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Neuropsychological, Physical Activity, and Psychological Interventions for Pediatric Cancer Survivors: A Systematic Review and Synthesis

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ABSTRACT

Background: Pediatric cancer survivors are at risk for negative cognitive, social and psychological late sequelae. In response to that, recent research endeavoured alleviating late sequelae and improving quality of life for pediatric cancer survivors. This review`s aim was to systematically evaluate and critically appraise the current state of evidence on non-pharmacological intervention studies following childhood cancer.
Methods: Randomized controlled trials and quasi-experimental trials addressing children and adolescents after childhood cancer (age: 0-21 years), who reported either cognitive, psychosocial, psychological or health-related quality of life outcomes, were screened. Twenty non-pharmacological studies were identified, and studies were further categorized into one of the three groups: *Cognitive, physical activity* and *psychosocial/psychological interventions studies*.
Results: We critically discuss the methodological quality of these studies, and explore what outcomes can be tackled through what kind of intervention.
Conclusions: Reviewing the existing studies and integrating the current empirical evidence, we conclude that for most aspects of children`s cognitive and social-emotional functioning more well-designed studies are needed.

Keywords: *Aftercare; Survivors of childhood cancer; Intervention studies; Neuropsychological deficits; Health-related quality of life.*

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Introduction[1]

Pediatric cancer and its treatment profoundly affect child development. Cognitive, psychosocial and psychological long-term effects have been reported in pediatric cancer survivors (PCS) (Arceci, 2016). Long-term sequelae comprise difficulties in cognitive functions (i.e. attention, working memory, processing speed, and executive function), social functioning (i.e. social skills, peer relations), and psychological functioning (i.e. post-traumatic stress symptoms, depression (Arceci, 2016; Bonner et al., 2008; Hardy, Krull, Wefel, & Janelsins, 2018; Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018). Widespread negative consequences are reported in terms of daily activities, school performance and health-related quality of life (HRQL) (Liptak, Chow, Zhou, & Recklitis, 2016).

Cognitive challenges are experienced by about 40 percent of PCS (in one or more cognitive functions), and predominantly affect higher-order functions such as attention, processing speed, memory, visual-motor integration, and executive functions (Askins, Ann-Yi, & Moore, 2015; Van Der Plas et al., 2018; Walsh & Paltin, 2015; Zeltzer et al., 2009). Difficulties in core cognitive functions affect the ability to process, and acquire new skills and information, and are associated with lower levels on academic achievement (Mulhern & Palmer, 2003). The extent of cognitive dysfunction varies with tumor factors (i.e., location, size, and brain metastasis), cancer treatments (i.e., chemotherapy, cranial irradiation, field, and dosage), and host factors (i.e., socio-economic status, gender, genetics, and family functioning) (Castellino, Ullrich, Whelen, & Lange, 2014; Nortz, Hemme-Phillips, & Ris, 2007). Factors that increase the risk of experiencing cognitive difficulties include cancer of the central nervous system (CNS), acute lymphoblastic leukemia (ALL), chemotherapy and cranial radiation therapy, female sex, and young age at the time of diagnosis (Buizer, de Sonneville, & Veerman, 2009; Patel, Schulte, Kelly, & Steele, 2016). Environmental factors such as socio-economic status may also moderate the extent of cognitive sequelae of cancer and its treatment (Patel et al., 2016; Sahler et al., 2002).

Beside difficulties in cognitive functions, studies suggest that PCS have an increased risk of experiencing difficulties in social functioning, including having only few close friends (Maru Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005), showing reduced levels of social

[1] **Abbreviations**
PCS: Pediatric cancer survivors
HRQL: Health-related quality of life
RCT: Randomized controlled trials
ALL: Acute lymphoblastic leukemia
BT: Brain tumors
CNS: Central nervous system
CRP: Cognitive remediation program

adjustment (for review see (Schulte & Barrera, 2010), and having problems in the interpretation of facial expressions (Bonner et al., 2008). Interestingly, difficulties in social functioning have been shown to be related to lower cognitive functioning (Bonner et al., 2008; Hocking et al., 2015; Moyer et al., 2012; Wolfe et al., 2013). Moreover, difficulties in social functioning in PCS are associated with increased vulnerability to psychological problems such as depression, and social withdrawal and lower self-esteem (Barrera, Schulte, & Spiegler, 2008; Schulte & Barrera, 2010). Overall, the majority of PCS adapt positively to the stressful challenges of cancer and its treatment, however, almost 20 percent of PCS experience impairments in psychological functioning, such as higher levels of depression, anxiety and post-traumatic stress symptoms compared to controls (Liptak, Chow, Zhou, & Recklitis, 2016).

Finally, long-term sequelae are associated with decreased levels of HRQL(Bradley Eilertsen, Jozefiak, Rannestad, Indredavik, & Vik, 2012; Noeker, 2012; Zeltzer et al., 2009). HRQL involves the perceived functioning regarding the physical, social, and psychological dimension, and is considered to be an important outcome measure within the research of cancer survivorship (Rueegg et al., 2013; The Whoqol Group, 1998).

As an extensive body of research has documented the specific nature of long-term sequelae following childhood cancer, the lessons learned have guided more recent research efforts into intervention methods aimed at reducing long-term sequelae. For practitioners, families, and investigators working in this area, it is of great theoretical and practical importance to disseminate information about available, evidence-based rehabilitation methods. Both non-pharmacological and pharmacological intervention studies have recently been developed aimed at alleviating long-term sequelae in PCS. In this review of the literature, we will focus on non-pharmacological interventions.

Most of the existing reviews on non-pharmacological interventions addressing long-term sequelae in pediatric oncology focused on a particular intervention approach, such as cognitive trainings (Olson & Sands, 2016), physical exercise trainings (Baumann, Bloch, & Beulertz, 2013; Braam et al., 2013; T.-T. Huang & Ness, 2011), and psychological interventions (Hocking et al., 2015; Kazak, 2005). Only a few have attempted to bring together different interventional approaches. In sum, the majority of reviews concur that promising findings for different interventional approaches exist, but the research is too limited to yet provide “best practice” guidelines. Given that PCS may experience late-effects on a wide range of domains, this review`s approach widens the lens to domains that are typically described as vulnerable in PCS. Thereby, we aim to best capture a broad range of possible

interventions that may be beneficial in reducing late-effects occurring after childhood cancer. Instead of focusing on a particular intervention, here we broaden the scope by systematically evaluating and critically appraising the current state of evidence on non-pharmacological intervention studies for PCS addressing cognitive, psychosocial, psychological or HRQL outcomes. With this approach we aim to find out which interventions exist that target domains that are typically at risk after childhood cancer and its treatment. More specifically, we attempt to examine what domain can be tackled through what kind of intervention. In addition, we aim to inform practitioners about existing interventions, and aim to help clinicians in their decision-making process regarding interventions based on the current state of research. This enables them to choose the appropriate intervention or a combination of interventions tailored specifically to the child`s profile.

This review intends to add to the literature by: (a) integrating the literature on non-pharmacological interventions addressing a broad range of outcomes, namely cognitive, psychosocial, psychological or HRQL outcomes, rather than a specific type of intervention; (b) evaluating the current evidence base of interventions and incorporating recently published interventional studies that have not been included in previous review papers; and (c) deriving recommendations for clinical practice and future research.

Methods

Study selection and search strategy

We developed a review protocol a priori and determined the in- and exclusion criteria using the PICOS criteria (Tacconelli; 2010). The in- and exclusion criteria along the PICOS criteria are defined in Table 1.

We sought to identify and integrate literature on non-pharmacological interventions addressing cognitive, psychosocial, psychological, and HRQL outcomes. Review questions were: a) which interventions addressing cognitive, psychosocial, psychological, and HRQL outcomes for PCS have been evaluated in the current literature? b) what is the effectiveness of the non-pharmacological interventions on one or more outcomes of interest? c) considering the methodological strengths and limitations of the existing studies, what implications does the current state of research provide for clinical practice on the one side, and for future research on the other?

	Inclusion Criteria	Exclusion Criteria
Participants	-children and adolescents <21 who had completed primary treatment or underwent maintenance therapy of any type of childhood cancer.	-participants during early treatment -mixed samples of adults and adolescents/children -mixed time points of treatment (during and after completion of therapy).
Interventions	-any non-pharmacological intervention delivered in different settings and over various time frames designed to improve cognitive, psychosocial, psychological and HQOL outcomes	-pharmacological interventions -only feasibility interventions or neuroimaging measures to evaluate intervention effects -studies only focusing on parent or sibling of childhood cancer survivors
Comparators	-studies using any active control group -studies using waitlist control group	-studies not using any comparative group
Outcomes	- cognitive, psychosocial psychological and quality of life outcomes	-studies not including a quantitative evaluation of treatment effects -papers only targeting neuroimaging measures, physical or feasibility outcomes
Study design	- RCT, quasi-experimental and pilot trials with a comparison group, if the intervention study was not published, follow up studies	-review articles -study protocols - conference proceedings -preceding pilot trials that were followed by published intervention studies -case series/single arm trials without any control group

Table 1 - *PICOS Criteria*

A systematic literature search (figure 1) was conducted and last updated in June 2018. We only included articles that were published in a peer-reviewed journal during the last 18 years (2000-2018). In addition to randomized controlled trials (RCT), we decided to also include quasi-experimental trials due to the few number of RCT interventions for PCS. Electronic searches of Web of Science, Pubmed and Scopus were conducted using predetermined search terms. We also searched the reference lists and when necessary, searched for grey literature. Detailed search terms and exact search strategies can be seen in Appendix A. One reviewer (J.S.) screened the titles and abstracts of the papers found in the search strategy and made a preselection of eligible studies. Both reviewers discussed and agreed to 100% on the selection of studies to include in the review.

Quality appraisal and data extraction

The methodological quality of the studies was assessed with the CONSORT (Consolidated Standards of Reporting Trials) checklist that contains 23 items. We chose to use the CONSORT checklist, because it offers a standardized way to assess the quality of randomized trials, in particular non-pharmacological trials (Boutron, Moher, Altman, Schulz, & Ravaud, 2008).

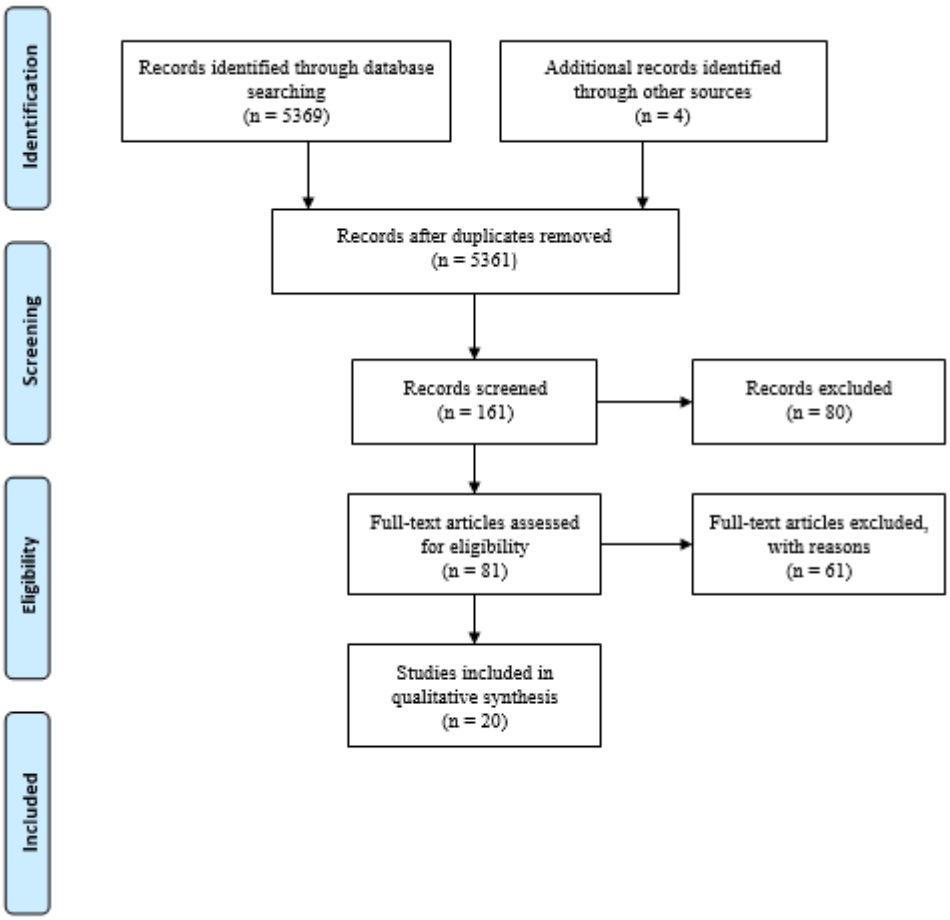

Figure 1 - *Prisma Flow diagram.* Adapted study flow diagram from Moher, Liberati, Tetzlaff & Altman, 2009

The 23-item checklist can be found at http://www.consortstatement.org/extensions/overview/non-pharmacologic-treatment-interventions. One reviewer (J.S.) extracted the data on the 23-item checklist, the other reviewer (C.R.) verified the completeness and correctness of the data. Based on the data of the checklist, both reviewers discussed the disagreements and the final score for each study. Agreement between the two raters was 96 percent. Disagreements were solved by consensus.

The score for each study regarding the methodological quality is included in Table 2. In addition, for each study, data regarding sample characteristics, cancer type, age, intervention type, design, type of control group, randomization procedure, and outcome measures are listed in Table 2.

Table 2 - *Characteristics of Included Studies*

Study	Age	Target		Comparison		Design	Randomization	Intervention	MQR[a]	Intervention characteristics	Outcomes assessed	Effect [b]
		Sample	*N*	Sample	*N*				(0-27)			
Cognitive Interventions (2 studies, 1 pilot study & 1 follow-up study)												
(1) Butler et al., 2008	6 - 17	BT, ALL	108	BT, ALL	53	RCT	Central data manager (2:1 ratio)	CRP	21	Center-based 20 sessions 2 hours each 4 - 5 months	Academic achievement Attention Learning strategies Memory Self-esteem Working memory	+ 0 + 0 0 0
(2) Conklin et al., 2015	8 - 16	BT, ALL	34	BT, ALL	34	RCT	Block	Cogmed CWMT	18	Home-based 25 sessions 40 min each 5 - 9 weeks	Academic achievement Attention Processing speed Working memory	0 + + +
(3) Conklin et al., 2016 (Follow-up study)	8 - 16	BT, ALL	34	BT, ALL	34	RCT	Block	Cogmed CWMT	18	Home-based 25 sessions 40 min each 5 - 9 weeks	Academic achievement Attention Processing speed Working memory	0 0 + +
(4) Patel et al., 2014 (pilot study)	6 - 18	BT, ALL	22	BT, ALL	22	RCT	Block	Parent-Directed Intervention	19	Clinic-based 8 sessions 120 min/week 3 months	Academic achievement EFs Learning Strategies	+ 0 +

Physical activity interventions (6 studies, 3 pilot studies & 1 follow-up study)												
(5) Chung et al., 2015 (follow-up study Li)	9 - 16	BT, ALL	33	BT, ALL	36	RCT	Envelope	Adventure & health education	11	Community 8 activities 4 days	HRQL Physical activity Self-efficacy	+ + +
(6) Dubnov-Raz et al., 2015	7 - 14	BT, ALL	10	BT, ALL	12	Quasi-experimental study	N.A.	Physical Exercise program	12	Gym/Group-based 9 sessions 1 hour each	Aerobic Fitness HRQL Mood	0 0 0
(7) Huang et al., 2014	8 - 18	ALL	18	ALL	17	RCT	stratified by age	Weight management intervention (Fit4Life)	14	Home-based n.d. n.d. 4 months	Mood Self-esteem Social Functioning	+ 0 0
(8) Li et al., 2013	9 - 16	BT, ALL	34	BT, ALL	37	RCT	Envelope	Adventure & health education	18	Community 8 activities 4 days	HRQL Physical activity Self-efficacy	0 + +
(9) Marchese et al., 2004	4 - 18	ALL	13	ALL	15	RCT	Envelope	Physical therapy & Exercise program	15	Clinic- and home-based 5 sessions 20 - 60 min	Aerobic Fitness HRQL Motor Performance Physical activity	+ 0 + +
(10) Riggs et al., 2017	6 - 17	BT	16	BT	12	RCT Cross-over	Quasi-random order	Aerobic exercise training	20	Clinic- and home-based 24 sessions 30 – 90 min 3 months	Attention Processing speed Neuroimaging Short-term memory	+[c] +[c] + +[c]
(11) Ruble et al., 2016 (pilot study)	8 - 12	BT, ALL	9	BT, ALL	10	RCT	n.d.	Physical Exercise program	14	Group-based 5 day camp	Self-efficacy Physical activity	+ 0
(12) Sabel et al., 2016 (pilot study)	7-17	BT	7	BT	6	RCT Cross-over	Minimization	Active video gaming	21	Home-based 30 min/day 5 times/week 10-12 weeks	Attention Inhibition Memory Motor performance Process skills Processing speed Verbal Fluency Working memory	0 0 0 + + 0 0 0
(13) Tanir et al., 2013	8 - 12	ALL	19	ALL	21	RCT	Randomized Selection	Physical Exercise program	12	Home-based 1 - 3 times/ day 3 - 5 times/ week 3 months	Anxiety HRQL Motor performance Social functioning	0 0 + 0
(14) Yeh et al., 2011 (pilot study)	<18	ALL	12	ALL	10	Quasi-experimental study	N.A.	Aerobic exercise intervention	13	Home-based 30 min/day 3 times/week 6 weeks	Fatigue	+[d]

Psychosocial/Psychological interventions (5 studies and 1 pilot study)												
(15) Barrera et al., 2018	8-16	BT	43	BT	48	RCT	Minimization	Social skills training	23	Clinic-based 8 sessions 120 min 8 weeks	HRQL Social functioning	0 +[e]
(16) Devine et al., 2017 (pilot study)	6–14	BT	8	BT	4	Quasi-experimental study	N.A.	Peer-mediated classroom intervention	15	School-based 5-8 sessions 30-40 min 4-6 weeks	Social functioning	+
(17) Dijk-Lokkart et al., 2016	8 – 18	BT, ALL	30	BT, ALL	38	RCT	Block	Socio-emotional & Physical Exercise program	19	Physiotherapy practice- and clinic-based 3 months	Anxiety Fatigue HRQL Social functioning	0[f] 0 0[g] 0
(18) Kazak et al., 2004	11-19	mixed	75	mixed	74	RCT	Stratified by gender and age	Cognitive–behavioral and family therapy (SCCIP)	17	Clinic-based 4 sessions 60-90 min 1-day	Anxiety Post-traumatic stress symptoms	0 +
(19) Poggi et al, 2009	4 – 18	BT	17	BT	23	Quasi-experimental study	N.A.	Cognitive and behavioural therapy	9	Clinic-based 2 - 3 sessions/week 45 - 60 min 4 - 8 months	Adaptive functioning Motor performance Social functioning	+ 0 +
(20) Ruiter et al., (2016)	8-18	BT	34	BT	37	RCT	n.d.	Neurofeed-back	26	Home and school-based 30 sessions 30 min 2-5 months	Attention EFs HRQL Fatigue Memory Processing speed Self-esteem Social functioning Working memory Visuomotor integration	0[h] 0[h] 0[h] 0[h] 0[h] 0[h] 0[h] 0[h] 0[h] 0[h]

Note. BT, Brain Tumor; ALL, Acute Lymphoblastic Leukemia; CRP, Cognitive Remediation Program; n.d, not definded; N.A., Not Applicable; Cogmed CWMT, Cogmed Computerized Working Memory Training; RCT, Randomized Controlled Trial; SCCIP, Surviving Cancer Competently Intervention Program; EFs, Executive Functions; HRQL, Health-Related Quality of Life.

[a] MQR, Methodological Quality Rating: Quality check was performed with Items of the Consort Checklist for reporting trials of nonpharmacological treatments.

[b] +, Statistical significant improvement in the outcome in experimental group compared to control group.

[b] 0, No statistical significant treatment effect in the experimental group compared to control group.

[c] Statistical significant improvements only in reaction time, but not in accuracy, and only in the group setting.

[d] Fatigue = only for the per-protocol analysis, experimental group showed lower fatigue scores at 1-month follow-up, but immediately after the intervention.

[e] Treatment effect was statistically significant after the intervention (T2) and at T3 (6 months follow- up).

f Statistical significant group difference at T2 (post treatment assessment) on procedural anxiety according to parent report.

g Statistical significant difference at T2 and T3 (12 months) on pain-related HRQL according to parent report.

h No statistical significant group differences after the intervention (T2) and at T3 (6months follow-up

Results

We identified twenty articles, consisting of eleven RCT {Studies: (Butler et al., 2008) (1), (Conklin et al., 2015) (2), (Huang et al., 2014) (7), (Li, Chung, Ho, Chiu, & Lopez, 2013) (8), (Marchese, Chiarello, & Lange, 2004) (9), (Riggs et al., 2016) (10), (Tanir & Kuguoglu, 2013) (13), (Barrera et al., 2018) (15), (van Dijk-Lokkart et al., 2016) (17), (Kazak, 2005) (18), (de Ruiter et al., 2016) (20) with two follow-up studies (Studies: (Conklin et al., 2016) (3), (Chung, Li, Chiu, Ho, & Lopez, 2015) (5)}. Additionally, three pilot RCT {Studies: (Patel et al., 2014) (4) , (Ruble, Scarvalone, Gallicchio, Davis, & Wells, 2016) (11), (Sabel et al., 2016) (12)}, two quasi-experimental trials {(Studies: (Dubnov-Raz et al., 2015) (6), (Poggi et al., 2009) (19)} and two pilot quasi-experimental trials {(Studies: (Yeh, Man Wai, Lin, & Chiang, 2011) (14), (Devine et al., 2016) (16)}. Studies were published between 2004 and 2018. In total, 1119 children and adolescents (mean sample size = 56; range = 12 - 161) with a mean age of 11.43 years participated in the studies. Forty-five percent of the studies included survivors of both brain tumors (BT) and ALL, 30 percent of studies included only survivors of BT, 20 percent included only survivors of ALL, and 5 percent included survivors of various cancer types. Based on the studies included, we further categorized studies into cognitive (studies: 1, 2, 3, 4), physical activity (studies: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14) and psychosocial/psychological intervention studies (studies: 15, 16, 17, 18, 19, 20).

Methodologic quality of studies

The methodological quality score for each study is included in Table 2. The studies` methodological quality ranged from a score of 9 to 26 (maximum: 27) with a mean score of 16.75. Not surprisingly, the RCT (mean = 17.85) and pilot RCT (mean = 18.00) had higher scores than the quasi-experimental studies (mean = 10.50) and the pilot quasi-experimental studies (mean = 14.00). In short, half of the studies provided details of how the interventions were standardized (Studies: 1, 2, 4, 12, 14, 15, 16, 17, 18, 20), and 20 percent of the studies provided details of how adherence of care providers with the protocol was assessed or enhanced (Studies: 1, 15, 16, 18). Less than half of the studies (45 percent) provided information on how sample sizes were determined (Studies: 1, 2, 3, 7, 10, 12, 15, 17, 20). There was a variety of randomization methods including envelopes to more sophisticated methods like computerized minimization algorithms. Sixty percent of the studies provided details on the method used to generate the randomization procedure (Studies: 1, 2, 3, 4, 8, 9, 10, 12, 15, 17, 18, 20). In non-pharmacological interventions, blinding participants and those

administering the interventions to group assignment was not viable. However, blinding the examiners assessing the outcomes to group assignment was implemented in 40 percent of the studies (Studies: 2, 3, 4, 8, 9, 10, 12, 20). In terms of adverse events, 35 percent of the studies reported on adverse events or side effects in any of the intervention groups (Studies: 1, 3, 9, 10, 11, 16, 20). The methodological quality score of each study should be taken into account when considering the corresponding study results.

Cognitive intervention studies

Four cognitive studies (Studies: 1, 2, 3, 4) consisting of two RCT with one follow-up study, and one pilot RCT study including 341 participants were identified (Table 2). The reviewed cognitive studies used different interventional approaches: (a) direct approach using a computerized working memory training (Studies: 2, 3); (b) compensatory technique using a parent-directed intervention (Study: 4); (c) cognitive remediation program (CRP) including approaches of brain injury rehabilitation, educational psychology, and child clinical psychology (for details see Butler & Copeland, 2002, Study: 1). The cognitive studies varied in terms of setting, the direct approach, namely the computerized working memory training was home-based (Studies: 2, 3) while the parent-directed intervention and the CRP were clinic-based interventions (Studies: 1, 4). Range of the interventions duration lasted from three to five months. While the direct training approach showed more sessions of shorter durations (Studies: 2, 3), the compensatory approach showed fewer sessions of longer durations (Study: 4).

The specific cognitive outcomes that were assessed in the cognitive interventions are listed in Table 3. Two RCT and one follow-up study investigated the effect of the intervention on the participants' *attention* (Studies: 1, 2, 3). The computerized working memory showed improvements on attention after the training (Study: 2), that did not persist over a six months delay (Study: 3). The CRP showed improvements in attention by parents' reports, but not in the children's reports (Study: 1). Two RCT and one follow-up study examined the effects of treatment on *working memory* performance (Studies: 1, 2, 3). The computerized working memory intervention reported that working memory could be significantly increased after the training (Study: 2). Remarkably, this effect remained present after six months (Study: 3). Furthermore, the computerized working memory showed improvements on *processing speed* (Studies: 2), that persisted six months later (Study: 3). The CRP and the parent-directed intervention showed improvements on *learning strategies* (Studies: 1, 4). Three studies were described as feasible, that means that at least 70 percent of the participants completed the

intervention (Studies: 2, 3, 4). However, in CRP the completion rate of participants was under 70 percent (Study: 1).

Physical activity studies

Ten physical activity interventions including six RCT with one follow-up, two pilot RCT and one pilot quasi-experimental study (Studies: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14) including 347 PCS were identified (Table 2). The reviewed physical activity interventions used different interventional settings: (1) home-based physical exercise programs (Studies: 7, 12, 13, 14); (2) both, clinic and home-based interventions (Studies: 9, 10); (3) community interventions within a group-based format supplemented with psychoeducational components (Studies: 5, 8, 11), and without psychoeducational components (Study: 6). The duration of training varied between a short and intense 5 day training to six months. Aerobic exercises in combination with other forms of training appeared to be the most frequent type of training across studies.

The included physical activity interventions evaluated predominantly psychological and physical activity outcomes as outlined in Table 3. One pilot RCT and one RCT study reported statistically significant benefits on *self-efficacy* (Studies: 11, 8). Remarkably, this effect remained substantial over after18 months (Study: 5). None of the studies found benefits on *self-esteem* (Study: 7), *anxiety* (Study: 13), and *social functioning* (Studies: 7, 13). One pilot quasi-experimental study found significant decreases in *fatigue* (Study: 14) compared to the control group. One RCT and one quasi-experimental study examined the effects of treatment on *mood* (Studies: 6, 7). However, mood was significantly increased compared to the control group only in the RCT study (Study: 7). Improvements in *HRQL* could be achieved in one study (Study: 5), while the others failed to show improvements in *HRQL* (Studies: 6, 8, 9, 13)

The majority of physical activity intervention reported statistically significant benefits on physical activity outcomes in the treatment groups. Positive effects were reported on *motor performance* (Studies: 9, 12, 13), and *process skills* (Study: 12). Three RCT reported significant findings on *physical activity measures* (Studies: 8, 9, 10), and that effect remained stable over after 18 months (Study: 5). One (Study: 9; RCT) out of two (Study: 6; quasi-experimental study) studies demonstrated a significant result on *aerobic fitness* in the treatment group compared to the control group.

Two physical activity studies examined the effect of the intervention on the participants' *cognitive outcomes* (Studies: 10, 12; 2 RCT). One study (Study: 10) demonstrated significant improvements on *attention* compared to the control group. None of the two studies revealed

significant treatment effects on *working memory*, *processing speed*, *verbal fluency*, and *memory*.

All but one physical activity studies provided information on how many participants completed the entire treatment (Studies: 5, 6, 7, 8, 9, 10, 11, 12, 14), and can be described as *feasible* (at least 70 percent of the participants completed the intervention).

Psychosocial/psychological studies

Six psychosocial and psychological interventions including four RCT (Studies: 15, 17, 18, 20), one quasi-experimental study (Study: 19), and one pilot quasi-experimental study (Study: 16) including 431 PCSs were identified (Table 2). These interventions used different interventional settings: (a) hospital-based (Studies: 15, 18, 19), (b) community and hospital-based (Study: 17) (c) school-based (Study: 16), and (d) home-and school-based (20). Therapeutic approaches differed across studies: (a) social skill training (Study: 15); (b) peer-mediated classroom intervention (Study: 16); (c) cognitive behavioral therapy (Studies: 19) supplemented with a family therapy (Study: 18), and supplemented with psychoeducation and a physical training (Study: 17); (d) Neurofeedback (Study: 20). The duration of training varied between one day and eight months.

The included psychosocial/psychological interventions evaluated predominantly *psychological and psychosocial* outcomes as outlined in Table 3. In detail, three RCT studies (Studies: 15, 17, 20) failed to provide statistical significant effects on *HRQL*. Moreover, no statistical significant effects were reported on *anxiety* (Study: 18; RCT), *fatigue* (Studies: 17; 20; RCT), and *self-esteem* (Study: 20, RCT). However, there is evidence for positive results on *adaptive functioning* (Study: 19, quasi-experimental study), *post-traumatic stress symptoms* (Study: 18, RCT), and *social functioning* (Studies: 15, 16, 19; RCT and two quasi-experimental studies). Two psychological studies examined treatment effects on *physical activity outcomes*, but did not provide evidence on benefits for *motor performance* (Study: 19; quasi-experimental study), and *visuomotor integration* (Study: 20; RCT). One study, namely the neurofeedback study (Study: 20; RCT), investigated the effect of the intervention on cognitive outcomes measures (attention, working memory, processing speed, memory). However, no positive effect was reported in any of the cognitive measures in the treatment group. *Feasibility* rates could be determined in five out (Studies: 15, 16, 17, 18, 20) of six studies, and can be described as feasible.

	Cognitive Studies (n = 4)	Physical Studies (n = 10)	Psychological Studies (n = 6)	All Studies (n = 20)
Cognitive Outcomes				
attention	2/3	1/2	0/1	3/6
working memory	2/3	0/2	0/1	2/6
processing speed	2/2	0/2	0/1	2/5
learning strategies	2/2	N A	N A	2/2
memory	0/1	0/1	0/1	0/3
academic achievement	2/4	N A	N A	2/4
Psychological Outcomes				
quality of life	N A	1/5	0/3	1/8
self-efficacy	N A	3/3	N A	2/3
anxiety	N A	0/1	0/2	0/3
social functioning	N A.	0/2	3/5	3/7
fatigue	N A	1/1	0/2	1/3
self-esteem	0/1	0/1	0/1	0/3
mood	N A	1/2	N A	1/2
Physical Activity Outcomes				
motor performance	N A	3/3	0/1	3/4
physical activity	N A	4/5	N A	4/5
aerobic fitness	N A	1/2	N A	1/2
Feasibility	3/4	9 / 9	5/5	17/18

Table 3 - *Synthesis of Significant Outcome Effects*

Discussion

This review`s aim was to systematically evaluate and critically appraise the current state of evidence on non-pharmacological intervention studies for PCSs to inform practitioners as well as investigators working in this area. We identified 20 non-pharmacological studies that we categorized into cognitive, physical activity and psychosocial/psychological interventions. The reviewed studies vary in terms of settings, training approaches, and outcomes, even within the single category. The interventions as well as the long-term effects PCS may experience are diverse and multifaceted to suggest that one approach is clearly superior to another. However, we sought to highlight the perspective from the outcome measures in light of the methodological quality of studies in order to document what kind of outcomes can be tackled – if at all – through what kind of intervention.

Cognitive interventions

Direct computerized working memory programs are the most straightforward approach for tackling core cognitive functions (i.e., working memory, attention and processing speed). The

cognitive studies reviewed here, seem to indicate some efficacy for improving trained cognitive functions (near-transfer). However, improvements in broader domains (i.e., academic performance) are less compelling. Although they appeared feasible, practitioners need to be aware that these interventions are demanding, and continuous motivation as well as close personal support seem warranted to prevent preterm termination of the training. For tackling academic achievement and learning strategies, the reviewed CRP and the parent-directed intervention provide preliminary support as useful intervention approaches. However, there was no evidence for improving core cognitive domains such as working memory and attention in compensatory studies.

Physical activity interventions

Fifty percent of our reviewed studies represent physical activity studies. The reason for the high percentage of physical activity interventions might be that physical activity most likely engage multiple mechanisms that benefit multiple domains important for PCS. Physical interventions reported predominantly positive findings on motor performance and physical activity parameters. In terms of psychological outcomes, these interventions seem promising in enhancing self-efficacy. There is preliminary support that physical activity studies can promote cognitive skills, namely attention in PCS, when conducted in a group setting. While there are first promising findings, research in this field has only recently emerged and more physical activity interventions also incorporating cognitive measures are needed to determine the effect of physical activity on cognitive functions in this population.

Psychosocial/psychological interventions

In order to improve psychosocial functioning, social skill trainings and cognitive and behavioral therapy, seem to be promising for children and adolescents surviving brain tumors. More precisely, social skill trainings are in particular helpful for those children and adolescents surviving brain tumors who demonstrate low scores on social skills at baseline (Study: 17). Further, when addressing psychological outcomes, such as post-traumatic stress symptoms, cognitive behavioral and family therapy provides preliminary support to consider as suitable approach. When considering neurofeedback as an intervention approach, it should be noted that this type of intervention showed no favourable effects on psychosocial and cognitive measures in survivors of BT (Study: 20).

Implications for research

There is a positive trend towards higher quality studies and an increasing awareness towards methodological considerations within the latest published studies reviewed here (mean methodological quality rate of 19.5 for reviewed studies published within the last three years versus mean methodological quality rate of 14.9 for reviewed studies published between 2000 and 2015). Researchers are encouraged to pursue this positive trend by employing adequate and standardized methodological criteria allowing to investigate "pure" intervention effects. Besides core methodological criteria, an increased statistical power through the inclusion of larger samples, reporting effect sizes, confidence intervals, and correction for multiple significance tests are highly recommended. Further, consideration needs to be given to complete and transparent reporting of how the trials were designed, analysed, and interpreted. Using established guidelines and checklists such as the CONSORT (CONsolidated Standards of Reporting Trials) when preparing reports of trail findings are highly recommended to bring this young research field forward.

Given the multifactorial nature of intervention mechanisms, a broader scope of domains that are potentially targeted by the intervention should be taken into account. Cognitive studies for instance may need to incorporate other outcomes than cognitive measures alone such as psychological, psychosocial and health-related quality of life outcomes. Some of the reviewed physical activity interventions give a good example in targeting a broad spectrum of outcomes including, cognitive, psychological, psychosocial, physical activity and HRQL outcomes.

Moreover, the long-term retention of intervention effects is hard to estimate on the existing data and warrants long-term follow-up assessments. Following the study of Riggs and colleagues (2017), and Conklin and colleagues (2015), collecting neuroimaging data embedded in longitudinal study seem to provide a fruitful approach. These may provide a better understanding of the underlying mechanisms – if substantial improvements in one or more domains can be achieved – by providing insights on persistent, post-intervention changes in brain structure and function.

It should be noted that individual factors (i.e., developmental stage, treatment history, former and current experiences, motivation etc.) as well as environmental resources (i.e., family situation, parental involvement, school involvement, etc.) considerably influence the child's response to an intervention. Until now, it remains unclear how these factors interact with each other. In future studies, consideration needs to be given to these factors and research in this area will provide important insights into moderating factors of the effectiveness of interventions.

In conclusion, readers are reminded that yet most of the reviewed studies apply one-dimensional interventions (i.e., pure cognitive trainings) based on the targeted late-effect (i.e., cognitive, psychosocial, physical etc.). Combining different types of interventions using a multimodal approach (e.g., cognitive-behavioral and physical, pharmacologic and cognitive) that are matched to the level of needs of former pediatric patients may lead to synergistic benefits (Olson & Sands, 2016).

Implications for clinical practice

Although the described interventions are based on different underlying mechanisms, they share common characteristics, pointing towards important implications for clinical practice. Firstly, a supportive environment such as parent-directed approaches or the support of coaches are crucial for interventions to be beneficial. In particular, a supportive environment enables and helps the child to adhere to the interventions, and thereby optimizes interventional outcomes of the child. This is in accordance with the literature emphasizing the important role of environmental factors in the recovery processes after early brain insult (Anderson et al., 2011). Secondly, the involvement of peers seems to offer another beneficial opportunity for interventions in particular for physical activity interventions. This might be in particular important for survivors reaching adolescence since this time is specifically marked by the importance of peer relationships (Brown & Larson, 2009). Thirdly, given that the described non-pharmacological interventions may improve recovery in a broad range of domains, a profound neuropsychological assessment that enables to identify vulnerable domains appears mandatory. In a next step, then, the intervention can be tailored individually to the child`s strengths and weaknesses. Finally, children and adolescents showing the lowest performance across domains seem to benefit the most from the interventions. Thus, “high risk” children not only need interventions the most, but also seem to benefit the most.

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Supplemental Appendix A: Search Terms

The first group included participant-related keywords ("child*" or "paediatric" or "pediatric" "adolescent" or "schoolchild" or "adolescent*" or "adolescence" or "cancer" or "oncology" or "pediatric oncology" or "brain tumor" or "pediatric brain tumors" or "childhood cancer" or "childhood cancer patients" or "survivors" or "central nervous system tumors" or "childhood brain tumor survivors" or "survivorship" or "childhood acute lymphoblastic leukemia" or "acute lymphoblastic leukemia" or "all" or "leukemia" or "pediatric cancer survivors" or "survivors of pediatric cancer" or "pediatric cancer patients" or "childhood cancer survivors" or "former cancer patients") and a second group of intervention-related keywords ("cognitive remediation" or "cognitive remediation program" or "computerized cognitive training" or "cognitive rehabilitation" or "cognitive rehabilitation program" or "working memory training" or "psychosocial intervention" or "psycho-social intervention" or "psycho social intervention" or "cognitive behavioural therapy" or "social-skills training" or "group social skills" or "social problem solving" or "social performance" or "group social skills intervention" or "psychological training"or "psychological therapy" or "psychotherapy" or "physical activity" or "physical therapy" or "physical therapy intervention" or "physical fitness" or "group physical activity" or "exercise" or "exercise intervention" or "exercise training" or "exercise program" or "fitness" "psychological" or "psychotherapy") and a third group of outcome-related keywords ("cognitive functioning" or "cognitive late effects" or "attention" or "attention problems" or "executive function" or "executive function skills" or "working memory" or "academic" or "neuropsychology*" or "social" or "psychosocial" or "psycho-social" or "psycho social" or "psychosocial functioning" or "psycho-social functioning" or "psycho social functioning" or "psychological problems" or "social skills" or "self-efficacy" or "health related quality of life" or "HRQL" or "quality of life" or "qol" or "well-being").