and social attainment in adult survivors of retinoblastoma: a report from the St. Jude Lifetime Cohort Study. *Cancer, 121*(1), 123-131, doi:10.1002/cncr.28924.
28. Bruce, B. S., Newcombe, J., & Chapman, A. (2012). School liaison program for children with brain tumors. *J Pediatr Oncol Nurs, 29*(1), 45-54, doi:10.1177/1043454211432296.
29. Northman, L., Ross, S., Morris, M., & Tarquini, S. (2015). Supporting pediatric cancer survivors with neurocognitive late effects: a model of care. *J Pediatr Oncol Nurs, 32*(3), 134-142, doi:10.1177/1043454214554012.
30. Van't Hooft, I., Lindahl Norberg, A., Bjorklund, A., Lonnerblad, M., & Stromberg, B. (2016). Multiprofessional follow-up programmes are needed to address psychosocial, neurocognitive and educational issues in children with brain tumours. *Acta Paediatr, 105*(6), 676-683, doi:10.1111/apa.13207.
31. Andersen, K. K., Duun-Henriksen, A. K., Frederiksen, M. H., & Winther, J. F. (2017). Ninth grade school performance in Danish childhood cancer survivors. *Br J Cancer, 116*(3), 398-404, doi:10.1038/bjc.2016.438.
32. Ahomaki, R., Harila-Saari, A., Matomaki, J., & Lahteenmaki, P. M. (2017). Non-graduation after comprehensive school, and early retirement but not unemployment are prominent in childhood cancer survivors-a Finnish registry-based study. *J Cancer Surviv, 11*(2), 284-294, doi:10.1007/s11764-016-0574-z.
33. Krull, K. R., Okcu, M. F., Potter, B., Jain, N., Dreyer, Z., Kamdar, K., et al. (2008). Screening for neurocognitive impairment in pediatric cancer long-term survivors. *J Clin Oncol, 26*(25), 4138-4143, doi:10.1200/JCO.2008.16.8864.
34. Clanton, N. R., Klosky, J. L., Li, C., Jain, N., Srivastava, D. K., Mulrooney, D., et al. (2011). Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer, 117*(11), 2559-2568, doi:10.1002/cncr.25797.
35. Kahalley, L. S., Conklin, H. M., Tyc, V. L., Hudson, M. M., Wilson, S. J., Wu, S., et al. (2013). Slower processing speed after treatment for pediatric brain tumor and acute lymphoblastic leukemia. *Psychooncology, 22*(9), 1979-1986, doi:10.1002/pon.3255.

36. Ellenberg, L., Liu, Q., Gioia, G., Yasui, Y., Packer, R. J., Mertens, A., et al. (2009). Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. *Neuropsychology, 23*(6), 705-717, doi:10.1037/a0016674.
37. Kahalley, L. S., Wilson, S. J., Tyc, V. L., Conklin, H. M., Hudson, M. M., Wu, S., et al. (2013). Are the psychological needs of adolescent survivors of pediatric cancer adequately identified and treated? *Psychooncology, 22*(2), 447-458, doi:10.1002/pon.3021.
38. Tonning Olsson, I., Perrin, S., Lundgren, J., Hjorth, L., & Johanson, A. (2014). Long-term cognitive sequelae after pediatric brain tumor related to medical risk factors, age, and sex. *Pediatr Neurol, 51*(4), 515-521, doi:10.1016/j.pediatrneurol.2014.06.011.
39. Brinkman, T. M., Krasin, M. J., Liu, W., Armstrong, G. T., Ojha, R. P., Sadighi, Z. S., et al. (2016). Long-Term Neurocognitive Functioning and Social Attainment in Adult Survivors of Pediatric CNS Tumors: Results From the St Jude Lifetime Cohort Study. *J Clin Oncol, 34*(12), 1358-1367, doi:10.1200/JCO.2015.62.2589.
40. Scantlebury, N., Bouffet, E., Laughlin, S., Strother, D., McConnell, D., Hukin, J., et al. (2016). White matter and information processing speed following treatment with cranial-spinal radiation for pediatric brain tumor. *Neuropsychology, 30*(4), 425-438, doi:10.1037/neu0000258.
41. Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., et al. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. *J Clin Oncol, 31*(28), 3494-3500, doi:10.1200/JCO.2012.47.4775.
42. Palmer, S. L., Gajjar, A., Reddick, W. E., Glass, J. O., Kun, L. E., Wu, S., et al. (2003). Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology, 17*(4), 548-555, doi:10.1037/0894-4105.17.4.548.
43. Mulhern, R. K., Palmer, S. L., Reddick, W. E., Glass, J. O., Kun, L. E., Taylor, J., et al. (2001). Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. *J Clin Oncol, 19*(2), 472-479, doi:10.1200/JCO.2001.19.2.472.
44. Ris, M. D., Walsh, K., Wallace, D., Armstrong, F. D., Holmes, E., Gajjar, A., et al. (2013). Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. *Pediatr Blood Cancer, 60*(8), 1350-1357, doi:10.1002/pbc.24496.
45. Anderson, V., Spencer-Smith, M., Leventer, R., Coleman, L., Anderson, P., Williams, J., et al. (2009). Childhood brain insult: can age at insult help us predict outcome? *Brain, 132*(Pt 1), 45-56, doi:10.1093/brain/awn293.
46. Armstrong, G. T., Reddick, W. E., Petersen, R. C., Santucci, A., Zhang, N., Srivastava, D., et al. (2013). Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with

cranial radiotherapy. *J Natl Cancer Inst, 105*(12), 899-907, doi:10.1093/jnci/djt089.
47. Krull, K. R., Brinkman, T. M., Li, C., Armstrong, G. T., Ness, K. K., Srivastava, D. K., et al. (2013). Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. *J Clin Oncol, 31*(35), 4407-4415, doi:10.1200/JCO.2012.48.2315.
48. Peterson, C. C., Johnson, C. E., Ramirez, L. Y., Huestis, S., Pai, A. L., Demaree, H. A., et al. (2008). A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer, 51*(1), 99-104, doi:10.1002/pbc.21544.
49. Cheung, Y. T., & Krull, K. R. (2015). Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. *Neuroscience and Biobehavioral Reviews, 53*, 108-120, doi:10.1016/j.neubiorev.2015.03.016.
50. Schatz, J., Kramer, J. H., Ablin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: a developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14*(2), 189-200, doi:10.1037//0894-4105.14.2.189.
51. Palmer, S. L. (2008). Neurodevelopmental impact on children treated for medulloblastoma: a review and proposed conceptual model. *Developmental Disabilities Research Reviews, 14*(3), 203-210, doi:10.1002/ddrr.32.
52. Ehrstedt, C., Kristiansen, I., Ahlsten, G., Casar-Borota, O., Dahl, M., Libard, S., et al. (2016). Clinical characteristics and late effects in CNS tumours of childhood: Do not forget long term follow-up of the low grade tumours. *Eur J Paediatr Neurol, 20*(4), 580-587, doi:10.1016/j.ejpn.2016.04.009.
53. Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition*. San Antonio, TX: NCS Pearson.
54. Wechsler, D. (2014). *Wechsler intelligence scale for children–Fifth Edition (WISC-V)*. Bloomington, MN: Pearson.
55. Wechsler, D. (2012). *Wechsler preschool and primary scale of intelligence—fourth edition* (The Psychological Corporation). San Antonio, TX: The Psychological Corporation
56. Wechsler, D. (2008). *WAIS-IV Technical and Interpretive manual*. San Antonio, TX: Psychological Corporation.
57. Wechsler, D. (2013). *WISC-V Technical and Interpretive Manual*. Bloomington, MN: PsychCorp.
58. Turken, A., Whitfield-Gabrieli, S., Bammer, R., Baldo, J. V., Dronkers, N. F., & Gabrieli, J. D. (2008). Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *Neuroimage, 42*(2), 1032-1044, doi:10.1016/j.neuroimage.2008.03.057.
59. Penke, L., Munoz Maniega, S., Murray, C., Gow, A. J., Hernandez, M. C., Clayden, J. D., et al. (2010). A general factor of brain white matter integrity

predicts information processing speed in healthy older people. *J Neurosci, 30*(22), 7569-7574, doi:10.1523/JNEUROSCI.1553-10.2010.
60. Magistro, D., Takeuchi, H., Nejad, K. K., Taki, Y., Sekiguchi, A., Nouchi, R., et al. (2015). The relationship between processing speed and regional white matter volume in healthy young people. *PloS one, 10*(9), e0136386.
61. Kuznetsova, K. A., Maniega, S. M., Ritchie, S. J., Cox, S. R., Storkey, A. J., Starr, J. M., et al. (2016). Brain white matter structure and information processing speed in healthy older age. *Brain Struct Funct, 221*(6), 3223-3235, doi:10.1007/s00429-015-1097-5.
62. Reddick, W. E., Glass, J. O., Palmer, S. L., Wu, S., Gajjar, A., Langston, J. W., et al. (2005). Atypical white matter volume development in children following craniospinal irradiation. *Neuro Oncol, 7*(1), 12-19, doi:10.1215/S1152851704000079.
63. Campbell, L. K., Scaduto, M., Sharp, W., Dufton, L., Van Slyke, D., Whitlock, J. A., et al. (2007). A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer, 49*(1), 65-73, doi:10.1002/pbc.20860.
64. Bonner, M. J., Hardy, K. K., Willard, V. W., & Gururangan, S. (2009). Additional Evidence of a Nonverbal Learning Disability in Survivors of Pediatric Brain Tumors. *Children's Health Care, 38*(1), 49-63, doi:10.1080/02739610802615849.
65. Lonnerblad, M., Lovio, R., Berglund, E., & Van't Hooft, I. (2017). Affected Aspects Regarding Literacy and Numeracy in Children Treated for Brain Tumors. *J Pediatr Oncol Nurs, 34*(6), 397-405, doi:10.1177/1043454217717237.
66. Brière, M., Scott, J. G., McKnall-Knapp, R. Y., & Adams, R. L. (2008). Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. *Pediatric Blood & Cancer, 50*(2), 337-340.
67. Cheung, Y. T., Sabin, N. D., Reddick, W. E., Bhojwani, D., Liu, W., Brinkman, T. M., et al. (2016). Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: a longitudinal analysis. *The Lancet Haematology, 3*(10), e456-e466, doi:10.1016/S2352-3026(16)30110-7.
68. Schulte, F., Brinkman, T. M., Li, C., Fay-McClymont, T., Srivastava, D. K., Ness, K. K., et al. (2018). Social adjustment in adolescent survivors of pediatric central nervous system tumors: A report from the Childhood Cancer Survivor Study. *Cancer, 124*(17), 3596-3608, doi:10.1002/cncr.31593.
69. Hocking, M. C., McCurdy, M., Turner, E., Kazak, A. E., Noll, R. B., Phillips, P., et al. (2015). Social competence in pediatric brain tumor survivors: application of a model from social neuroscience and developmental psychology. *Pediatr Blood Cancer, 62*(3), 375-384, doi:10.1002/pbc.25300.
70. Hocking, M. C., Parish-Morris, J., Schultz, R. T., Minturn, J. E., Brodsky, C., Shabason, E. K., et al. (2020). Diminished social attention in pediatric brain

tumor survivors: Using eye tracking technology during naturalistic social perception. *Neuropsychology*.
71. Desjardins, L., Solomon, A., Janzen, L., Bartels, U., Schulte, F., Chung, J., et al. (2020). Executive functions and social skills in pediatric brain tumor survivors. *Applied neuropsychology: Child, 9*(1), 83-91, doi:10.1080/21622965.2018.1522589.
72. Wolfe, K. R., Walsh, K. S., Reynolds, N. C., Mitchell, F., Reddy, A. T., Paltin, I., et al. (2013). Executive functions and social skills in survivors of pediatric brain tumor. *Child Neuropsychol, 19*(4), 370-384, doi:10.1080/09297049.2012.669470.
73. de Ruiter, M. A., Schouten-van Meeteren, A. Y. N., van Vuurden, D. G., Maurice-Stam, H., Gidding, C., Beek, L. R., et al. (2016). Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints. *Qual Life Res, 25*(2), 435-446, doi:10.1007/s11136-015-1091-7.
74. Holland, A. A., Colaluca, B., Bailey, L., & Stavinoha, P. L. (2018). Impact of attention on social functioning in pediatric medulloblastoma survivors. *Pediatr Hematol Oncol, 35*(1), 76-89, doi:10.1080/08880018.2018.1440333.
75. Moyer, K. H., Willard, V. W., Gross, A. M., Netson, K. L., Ashford, J. M., Kahalley, L. S., et al. (2012). The impact of attention on social functioning in survivors of pediatric acute lymphoblastic leukemia and brain tumors. *Pediatr Blood Cancer, 59*(7), 1290-1295, doi:10.1002/pbc.24256.
76. Patel, S. K., Lai-Yates, J. J., Anderson, J. W., & Katz, E. R. (2007). Attention dysfunction and parent reporting in children with brain tumors. *Pediatr Blood Cancer, 49*(7), 970-974, doi:10.1002/pbc.21151.
77. Bonner, M. J., Hardy, K. K., Willard, V. W., Anthony, K. K., Hood, M., & Gururangan, S. (2008). Social functioning and facial expression recognition in survivors of pediatric brain tumors. *J Pediatr Psychol, 33*(10), 1142-1152, doi:10.1093/jpepsy/jsn035.
78. Willard, V. W., Hardy, K. K., & Bonner, M. J. (2009). Gender differences in facial expression recognition in survivors of pediatric brain tumors. *Psychooncology, 18*(8), 893-897, doi:10.1002/pon.1502.
79. Salley, C. G., Gerhardt, C. A., Fairclough, D. L., Patenaude, A. F., Kupst, M. J., Barrera, M., et al. (2014). Social self-perception among pediatric brain tumor survivors compared with peers. *J Dev Behav Pediatr, 35*(7), 427-434, doi:10.1097/DBP.0000000000000077.
80. Ehrhardt, M. J., Mulrooney, D. A., Li, C., Baassiri, M. J., Bjornard, K., Sandlund, J. T., et al. (2018). Neurocognitive, psychosocial, and quality-of-life outcomes in adult survivors of childhood non-Hodgkin lymphoma. *Cancer, 124*(2), 417-425, doi:10.1002/cncr.31019.
81. Hyman, S. L., Shores, A., & North, K. N. (2005). The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology, 65*(7), 1037-1044, doi:10.1212/01.wnl.0000179303.72345.ce.
82. Jacobson, L. A., Mahone, E. M., Yeates, K. O., & Ris, M. D. (2019). Processing speed in children treated for brain tumors: effects of radiation therapy and

age. *Child Neuropsychol, 25*(2), 217-231, doi:10.1080/09297049.2018.1456517.
83. Raghubar, K. P., Rothhaar, M. C., Yeates, K. O., Mahone, E. M., Grosshans, D. R., Scheurer, M. E., et al. (2019). Premorbid functioning as a predictor of outcome in pediatric brain tumor: An initial examination of the normalcy assumption. *Pediatric Blood & Cancer*, e28135.
84. Schwetye, K. E., & Gutmann, D. H. (2014). Cognitive and behavioral problems in children with neurofibromatosis type 1: challenges and future directions. *Expert Rev Neurother, 14*(10), 1139-1152, doi:10.1586/14737175.2014.953931.
85. Torres Nupan, M. M., Velez Van Meerbeke, A., Lopez Cabra, C. A., & Herrera Gomez, P. M. (2017). Cognitive and Behavioral Disorders in Children with Neurofibromatosis Type 1. [Review]. *Frontiers in Pediatrics, 5*(227), 227, doi:10.3389/fped.2017.00227.
86. Huijbregts, S., Swaab, H., & de Sonneville, L. (2010). Cognitive and motor control in neurofibromatosis type I: influence of maturation and hyperactivity-inattention. *Dev Neuropsychol, 35*(6), 737-751, doi:10.1080/87565641.2010.508670.
87. Payne, J. M., Arnold, S. S., Pride, N. A., & North, K. N. (2012). Does attention-deficit–hyperactivity disorder exacerbate executive dysfunction in children with neurofibromatosis type 1? *Developmental Medicine & Child Neurology, 54*(10), 898-904.
88. Lehtonen, A., Garg, S., Roberts, S. A., Trump, D., Evans, D. G., Green, J., et al. (2015). Cognition in children with neurofibromatosis type 1: data from a population-based study. *Dev Med Child Neurol, 57*(7), 645-651, doi:10.1111/dmcn.12734.
89. Champion, J. A., Rose, K. J., Payne, J. M., Burns, J., & North, K. N. (2014). Relationship between cognitive dysfunction, gait, and motor impairment in children and adolescents with neurofibromatosis type 1. *Developmental Medicine & Child Neurology, 56*(5), 468-474.
90. Ottenhoff, M. J., Rietman, A. B., Mous, S. E., Plasschaert, E., Gawehns, D., Brems, H., et al. (2020). Examination of the genetic factors underlying the cognitive variability associated with neurofibromatosis type 1. *Genet Med*, doi:10.1038/s41436-020-0752-2.
91. Dejong, M., & Fombonne, E. (2006). Depression in paediatric cancer: an overview. *Psychooncology, 15*(7), 553-566, doi:10.1002/pon.1002.
92. Mertens, A. C., & Gilleland Marchak, J. (2015). Mental health status of adolescent cancer survivors. *Clinical Oncology in Adolescents and Young Adults, 2015*, 87-95.
93. von Essen, L., Enskar, K., Kreuger, A., Larsson, B., & Sjoden, P. O. (2000). Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment. *Acta Paediatr, 89*(2), 229-236, doi:10.1080/080352500750028889.
94. Hedstrom, M., Kreuger, A., Ljungman, G., Nygren, P., & von Essen, L. (2006). Accuracy of assessment of distress, anxiety, and depression by physicians and

nurses in adolescents recently diagnosed with cancer. *Pediatr Blood Cancer, 46*(7), 773-779, doi:10.1002/pbc.20693.
95. Schultz, K. A., Ness, K. K., Whitton, J., Recklitis, C., Zebrack, B., Robison, L. L., et al. (2007). Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol, 25*(24), 3649-3656, doi:10.1200/JCO.2006.09.2486.
96. Brinkman, T. M., Li, C., Vannatta, K., Marchak, J. G., Lai, J. S., Prasad, P. K., et al. (2016). Behavioral, Social, and Emotional Symptom Comorbidities and Profiles in Adolescent Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol, 34*(28), 3417-3425, doi:10.1200/JCO.2016.66.4789.
97. Zeltzer, L. K., Lu, Q., Leisenring, W., Tsao, J. C., Recklitis, C., Armstrong, G., et al. (2008). Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev, 17*(2), 435-446, doi:10.1158/1055-9965.EPI-07-2541.
98. Zeltzer, L. K., Recklitis, C., Buchbinder, D., Zebrack, B., Casillas, J., Tsao, J. C., et al. (2009). Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol, 27*(14), 2396-2404, doi:10.1200/JCO.2008.21.1433.
99. Zebrack, B. J., Gurney, J. G., Oeffinger, K., Whitton, J., Packer, R. J., Mertens, A., et al. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol, 22*(6), 999-1006, doi:10.1200/JCO.2004.06.148.
100. Shah, S. S., Dellarole, A., Peterson, E. C., Bregy, A., Komotar, R., Harvey, P. D., et al. (2015). Long-term psychiatric outcomes in pediatric brain tumor survivors. *Childs Nerv Syst, 31*(5), 653-663, doi:10.1007/s00381-015-2669-7.
101. Gunnes, M. W., Lie, R. T., Bjørge, T., Ghaderi, S., Syse, A., Ruud, E., et al. (2017). Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood—a national cohort study. *International journal of cancer, 140*(3), 575-580.
102. Recklitis, C. J., Diller, L. R., Li, X., Najita, J., Robison, L. L., & Zeltzer, L. (2010). Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 28*(4), 655.
103. Dittner, A. J., Wessely, S. C., & Brown, R. G. (2004). The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res, 56*(2), 157-170, doi:10.1016/S0022-3999(03)00371-4.
104. Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology, 80*(4), 409-416, doi:10.1212/WNL.0b013e31827f07be.
105. Wylie, G. R., & Flashman, L. A. (2017). Understanding the interplay between mild traumatic brain injury and cognitive fatigue: models and treatments. *Concussion, 2*(4), CNC50, doi:10.2217/cnc-2017-0003.

106. de Raaf, P. J., de Klerk, C., & van der Rijt, C. C. (2013). Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature. *Psychooncology, 22*(9), 1919-1929, doi:10.1002/pon.3225.
107. Centers for Disease Control and Prevention (2020). International Classification of Diseases, Tenth revision, Clinical Modification (ICD-10 CM).
108. Donovan, K. A., McGinty, H. L., & Jacobsen, P. B. (2013). A systematic review of research using the diagnostic criteria for cancer-related fatigue. *Psycho-Oncology, 22*(4), 737-744.
109. Kuhnt, S., Friedrich, M., Schulte, T., Cella, D., & Hinz, A. (2019). Screening Properties of the Diagnostic Criteria for Cancer-Related Fatigue. *Oncology research and treatment, 42*(9), 440-447.
110. Berger, A. M., Mooney, K., Alvarez-Perez, A., Breitbart, W. S., Carpenter, K. M., Cella, D., et al. (2015). Cancer-Related Fatigue, Version 2.2015. *J Natl Compr Canc Netw, 13*(8), 1012-1039, doi:10.6004/jnccn.2015.0122.
111. van Deuren, S., Boonstra, A., van Dulmen-den Broeder, E., Blijlevens, N., Knoop, H., & Loonen, J. (2020). Severe fatigue after treatment for childhood cancer. *Cochrane Database Syst Rev, 3*, CD012681, doi:10.1002/14651858.CD012681.pub2.
112. Bower, J. E., Ganz, P. A., Desmond, K. A., Bernaards, C., Rowland, J. H., Meyerowitz, B. E., et al. (2006). Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer, 106*(4), 751-758, doi:10.1002/cncr.21671.
113. Nowe, E., Friedrich, M., Leuteritz, K., Sender, A., Stobel-Richter, Y., Schulte, T., et al. (2019). Cancer-Related Fatigue and Associated Factors in Young Adult Cancer Patients. *Journal of Adolescent and Young Adult Oncology, 8*(3), 297-303, doi:10.1089/jayao.2018.0091.
114. Xiao, C., Miller, A. H., Felger, J., Mister, D., Liu, T., & Torres, M. A. (2017). Depressive symptoms and inflammation are independent risk factors of fatigue in breast cancer survivors. *Psychol Med, 47*(10), 1733-1743, doi:10.1017/S0033291717000150.
115. Schubert, C., Hong, S., Natarajan, L., Mills, P. J., & Dimsdale, J. E. (2007). The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun, 21*(4), 413-427, doi:10.1016/j.bbi.2006.11.004.
116. Bower, J. E. (2014). Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol, 11*(10), 597-609, doi:10.1038/nrclinonc.2014.127.
117. Cheung, Y. T., Brinkman, T. M., Mulrooney, D. A., Mzayek, Y., Liu, W., Banerjee, P., et al. (2017). Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *Cancer, 123*(17), 3410-3419, doi:10.1002/cncr.30742.
118. Person, H., Guillemin, F., Conroy, T., Velten, M., & Rotonda, C. (2020). Factors of the evolution of fatigue dimensions in patients with breast cancer

during the 2 years after surgery. *International Journal of Cancer, 146*(7), 1827-1835.
119. Donovan, K. A., Jacobsen, P. B., Andrykowski, M. A., Winters, E. M., Balducci, L., Malik, U., et al. (2004). Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *Journal of pain and symptom management, 28*(4), 373-380.
120. Dhruva, A., Dodd, M., Paul, S. M., Cooper, B. A., Lee, K., West, C., et al. (2010). Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. *Cancer nursing, 33*(3), 201.
121. Geinitz, H., Zimmermann, F. B., Thamm, R., Keller, M., Busch, R., & Molls, M. (2004). Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. *J Cancer Res Clin Oncol, 130*(6), 327-333, doi:10.1007/s00432-003-0540-9.
122. Schmidt, M. E., Wiskemann, J., Schneeweiss, A., Potthoff, K., Ulrich, C. M., & Steindorf, K. (2018). Determinants of physical, affective, and cognitive fatigue during breast cancer therapy and 12 months follow-up. *Int J Cancer, 142*(6), 1148-1157, doi:10.1002/ijc.31138.
123. Zeller, B., Loge, J. H., Kanellopoulos, A., Hamre, H., Wyller, V. B., & Ruud, E. (2014). Chronic fatigue in long-term survivors of childhood lymphomas and leukemia: persistence and associated clinical factors. *J Pediatr Hematol Oncol, 36*(6), 438-444, doi:10.1097/MPH.0000000000000051.
124. Puhr, A., Ruud, E., Anderson, V., Due-Tonnesen, B. J., Skarbo, A. B., Finset, A., et al. (2019). Self-Reported Executive Dysfunction, Fatigue, and Psychological and Emotional Symptoms in Physically Well-Functioning Long-Term Survivors of Pediatric Brain Tumor. *Dev Neuropsychol, 44*(1), 88-103, doi:10.1080/87565641.2018.1540007.
125. Barsevick, A. M., Irwin, M. R., Hinds, P., Miller, A., Berger, A., Jacobsen, P., et al. (2013). Recommendations for high-priority research on cancer-related fatigue in children and adults. *Journal of the National Cancer Institute, 105*(19), 1432-1440, doi:10.1093/jnci/djt242.
126. Meeske, K., Siegel, S., Globe, D., Mack, W., & Bernstein, L. (2005). Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *J Clin Oncol, 23*(24), 5501-5510, doi:10.1200/JCO.2005.03.210.
127. Whitsett, S. F., Gudmundsdottir, M., Davies, B., McCarthy, P., & Friedman, D. (2008). Chemotherapy-related fatigue in childhood cancer: correlates, consequences, and coping strategies. *J Pediatr Oncol Nurs, 25*(2), 86-96, doi:10.1177/1043454208315546.
128. Gordijn, M. S., van Litsenburg, R. R., Gemke, R. J., Huisman, J., Bierings, M. B., Hoogerbrugge, P. M., et al. (2013). Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer, 60*(3), 479-485, doi:10.1002/pbc.24261.
129. Langeveld, N. E., Grootenhuis, M. A., Voute, P. A., de Haan, R. J., & van den Bos, C. (2003). No excess fatigue in young adult survivors of childhood cancer. *Eur J Cancer, 39*(2), 204-214, doi:10.1016/s0959-8049(02)00629-9.

130. Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol, 18*(4), 743-753, doi:10.1200/JCO.2000.18.4.743.
131. Mulrooney, D. A., Ness, K. K., Neglia, J. P., Whitton, J. A., Green, D. M., Zeltzer, L. K., et al. (2008). Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). *Sleep, 31*(2), 271-281, doi:10.1093/sleep/31.2.271.
132. Organization, W. H. (1993). *The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research* (Vol. 2): World Health Organization.
133. Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.
134. Johansson, B., & Ronnback, L. (2014). Long-Lasting Mental Fatigue After Traumatic Brain Injury – A Major Problem Most Often Neglected Diagnostic Criteria, Assessment, Relation to Emotional and Cognitive Problems, Cellular Background, and Aspects on Treatment. In F. Sadaka (Ed.), *Traumatic Brain Injury*. Rijeka: InTech.
135. Shah, A. (2009). Fatigue in multiple sclerosis. *Phys Med Rehabil Clin N Am, 20*(2), 363-372, doi:10.1016/j.pmr.2008.12.003.
136. Friedman, J. H., Brown, R. G., Comella, C., Garber, C. E., Krupp, L. B., Lou, J. S., et al. (2007). Fatigue in Parkinson's disease: a review. *Mov Disord, 22*(3), 297-308, doi:10.1002/mds.21240.
137. Huang, C. Y., Daniels, R., Lembo, A., Hartog, C., O'Brien, J., Heymann, T., et al. (2019). Life after sepsis: an international survey of survivors to understand the post-sepsis syndrome. *Int J Qual Health Care, 31*(3), 191-198, doi:10.1093/intqhc/mzy137.
138. Goretti, B., Portaccio, E., Ghezzi, A., Lori, S., Moiola, L., Falautano, M., et al. (2012). Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis. *Mult Scler, 18*(3), 329-334, doi:10.1177/1352458511420846.
139. de Kloet, A. J., Lambregts, S. A., Berger, M. A., van Markus, F., Wolterbeek, R., & Vliet Vlieland, T. P. (2015). Family impact of acquired brain injury in children and youth. *J Dev Behav Pediatr, 36*(5), 342-351, doi:10.1097/DBP.0000000000000169.
140. Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *Lancet, 363*(9413), 978-988, doi:10.1016/S0140-6736(04)15794-2.
141. Moller, M. C., Nordin, L. E., Bartfai, A., Julin, P., & Li, T. Q. (2017). Fatigue and Cognitive Fatigability in Mild Traumatic Brain Injury are Correlated with Altered Neural Activity during Vigilance Test Performance. *Front Neurol, 8*(496), 496, doi:10.3389/fneur.2017.00496.
142. Moller, M. C., Nygren de Boussard, C., Oldenburg, C., & Bartfai, A. (2014). An investigation of attention, executive, and psychomotor aspects of cognitive fatigability. *J Clin Exp Neuropsychol, 36*(7), 716-729, doi:10.1080/13803395.2014.933779.

143. Johansson, B., Berglund, P., & Ronnback, L. (2009). Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Inj, 23*(13-14), 1027-1040, doi:10.3109/02699050903421099.
144. Johansson, B., & Ronnback, L. (2014). Evaluation of the mental fatigue scale and its relation to cognitive and emotional functioning after traumatic brain injury or stroke. *International Journal of Physical Medicine & Rehabilitation, 2*(182).
145. Johansson, B., Starmark, A., Berglund, P., Rodholm, M., & Ronnback, L. (2010). A self-assessment questionnaire for mental fatigue and related symptoms after neurological disorders and injuries. *Brain Inj, 24*(1), 2-12, doi:10.3109/02699050903452961.
146. Jonasson, A., Levin, C., Renfors, M., Strandberg, S., & Johansson, B. (2018). Mental fatigue and impaired cognitive function after an acquired brain injury. *Brain and Behaviour, 8*(8), e01056, doi:10.1002/brb3.1056.
147. Johansson, B., Wentzel, A. P., Andrell, P., Mannheimer, C., & Ronnback, L. (2015). Methylphenidate reduces mental fatigue and improves processing speed in persons suffered a traumatic brain injury. *Brain Inj, 29*(6), 758-765, doi:10.3109/02699052.2015.1004747.
148. van der Linden, D., Frese, M., & Meijman, T. F. (2003). Mental fatigue and the control of cognitive processes: effects on perseveration and planning. *Acta Psychol (Amst), 113*(1), 45-65, doi:10.1016/s0001-6918(02)00150-6.
149. Boksem, M. A., Meijman, T. F., & Lorist, M. M. (2005). Effects of mental fatigue on attention: an ERP study. *Brain Res Cogn Brain Res, 25*(1), 107-116, doi:10.1016/j.cogbrainres.2005.04.011.
150. Faber, L. G., Maurits, N. M., & Lorist, M. M. (2012). Mental fatigue affects visual selective attention. *PLoS One, 7*(10), e48073, doi:10.1371/journal.pone.0048073.
151. Lindqvist, G., & Malmgren, H. (1993). Organic mental disorders as hypothetical pathogenetic processes. *Acta Psychiatr Scand Suppl, 373*(S373), 5-17, doi:10.1111/j.1600-0447.1993.tb05611.x.
152. Lorist, M. M., Klein, M., Nieuwenhuis, S., De Jong, R., Mulder, G., & Meijman, T. F. (2000). Mental fatigue and task control: planning and preparation. *Psychophysiology, 37*(5), 614-625, doi:10.1111/1469-8986.3750614.
153. Wirz-Justice, A. (2008). Diurnal variation of depressive symptoms. *Dialogues in clinical neuroscience, 10*(3), 337-343.
154. Courtet, P., & Olié, E. (2012). Circadian dimension and severity of depression. *Eur Neuropsychopharmacol, 22 Suppl 3*, S476-481, doi:10.1016/j.euroneuro.2012.07.009.
155. Germain, A., & Kupfer, D. J. (2008). Circadian rhythm disturbances in depression. *Human psychopharmacology, 23*(7), 571-585, doi:10.1002/hup.964.
156. Wilkinson, J., Marmol, N. L., Godfrey, C., Wills, H., van Eijndhoven, Q., Botchway, E. N., et al. (2018). Fatigue following Paediatric Acquired Brain

Injury and its Impact on Functional Outcomes: A Systematic Review. *Neuropsychol Rev, 28*(1), 73-87, doi:10.1007/s11065-018-9370-z.
157. Crichton, A., Oakley, E., Babl, F. E., Greenham, M., Hearps, S., Delzoppo, C., et al. (2018). Predicting Fatigue 12 Months after Child Traumatic Brain Injury: Child Factors and Postinjury Symptoms. *J Int Neuropsychol Soc, 24*(3), 224-236, doi:10.1017/S1355617717000893.
158. Crichton, A., Babl, F., Oakley, E., Greenham, M., Hearps, S., Delzoppo, C., et al. (2017). Prediction of Multidimensional Fatigue After Childhood Brain Injury. *J Head Trauma Rehabil, 32*(2), 107-116, doi:10.1097/HTR.0000000000000248.
159. van Markus-Doornbosch, F., de Kloet, A. J., Berger, M. A., Lambregts, S. A., Wolterbeek, R., & Vliet Vlieland, T. P. (2016). Factors related to fatigue after paediatric acquired brain injury (ABI). *Brain Inj, 30*(13-14), 1533-1541, doi:10.1080/02699052.2016.1197968.
160. Ronnback, L., & Hansson, E. (2004). On the potential role of glutamate transport in mental fatigue. *J Neuroinflammation, 1*(1), 22, doi:10.1186/1742-2094-1-22.
161. Schousboe, A., Scafidi, S., Bak, L. K., Waagepetersen, H. S., & McKenna, M. C. (2014). Glutamate metabolism in the brain focusing on astrocytes. *Advances in Neurobiology, 11*, 13-30, doi:10.1007/978-3-319-08894-5_2.
162. Asher, A., Fu, J. B., Bailey, C., & Hughes, J. K. (2016). Fatigue among patients with brain tumors. *CNS oncology, 5*(2), 91-100, doi:10.2217/cns-2015-0008.
163. Annane, D., & Sharshar, T. (2015). Cognitive decline after sepsis. *The Lancet Respiratory Medicine, 3*(1), 61-69, doi:10.1016/s2213-2600(14)70246-2.
164. Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry, 172*(11), 1075-1091, doi:10.1176/appi.ajp.2015.15020152.
165. Miller, A. A., & Spencer, S. J. (2014). Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun, 42*, 10-21, doi:10.1016/j.bbi.2014.04.001.
166. Green, D. M., Cox, C. L., Zhu, L., Krull, K. R., Srivastava, D. K., Stovall, M., et al. (2012). Risk factors for obesity in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol, 30*(3), 246-255, doi:10.1200/JCO.2010.34.4267.
167. Belle, F. N., Weiss, A., Schindler, M., Goutaki, M., Bochud, M., Zimmermann, K., et al. (2018). Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study. *Am J Clin Nutr, 107*(1), 3-11, doi:10.1093/ajcn/nqx006.
168. Pietila, S., Makipernaa, A., Sievanen, H., Koivisto, A. M., Wigren, T., & Lenko, H. L. (2009). Obesity and metabolic changes are common in young childhood brain tumor survivors. *Pediatr Blood Cancer, 52*(7), 853-859, doi:10.1002/pbc.21936.
169. Garmey, E. G., Liu, Q., Sklar, C. A., Meacham, L. R., Mertens, A. C., Stovall, M. A., et al. (2008). Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report

from the Childhood Cancer Survivor Study. *J Clin Oncol, 26*(28), 4639-4645, doi:10.1200/JCO.2008.16.3527.
170. Lumniczky, K., Szatmari, T., & Safrany, G. (2017). Ionizing Radiation-Induced Immune and Inflammatory Reactions in the Brain. *Front Immunol, 8*, 517, doi:10.3389/fimmu.2017.00517.
171. Walker, L. A. S., Lindsay-Brown, A. P., & Berard, J. A. (2019). Cognitive Fatigability Interventions in Neurological Conditions: A Systematic Review. *Neurology and Therapy, 8*(2), 251-271, doi:10.1007/s40120-019-00158-3.
172. Johansson, B., Andrell, P., Ronnback, L., & Mannheimer, C. (2020). Follow-up after 5.5 years of treatment with methylphenidate for mental fatigue and cognitive function after a mild traumatic brain injury. *Brain Inj, 34*(2), 229-235, doi:10.1080/02699052.2019.1683898.
173. Day, J., Yust-Katz, S., Cachia, D., Wefel, J., Katz, L. H., Tremont, I., et al. (2016). Interventions for the management of fatigue in adults with a primary brain tumour. *Cochrane Database Syst Rev, 4*(4), CD011376, doi:10.1002/14651858.CD011376.pub2.
174. Su, H. L., Wu, L. M., Chiou, S. S., Lin, P. C., & Liao, Y. M. (2018). Assessment of the effects of walking as an exercise intervention for children and adolescents with cancer: A feasibility study. *Eur J Oncol Nurs, 37*, 29-34, doi:10.1016/j.ejon.2018.10.006.
175. Johansson, B., Carlsson, A., Carlsson, M. L., Karlsson, M., Nilsson, M. K., Nordquist-Brandt, E., et al. (2012). Placebo-controlled cross-over study of the monoaminergic stabiliser (-)-OSU6162 in mental fatigue following stroke or traumatic brain injury. *Acta Neuropsychiatrica, 24*(5), 266-274, doi:10.1111/j.1601-5215.2012.00678.x.
176. Johansson, B., Wentzel, A. P., Andrell, P., Ronnback, L., & Mannheimer, C. (2017). Long-term treatment with methylphenidate for fatigue after traumatic brain injury. *Acta Neurol Scand, 135*(1), 100-107, doi:10.1111/ane.12587.
177. Johansson, B., Bjuhr, H., Karlsson, M., Karlsson, J-O., Ronnback, L. (2015). Mindfulness-Based Stress Reduction (MBSR) delivered live on the internet to individuals suffering from mental fatigue after an acquired brain injury. *Mindfulness, 6*(6), 1356-1365.
178. Johansson, B., Bjuhr, H., & Ronnback, L. (2012). Mindfulness-based stress reduction (MBSR) improves long-term mental fatigue after stroke or traumatic brain injury. *Brain Inj, 26*(13-14), 1621-1628, doi:10.3109/02699052.2012.700082.
179. Folkhälsomyndigheten (2019). Skolbarns hälsovanor i Sverige 2017/18.
180. Arpaci, T., & Kilicarslan Toruner, E. (2016). Assessment of problems and symptoms in survivors of childhood acute lymphoblastic leukaemia. *Eur J Cancer Care (Engl), 25*(6), 1034-1043, doi:10.1111/ecc.12561.
181. Phillips, N. S., Howell, C. R., Lanctot, J. Q., Partin, R. E., Pui, C. H., Hudson, M. M., et al. (2020). Physical fitness and neurocognitive outcomes in adult survivors of childhood acute lymphoblastic leukemia: A report from the St. Jude Lifetime cohort. *Cancer, 126*(3), 640-648, doi:10.1002/cncr.32510.

182. Hartman, S. J., Nelson, S. H., Myers, E., Natarajan, L., Sears, D. D., Palmer, B. W., et al. (2018). Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. *Cancer, 124*(1), 192-202, doi:10.1002/cncr.30987.
183. Hartman, S. J., Marinac, C. R., Natarajan, L., & Patterson, R. E. (2015). Lifestyle factors associated with cognitive functioning in breast cancer survivors. *Psychooncology, 24*(6), 669-675, doi:10.1002/pon.3626.
184. Crowgey, T., Peters, K. B., Hornsby, W. E., Lane, A., McSherry, F., Herndon, J. E., 2nd, et al. (2014). Relationship between exercise behavior, cardiorespiratory fitness, and cognitive function in early breast cancer patients treated with doxorubicin-containing chemotherapy: a pilot study. *Appl Physiol Nutr Metab, 39*(6), 724-729, doi:10.1139/apnm-2013-0380.
185. Marinac, C. R., Godbole, S., Kerr, J., Natarajan, L., Patterson, R. E., & Hartman, S. J. (2015). Objectively measured physical activity and cognitive functioning in breast cancer survivors. *J Cancer Surviv, 9*(2), 230-238, doi:10.1007/s11764-014-0404-0.
186. Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature reviews neuroscience, 9*(1), 58.
187. Davis, C. L., Tomporowski, P. D., McDowell, J. E., Austin, B. P., Miller, P. H., Yanasak, N. E., et al. (2011). Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. *Health Psychol, 30*(1), 91-98, doi:10.1037/a0021766.
188. Stern, Y., Lee, S., Predovan, D., & R, P. S. (2019). Sex Moderates the Effect of Aerobic Exercise on Some Aspects of Cognition in Cognitively Intact Younger and Middle-Age Adults. *Journal of Clinical Medicine, 8*(6), doi:10.3390/jcm8060886.
189. Stern, Y., MacKay-Brandt, A., Lee, S., McKinley, P., McIntyre, K., Razlighi, Q., et al. (2019). Effect of aerobic exercise on cognition in younger adults: A randomized clinical trial. *Neurology, 92*(9), e905-e916, doi:10.1212/WNL.0000000000007003.
190. Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med, 52*(3), 154-160, doi:10.1136/bjsports-2016-096587.
191. Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci, 14*(2), 125-130, doi:10.1111/1467-9280.t01-1-01430.
192. Prien, A., Besuden, C., Junge, A., Feddermann-Demont, N., Brugger, P., & Verhagen, E. (2020). Cognitive Ageing in Top-Level Female Soccer Players Compared to a Normative Sample from the General Population: A Cross-sectional Study. *Journal of the International Neuropsychological Society : JINS, 26*(7), 645-653, doi:10.1017/S1355617720000119.

193. Kall, L. B., Nilsson, M., & Linden, T. (2014). The impact of a physical activity intervention program on academic achievement in a Swedish elementary school setting. *J Sch Health, 84*(8), 473-480, doi:10.1111/josh.12179.
194. Ericsson, I., & Karlsson, M. K. (2014). Motor skills and school performance in children with daily physical education in school – a 9-year intervention study. *Scand J Med Sci Sports, 24*(2), 273-278, doi:10.1111/j.1600-0838.2012.01458.x.
195. Svensson, M., Brundin, L., Erhardt, S., Madaj, Z., Hallmarker, U., James, S., et al. (2019). Long distance ski racing is associated with lower long-term incidence of depression in a population based, large-scale study. *Psychiatry Res, 281*, 112546, doi:10.1016/j.psychres.2019.112546.
196. Schuch, F. B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P. B., Silva, E. S., et al. (2018). Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *Am J Psychiatry, 175*(7), 631-648, doi:10.1176/appi.ajp.2018.17111194.
197. Wegner, M., Helmich, I., Machado, S., Nardi, A. E., Arias-Carrion, O., & Budde, H. (2014). Effects of exercise on anxiety and depression disorders: review of meta- analyses and neurobiological mechanisms. *CNS Neurol Disord Drug Targets, 13*(6), 1002-1014, doi:10.2174/18715273136661406121028 41.
198. Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian journal of medicine & science in sports, 25*, 1-72.
199. Hennings, A., Schwarz, M. J., Riemer, S., Stapf, T. M., Selberdinger, V. B., & Rief, W. (2013). Exercise affects symptom severity but not biological measures in depression and somatization – results on IL-6, neopterin, tryptophan, kynurenine and 5-HIAA. *Psychiatry research, 210*(3), 925-933.
200. Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., et al. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc, 51*(11), 2375-2390, doi:10.1249/MSS.0000000000002116.
201. Field, T. (2012). Exercise research on children and adolescents. *Complement Ther Clin Pract, 18*(1), 54-59, doi:10.1016/j.ctcp.2011.04.002.
202. Larun, L., Nordheim, L. V., Ekeland, E., Hagen, K. B., & Heian, F. (2006). Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database Syst Rev*(3), CD004691, doi:10.1002/14651858.CD004691.pub2.
203. Biddle, S. J., & Asare, M. (2011). Physical activity and mental health in children and adolescents: a review of reviews. *Br J Sports Med, 45*(11), 886-895, doi:10.1136/bjsports-2011-090185.
204. Van Dijk-Lokkart, E. M., Steur, L. M. H., Braam, K. I., Veening, M. A., Huisman, J., Takken, T., et al. (2019). Longitudinal development of cancer-related fatigue and physical activity in childhood cancer patients. *Pediatr Blood Cancer, 66*(12), e27949, doi:10.1002/pbc.27949.

205. Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., et al. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc, 42*(7), 1409-1426, doi:10.1249/MSS.0b013e3181e0c112.
206. Cramp, F., & Byron-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev, 11*(11), CD006145, doi:10.1002/14651858.CD006145.pub3.
207. Puetz, T. W., & Herring, M. P. (2012). Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. *Am J Prev Med, 43*(2), e1-24, doi:10.1016/j.amepre.2012.04.027.
208. Jakobsson, M., Josefsson, K., Jutengren, G., Sandsjo, L., & Hogberg, K. (2019). Sleep duration and sleeping difficulties among adolescents: exploring associations with school stress, self-perception and technology use. *Scand J Caring Sci, 33*(1), 197-206, doi:10.1111/scs.12621.
209. Norell-Clarke, A., & Hagquist, C. (2017). Changes in sleep habits between 1985 and 2013 among children and adolescents in Sweden. *Scandinavian Journal of Public Health, 45*(8), 869-877, doi:10.1177/1403494817732269.
210. Titova, O. E., Hogenkamp, P. S., Jacobsson, J. A., Feldman, I., Schioth, H. B., & Benedict, C. (2015). Associations of self-reported sleep disturbance and duration with academic failure in community-dwelling Swedish adolescents: sleep and academic performance at school. *Sleep Med, 16*(1), 87-93, doi:10.1016/j.sleep.2014.09.004.
211. Könen, T., Dirk, J., & Schmiedek, F. (2015). Cognitive Benefits of Last Night's Sleep: Daily Variations in Children's Sleep Behavior Are Related to Working Memory Fluctuations. *Journal of Child Psychology and Psychiatry, 56*(2), 171-182.
212. Cusick, C. N., Isaacson, P. A., Langberg, J. M., & Becker, S. P. (2018). Last night's sleep in relation to academic achievement and neurocognitive testing performance in adolescents with and without ADHD. *Sleep Med, 52*, 75-79, doi:10.1016/j.sleep.2018.07.014.
213. Dahl, R. E. The impact of inadequate sleep on children's daytime cognitive function. In *Seminars in pediatric neurology, 1996* (Vol. 3, pp. 44-50, Vol. 1): Elsevier
214. Fallone, G., Acebo, C., Arnedt, J. T., Seifer, R., & Carskadon, M. A. (2001). Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Percept Mot Skills, 93*(1), 213-229, doi:10.2466/pms.2001.93.1.213.
215. Shochat, T., Cohen-Zion, M., & Tzischinsky, O. (2014). Functional consequences of inadequate sleep in adolescents: a systematic review. *Sleep Med Rev, 18*(1), 75-87, doi:10.1016/j.smrv.2013.03.005.
216. Ruan, H., Xun, P., Cai, W., He, K., & Tang, Q. (2015). Habitual Sleep Duration and Risk of Childhood Obesity: Systematic Review and Dose-response Meta-analysis of Prospective Cohort Studies. *Scientific reports, 5*, 16160-16160, doi:10.1038/srep16160.

217. Brinkman, T. M., Zhang, N., Ullrich, N. J., Brouwers, P., Green, D. M., Srivastava, D. K., et al. (2013). Psychoactive medication use and neurocognitive function in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *Pediatr Blood Cancer, 60*(3), 486-493, doi:10.1002/pbc.24255.
218. Prasad, P. K., Hardy, K. K., Zhang, N., Edelstein, K., Srivastava, D., Zeltzer, L., et al. (2015). Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 33*, 2545-U2591, doi:10.1200/JCO.2014.57.7528.
219. Jacola, L. M., Edelstein, K., Liu, W., Pui, C. H., Hayashi, R., Kadan-Lottick, N. S., et al. (2016). Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. *Lancet Psychiatry, 3*(10), 965-972, doi:10.1016/S2215-0366(16)30283-8.
220. van der Linden, S., Gehring, K., De Baene, W., Emons, W. H. M., Rutten, G. M., & Sitskoorn, M. M. (2020). Assessment of Executive Functioning in Patients with Meningioma and Low-Grade Glioma: A Comparison of Self-Report, Proxy-Report, and Test Performance. *J Int Neuropsychol Soc, 26*(2), 187-196, doi:10.1017/S1355617719001164.
221. Toplak, M. E., West, R. F., & Stanovich, K. E. (2013). Practitioner review: do performance-based measures and ratings of executive function assess the same construct? *J Child Psychol Psychiatry, 54*(2), 131-143, doi:10.1111/jcpp.12001.
222. O'Brien, A., Gaudino-Goering, E., Shawaryn, M., Komaroff, E., Moore, N. B., & DeLuca, J. (2007). Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Archives of Clinical Neuropsychology, 22*(8), 933-948.
223. Collins, B., Paquet, L., Dominelli, R., White, A., & MacKenzie, J. (2017). Metamemory function in chemotherapy-treated patients with breast cancer: an explanation for the dissociation between subjective and objective memory measures? *Psycho-oncology, 26*(1), 109-117.
224. Sølsnes, A. E., Skranes, J., Brubakk, A.-M., & Løhaugen, G. C. (2014). Executive functions in very-low-birth-weight young adults: a comparison between self-report and neuropsychological test results. *Journal of the International Neuropsychological Society, 20*(5), 506-515.
225. Elliott, C. S., & Fiszdon, J. M. (2014). Comparison of self-report and performance-based measures of everyday functioning in individuals with schizophrenia: implications for measure selection. *Cogn Neuropsychiatry, 19*(6), 485-494, doi:10.1080/13546805.2014.922062.
226. Kadan-Lottick, N. S., Zeltzer, L. K., Liu, Q., Yasui, Y., Ellenberg, L., Gioia, G., et al. (2010). Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. *J Natl Cancer Inst, 102*(12), 881-893, doi:10.1093/jnci/djq156.

227. Rueegg, C. S., Gianinazzi, M. E., Rischewski, J., Beck Popovic, M., von der Weid, N. X., Michel, G., et al. (2013). Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. *J Cancer Surviv, 7*(4), 511-522, doi:10.1007/s11764-013-0288-4.
228. Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *Behavior Rating Inventory of Executive Function: BRIEF*. Odessa, FL: Psychological Assessment Resources
229. Beck, J. (2004). Manual for the Beck Youth Inventories of Emotional and Social Impairment. Swedish version. San Antonio. *TX: The Psychological Corporation*.
230. Crichton, A., Knight, S., Oakley, E., Babl, F. E., & Anderson, V. (2015). Fatigue in child chronic health conditions: a systematic review of assessment instruments. *Pediatrics, 135*(4), e1015-1031, doi:10.1542/peds.2014-2440.
231. Brand, S. R., Chordas, C., Liptak, C., Manley, P., & Recklitis, C. (2016). Screening for fatigue in adolescent and young adult pediatric brain tumor survivors: accuracy of a single-item screening measure. *Support Care Cancer, 24*(8), 3581-3587, doi:10.1007/s00520-016-3150-1.
232. Hockenberry, M. J., Hinds, P. S., Barrera, P., Bryant, R., Adams-McNeill, J., Hooke, C., et al. (2003). Three instruments to assess fatigue in children with cancer: the child, parent and staff perspectives. *Journal of pain and symptom management, 25*(4), 319-328.
233. Harrison, P., & Oakland, T. (2003). Adaptive Behavior Assessment (ABAS II manual). San Antonio, TX: Harcourt Assessment.
234. Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2015). *BRIEF-2: Behavior Rating Inventory of Executive Function: Professional Manual*. Lutz, FL: Psychological Assessment Resources.
235. Nascimento, L. C., Nunes, M. D., Rocha, E. L., Bomfim, E. O., Floria-Santos, M., Dos Santos, C. B., et al. (2015). High validity and reliability of the PedsQL Multidimensional Fatigue Scale for Brazilian children with cancer. *J Pediatr Oncol Nurs, 32*(1), 57-64, doi:10.1177/1043454214554656.
236. Gordijn, M., Cremers, E. M., Kaspers, G. J., & Gemke, R. J. (2011). Fatigue in children: reliability and validity of the Dutch PedsQL Multidimensional Fatigue Scale. *Qual Life Res, 20*(7), 1103-1108, doi:10.1007/s11136-010-9836-9.
237. Compas, B. E., Desjardins, L., Vannatta, K., Young-Saleme, T., Rodriguez, E. M., Dunn, M., et al. (2014). Children and adolescents coping with cancer: self- and parent reports of coping and anxiety/depression. *Health Psychol, 33*(8), 853-861, doi:10.1037/hea0000083.
238. Lannering, B., Sandstrom, P. E., Holm, S., Lundgren, J., Pfeifer, S., Samuelsson, U., et al. (2009). Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984-2005. *Acta Paediatr, 98*(10), 1620-1627, doi:10.1111/j.1651-2227.2009.01417.x.
239. Annett, R. D., Patel, S. K., & Phipps, S. (2015). Monitoring and Assessment of Neuropsychological Outcomes as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer, 62 Suppl 5*, S460-513, doi:10.1002/pbc.25749.

240. Merchant, T. E., Conklin, H. M., Wu, S., Lustig, R. H., Xiong, X., Merchant, T. E., et al. (2009). Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *Journal of Clinical Oncology, 27*(22), 3691-3697, doi:10.1200/JCO.2008.21.2738.
241. Ris, M. D., Grosch, M., Fletcher, J. M., Metah, P., & Kahalley, L. S. (2017). Measurement of neurodevelopmental changes in children treated with radiation for brain tumors: what is a true 'baseline'? *Clin Neuropsychol, 31*(2), 307-328, doi:10.1080/13854046.2016.1216070.
242. Duff, K. (2012). Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. *Arch Clin Neuropsychol, 27*(3), 248-261, doi:10.1093/arclin/acr120.
243. Duda, T. A., Ris, M. D., Yeates, K. O., Mahone, E. M., Haut, J. S., & Raghubar, K. P. (2020). Reliable change in pediatric brain tumor: A preliminary investigation. *Child Neuropsychology, 26*(1), 15-26, doi:10.1080/09297049.2019.1620715.
244. Watkins, M. W., & Smith, L. G. (2013). Long-term stability of the Wechsler Intelligence Scale for Children – Fourth Edition. *Psychological Assessment, 25*(2), 477-483, doi:10.1037/a0031653.
245. Wechsler, D. (2003). *WISC-IV: Wechsler Intelligence Scale for Children: Technical and Interpretive Manual*. San Antonio, TX: Pearson.
246. Carlozzi, N. E., Beaumont, J. L., Tulsky, D. S., & Gershon, R. C. (2015). The NIH Toolbox Pattern Comparison Processing Speed Test: Normative Data. *Archives of Clinical Neuropsychology, 30*(5), 359-368, doi:10.1093/arclin/acv031.
247. Kahalley, L. S., Ris, M. D., Grosshans, D. R., Okcu, M. F., Paulino, A. C., Chintagumpala, M., et al. (2016). Comparing Intelligence Quotient Change After Treatment With Proton Versus Photon Radiation Therapy for Pediatric Brain Tumors. *J Clin Oncol, 34*(10), 1043-1049, doi:10.1200/JCO.2015.62.1383.
248. King, T. Z., Ailion, A. S., Fox, M. E., & Hufstetler, S. M. (2019). Neurodevelopmental model of long-term outcomes of adult survivors of childhood brain tumors. *Child Neuropsychol, 25*(1), 1-21, doi:10.1080/09297049.2017.1380178.
249. Conners, C. K. (2014). *Conners CPT3 - Conners Continuous Performance Test 3rd Edition*. Toronto, Canada: Multi-Health Systems Inc.
250. De Ruiter, M. A., Van Mourik, R., Schouten-van Meeteren, A. Y., Grootenhuis, M. A., & Oosterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: A meta-analysis. *Developmental Medicine & Child Neurology, 55*(5), 408-417.
251. Panepinto, J. A., Torres, S., Bendo, C. B., McCavit, T. L., Dinu, B., Sherman-Bien, S., et al. (2014). PedsQL Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability, and validity. *Pediatr Blood Cancer, 61*(1), 171-177, doi:10.1002/pbc.24776.

252. Pattyn, N., Van Cutsem, J., Dessy, E., & Mairesse, O. (2018). Bridging Exercise Science, Cognitive Psychology, and Medical Practice: Is "Cognitive Fatigue" a Remake of "The Emperor's New Clothes"? *Front Psychol, 9*, 1246, doi:10.3389/fpsyg.2018.01246.
253. Liptak, C., Manley, P., & Recklitis, C. J. (2012). The feasibility of psychosocial screening for adolescent and young adult brain tumor survivors: the value of self-report. *J Cancer Surviv, 6*(4), 379-387, doi:10.1007/s11764-012-0237-7.
254. Rey, J. M., Schrader, E., & Morris-Yates, A. (1992). Parent-child agreement on children's behaviours reported by the Child Behaviour Checklist (CBCL). *J Adolesc, 15*(3), 219-230, doi:10.1016/0140-1971(92)90026-2.
255. Socialstyrelsen (2020). Psykiatrisk vård och behandling till barn och unga.
256. Socialstyrelsen (2017). Nationella riktlinjer för vård vid depression och ångestsyndrom.
257. Seitz, D. C. M., Knaevelsrud, C., Duran, G., Waadt, S., Loos, S., & Goldbeck, L. (2014). Efficacy of an internet-based cognitive-behavioral intervention for long-term survivors of pediatric cancer: a pilot study. *Supportive Care in Cancer, 22*(8), 2075-2083, doi:10.1007/s00520-014-2193-4.
258. Van der Gucht, K., Takano, K., Labarque, V., Vandenabeele, K., Nolf, N., Kuylen, S., et al. (2017). A Mindfulness-Based Intervention for Adolescents and Young Adults after Cancer Treatment: Effects on Quality of Life, Emotional Distress, and Cognitive Vulnerability. *Journal of Adolescent and Young Adult Oncology, 6*(2), 307-317, doi:10.1089/jayao.2016.0070.
259. Hagström, J., Ander, M., Cernvall, M., Ljótsson, B., Wiman, H. W., von Essen, L., et al. (2020). Heeding the psychological concerns of young cancer survivors: a single-arm feasibility trial of CBT and a cognitive behavioral conceptualization of distress. *PeerJ, 8*, e8714, doi:10.7717/peerj.8714.
260. Sansom-Daly, U. M., Wakefield, C. E., Bryant, R. A., Patterson, P., Anazodo, A., Butow, P., et al. (2019). Feasibility, acceptability, and safety of the Recapture Life videoconferencing intervention for adolescent and young adult cancer survivors. *Psycho-Oncology, 28*(2), 284-292, doi:10.1002/pon.4938.
261. Trauer, J. M., Qian, M. Y., Doyle, J. S., Rajaratnam, S. M. W., & Cunnington, D. (2015). Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. *Annals of Internal Medicine, 163*(3), 191-204, doi:10.7326/M14-2841.
262. Dewald-Kaufmann, J., de Bruin, E., & Michael, G. (2019). Cognitive Behavioral Therapy for Insomnia (CBT-i) in School-Aged Children and Adolescents. *Sleep Med Clin, 14*(2), 155-165, doi:10.1016/j.jsmc.2019.02.002.
263. Lindblad, I., Westerlund, J., Gillberg, C., & Fernell, E. (2018). Har alla barn i grundskolan förutsättningar att klara nya läroplanens krav? *Läkartidningen, 115*.
264. Ach, E., Gerhardt, C. A., Barrera, M., Kupst, M. J., Meyer, E. A., Patenaude, A. F., et al. (2013). Family factors associated with academic achievement deficits

in pediatric brain tumor survivors. *Psycho-Oncology, 22*(8), 1731-1737, doi:10.1002/pon.3202.
265. Crump, C., Sundquist, J., Sieh, W., Winkleby, M. A., & Sundquist, K. (2015). Perinatal and familial risk factors for acute lymphoblastic leukemia in a Swedish national cohort. *Cancer, 121*(7), 1040-1047, doi:10.1002/cncr.29172.
266. Varni, J. W., Beaujean, A. A., & Limbers, C. A. (2013). Factorial invariance of pediatric patient self-reported fatigue across age and gender: a multigroup confirmatory factor analysis approach utilizing the PedsQL Multidimensional Fatigue Scale. *Qual Life Res, 22*(9), 2581-2594, doi:10.1007/s11136-013-0370-4.
267. Meeske, K. A., Patel, S. K., Palmer, S. N., Nelson, M. B., & Parow, A. M. (2007). Factors associated with health-related quality of life in pediatric cancer survivors. *Pediatric Blood & Cancer, 49*(3), 298-305, doi:10.1002/pbc.20923.
268. Kanellopoulos, A., Hamre, H. M., Dahl, A. A., Fosså, S. D., & Ruud, E. (2013). Factors associated with poor quality of life in survivors of childhood acute lymphoblastic leukemia and lymphoma. *Pediatric Blood & Cancer, 60*(5), 849-855, doi:10.1002/pbc.24375.
269. Ashman, T. A., Cantor, J. B., Gordon, W. A., Spielman, L., Egan, M., Ginsberg, A., et al. (2008). Objective measurement of fatigue following traumatic brain injury. *J Head Trauma Rehabil, 23*(1), 33-40, doi:10.1097/01.HTR.0000308719.70288.22.

Errata

Study I

Discussion, paragraph 5, first sentence should be: “In contrast to two previous, smaller studies, hydrocephalus was associated with baseline attention.”

Study II

Abstract, Results, first sentence under should be “Cognitive fatigue was prevalent in 70% of survivors of BT and in 30% of survivors of ALL."

Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

Sad, shattered or slow?

Elin Irestorm is a clinical neuropsychologist and researcher with an interest in cognition in neuropaediatric disorders. She is especially concerned with fatigue and its relationship to cognitive deficits, particularly after treatment for childhood cancer.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Paediatrics

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:17
ISBN 978-91-8021-023-2
ISSN 1652-8220