# A systematic review of interventions for neurocognitive dysfunctions in patients and survivors of a pediatric brain tumor.

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**Abstract**

Due to a high burden of neurocognitive impairment on patients with a pediatric brain tumor, interventions mitigating these symptoms are highly needed. Currently, evidence on the efficacy and feasibility of such interventions remain scarce. A systematic literature study was performed based on four different databases (PubMed, Web of Science Core Collection, Embase and PsycArticles). Resulting articles (n=2232) were screened based on title and abstract, and full text. We included 28 articles, investigating cognitive effects of either a lifestyle intervention (n=6), a cognitive training (n=15), or pharmacological intervention (n=7). The most frequently studied interventions were the Cogmed and methylphenidate. Most interventions showed short-term efficacy. Fewer interventions also showed long-term maintenance of positive results. Despite positive trends of these interventions, results are heterogeneous, suggesting relatively limited efficacy of existing interventions and more potential of more individualized as well as multimodal approaches for future interventions.

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A short running title

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Keywords

Brain tumor, children, neurocognitive intervention

Abbreviation List

| ABAS | Adaptive Behavior Assessment Scale |
|---|---|
| ASEBA | Achenbach System Empirically Based Assessment |
| BEERY VMI | Beery-Buktenica Developmental test of learning |
| BRIEF | Behavioral Rating Inventory of Executive Function |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CBCL | Child Behavior Checklist |
| ChT | Chemotherapy |
| CMS | Children Memory Scale |
| CPT | Continuous Performance Test |
| CRC | Cognitive rehabilitation curriculum |
| CRP | Cognitive remediation program |
| CSI | Craniospinal irradiation |
| D-KEFS | Delis Kaplan Executive System Sorting test |
| HRQoL | Health Related Quality of Life |
| MEG | Magnetoencephalography |
| MPH | Methylphenidate |
| MRI | Magnetic Resonance Imaging |
| N.A. | Not Applicable |
| N.R. | Not reported |
| NCI | Neurocognitive impairment |
| NIH Toolbox CB | National Institutes of Health Toolbox Cognition Battery |
| PBT | Pediatric brain tumor |
| PedsQL | Pediatric Quality of Life Inventory |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QoL | Quality of life |
| RCMAS | Revised child manifest anxiety scale |
| RCT | Randomized controlled trial |
| RT | Radiotherapy |
| SE | Standard error |
| SSRS | Social skills rating system |
| WAIS | Wechsler Adult Intelligence Scale |
| WASI | Wechsler Abbreviated Scale of Intelligence |
| WIAT | Wechsler Individual Achievement Test |
| WIE | Wechsler Intelligenztest fur Erwachsene |
| WISC | Wechsler Intelligence Scale for Children |
| WM | Working memory |

Declarations Section

**Ethical Approval**

Not applicable.

**Competing Interests**

Not applicable.

**Authors' Contributions**

Bullens Kristien: screening and review of articles, data analysis, data interpretation, and writing of the manuscript; Sleurs Charlotte: design of the review, screening and review of articles, data interpretation and

manuscript editing; Blommaert Jeroen: data interpretation and manuscript editing; Lemiere Jurgen and Jacobs Sandra, conceptualization, design of the review, data interpretation, and manuscript editing. All of the authors approved the final version of the manuscript for submission.

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**Abstract**Due to a high burden of neurocognitive impairment on patients with a pediatric brain tumor, interventions mitigating these symptoms are highly needed. Currently, evidence on the efficacy and feasibility of such interventions remain scarce. A systematic literature study was performed based on four different databases (PubMed, Web of Science Core Collection, Embase and PsycArticles). Resulting articles (n=2232) were screened based on title and abstract, and full text. We included 28 articles, investigating cognitive effects of either a lifestyle intervention (n=6), a cognitive training (n=15), or pharmacological intervention (n=7). The most frequently studied interventions were the Cogmed and methylphenidate. Most interventions showed short-term efficacy. Fewer interventions also showed long-term maintenance of positive results. Despite positive trends of these interventions, results are heterogeneous, suggesting relatively limited efficacy of existing interventions and more potential of more individualized as well as multimodal approaches for future interventions.

Introduction

Over 40% of survivors of a pediatric brain tumor (PBT) experience long-lasting neurocognitive impairment (NCI), which have a detrimental impact on other psychosocial domains such as academic achievement, marital status, and overall quality of life (QoL)[1–3]. Hence, the medical field encounters major challenges in minimizing these late effects during PBT survival[3,4].

Complex interactions between tumor-, cancer therapy-, and patient- related risk factors affect NCI[4,5]. Recently, treatment protocols are being innovated towards a careful trade-off between tumor treatment and sustaining neurocognitive and psychosocial functions[5]. Patient-related risk factors, such as access to healthcare, lifestyle, neurocognitive and social support, have been associated with less NCI[2,6]. Targeting these risk factors offer potential pathways to mitigate NCI and maintain psychosocial well-being[5]. In addition to addressing patient-specific risk factors, neurocognitive interventions aim to directly target and improve neurocognitive functioning. Three general categories of interventions can be distinguished, including: lifestyle-, cognitive- and pharmacological interventions through neuro-protective and restoring mechanisms. Physical exercise training has been shown to improve neurocognition through mechanisms such as increased cerebral blood flow, neurogenesis, and synaptic plasticity[7,8]. Furthermore, cognitive rehabilitation can assist to engage brain plasticity through retraining specific neurocognitive functions or by teaching compensatory strategies. Finally, pharmacological compounds can directly or indirectly ameliorate neurotransmission[4,8,9 7,8].

With this systematic review, we aim to provide a comprehensive overview as well as an insight into the efficacy of all possible interventions targeting NCI in patients with a PBT. In addition, a discussion of clinical implications and necessary efforts for future research are provided. Ultimately, these insights may facilitate evidence-based guidelines for interventions targeting NCI, to preserve and improve neurocognitive abilities of patients with a PBT.

Materials and Methods

2.1 Search Strategy This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[10]. Comprehensive literature searches were conducted within PubMed, Web of Science Core Collection, Embase and PsycArticles databases, based on three main

components: brain tumors, neurocognitive intervention, and children. The detailed search strategy is outlined in Supplementary Table 1.

### 2.2 Study Selection and data collection

Title and abstract screening were conducted by two independent reviewers (CS and KB) in Rayyan[11]. Interrater reliability between the reviewers was calculated using the Cohen's kappa coefficient and any disagreements were resolved by discussion until consensus[12]. The remaining articles were eligible for inclusion after full text screening, if a study investigated the efficacy of a neurocognitive intervention in patients with a PBT. Studies were also required to fulfil following criteria: published in English, sample size larger than 5, and at least 50% were patients with cancer. Systematic screening was complemented by a manual search of cited references from included articles.

Information was extracted from included studies using a predefined data extraction sheet, capturing details such as information on the author, publication year, type of intervention, study design, prescribed dose, total number of inclusions, age at start of the intervention, age at treatment/diagnosis, time since treatment/diagnosis, geographic location, neurocognitive assessment battery, compliance, and key results. Included articles were classified according to three intervention categories: lifestyle, cognitive, and pharmacological. Quality of individual studies were evaluated in accordance with the PRISMA guidelines and risk of bias assessment is described in supporting information[10].

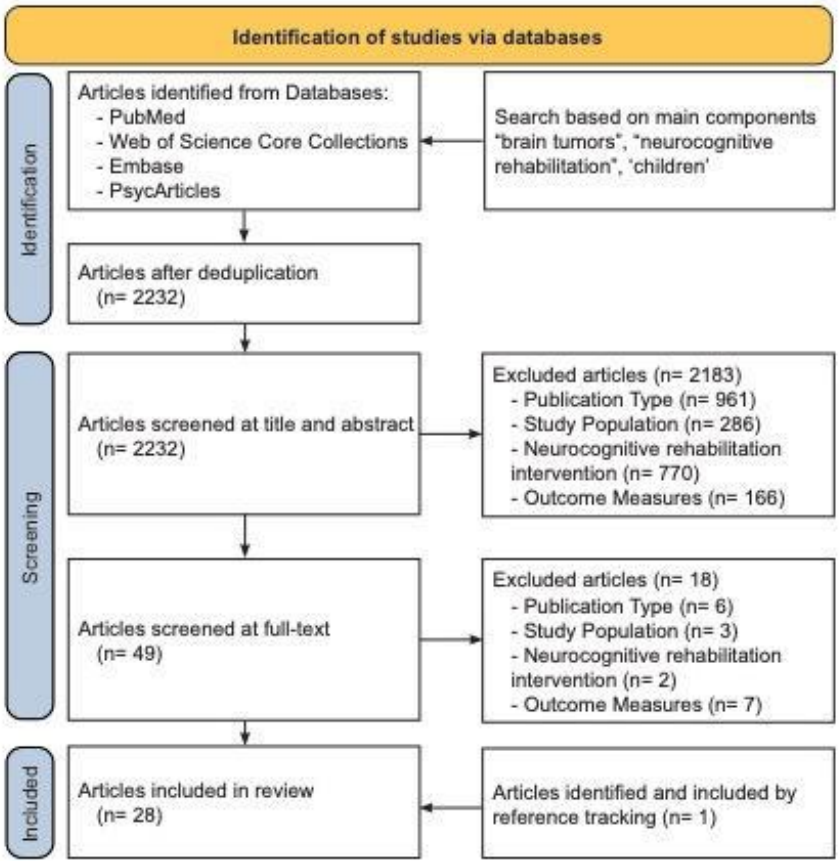


**FIGURE 1** Flow diagram showing the selection procedure

Results

3.1 Study Characteristics A total of 2 232 unique articles were identified from the search of which 27 were included upon full text screening (Figure 1). One additional paper was included based on manual reference tracking. Cohen's K=0.94 for interrater reliability.

The characteristics of the 28 included articles are presented in Table 1. Nineteen unique study populations were identified among all included articles. Studies were conducted in North America (USA: n=20, Canada: n=4), Europe (n=3), or Australia (n=1), and published between 2001 and 2022. Only 12 studies exclusively included patients with a PBT. Participants' mean age at diagnosis and at study inclusion ranged from 3.5 to 10.0 years and 10.3 to 19.8 years, respectively. Most studies recruited patients who completed cancer treatment, while two studies included patients during their cancer therapy, and one study included both[13–15]. Furthermore, fifteen articles implemented the inclusion criterion of NCI in at least one domain[16–30] .

The effectiveness of the interventions was measured in nearly all studies using objective neurocognitive assessments, or proxy-reported measurements of neurocognition (Table 2). Almost half (n=13) of the articles measured intervention efficacy immediately post-intervention (less than 3 weeks after intervention or indicated as post-intervention)[19–25,30–35]. The other half (n=15) also considered and measured maintenance of possible intervention effects (range 12 weeks – 2.9 years after intervention completion)[13–18,26–29,36–40]. For results of risk of bias, we refer to supplementary information (Supplementary Figure S1).

### 3.2 Types of interventions for NCI

Three categories of interventions were distinguished: 1) lifestyle interventions, 2) cognitive training, and 3) pharmacological interventions. An overview of different interventions and their results are given in table 1 and 2.

Lifestyle interventions

Four articles (3 study populations) implemented a 12-week aerobic exercise training program [13,33–35]. Immediate improvement in reaction times was seen when participants trained in a group setting, and these improvements could be predicted by improved fitness[33,35]. Furthermore, exercise training showed a positive impact on white matter microstructure (as indicated by higher fractional anisotropy based on diffusion-weighted MRI) as well as hippocampal volume, and on MEG-derived functional connectivity. The positive effect on white matter microstructure maintained at 12 weeks after completion of the training. Additionally, the training program led to an increase in cortical thickness which was also associated to a decrease in reaction time[35]. One study reported that no adverse events occurred, and that drop-out rate amounted 14.3%[35].

Another exercise training intervention, in which training consisted of individually tailored strength-based exercises and aerobic activities (modified every 3-4 weeks), showed no significant improvement in mental health nor in objective neurocognitive functioning. By contrast, self-reported measures of community use, home living, health and safety, leisure, and self-direction did improve. Thirty-five percent of the participants dropped out of the study and one fall without physical injury was reported[40].

A last exercise intervention implemented physical activity (strength, endurance, and speed exercises) with simultaneous attentional challenges (verbal stimuli). The exercise intervention was administered as a period of physical training followed by a period of combined training or reversed. Improvements were seen in all groups for verbal long-term memory (baseline compared to post-intervention), as well as for organization, and anxiety and emotional control (post-observation compared to post-intervention). Additionally, they found no difference between patients on or off cancer treatment They did not report on adverse events and drop-out rate was 16.7%[13].

Finally, eurythmy therapy is a form of mind-body therapy. One study demonstrated that all patients (n=7) completing 25hours of eurythmy therapy in a period of six-months, improved in full-scale IQ and processing speed. Working memory (WM), perceptual reasoning, verbal comprehension, and visual motor integration improved in six, five, three, and five patients, respectively. This study did not report on adverse events[36].

Cognitive training

Regarding cognitive training, six articles (5 study populations) employed the adaptive computerized working memory (WM) training, Cogmed[26–28,31,37,38]. Participants receiving Cogmed training showed improvement on attention, processing speed, WM, symbolic WM and executive functions immediately post-intervention[27,28,31]. WM scores and fluent cognition were improved at 9.1 weeks post-intervention, and improvement on fluent cognition remained stable at 14.5 weeks [38]. Improvement on processing speed, executive functions WM, visual-spatial WM, academic achievement, emotional and behavioral problems, and social skills and remained stable at six months post-intervention[27,28,38]. In contrast, scores on two attention tasks changed over time: spatial span forward (WISC-V) deteriorated and omissions on the CPT improved[27,28]. Finally, most stable improvement over time was observed for fluent cognition and executive functioning at 13.5 months post-intervention[38].

No difference was observed between adaptive and non-adaptive Cogmed training[38]. Compared to a non-adaptive WM training (MegaMemo), adaptive Cogmed training did show greater improvement in parent-reported learning difficulties[26]. Adaptive Cogmed did not show a difference in WM improvement compared to JumpMath (a workbook program directly targeting math skills), however the improvement in mathematics (greater improvement for JumpMath group) and symbolic WM (greater improvement for Cogmed group) was different among these interventions [31]. Higher pre-intervention IQ and greater number of completed sessions predicted greater post-intervention improvement[26,28]. Nevertheless, there was no significant difference between 25 and 35 Cogmed sessions[37] .

Functional MRI (fMRI) found that Cogmed training reduced activation of lateral prefrontal, left cingulate and bilateral medial frontal regions during a WM task, however, this was not associated with WM outcome[27]. Adverse events concerning Cogmed were either not reported, or the study stated that no adverse events had occurred[26,28,37]. Drop-out rates varied between 4.8% to 25%.

Another computerized intervention, Fast ForWord, focuses on training reading skills. This training effect was investigated in medulloblastoma patients during radiotherapy. Compared to the standard of care group, no significant differences were observed immediately post-intervention. At subsequent follow-up timepoints (up to five years post-intervention), specifically greater sound awareness was encountered at 2.9 years (range 1.6 – 4.5 years) post-intervention[14,15]. Only 16.3% of participants completed the prescribed sessions and 7.0% dropped-out of the study[14]. Patients were excluded from the study if they experienced an adverse event, however, it was not specified whether patients discontinued for this reason.

A last game-like cognitive training intervention that was investigated in pediatric brain tumors, was the Captain's Log (n=9), designed to improve multiple neurocognitive domains including memory, attention, concentration, listening skills, self-control, and processing speed. After on average 28.4 sessions (range 9-53), improvement was seen for digit-span forward (WISC-III) and parent-reported attentional problems. Results of the digit-span forward (WISC-III) task were positively correlated with pre-intervention IQ. No adverse events were reported[29].

In addition to interventions focusing on improving neurocognitive functioning, other interventions were identified with the aim of teaching compensatory strategies. Two studies applied a cognitive remediation program (CRP)[17,18]. CRP is a therapist-delivered framework designed to reinforce multidimensional aspects of attention processes, encompassing hierarchically graded massed practice, strategy acquisition, and cognitive-behavioral interventions[17,18]. Immediately post-intervention, improvement on academic achievement, parent- and teacher-reported attention and hyperactivity symptoms and attention, WM, memory recall, and vigilance was observed in the CRP group[17,18]. fMRI showed increased regional activity in the CRP group both immediately and six months after intervention, and these patterns were more closely resembling those of typical developing children[18]. There were no adverse events reported[17].

The cognitive rehabilitation curriculum (CRC) is an online training focusing on cognitive flexibility, attention and WM. Participants showed increased processing speed, cognitive flexibility, and verbal- and visual memory immediate post-intervention. Additionally, fMRI demonstrated increased activation in the inferior, superior,

and middle frontal gyrus compared to pre-intervention activation patterns. They did not report on possible adverse events[30].

Two therapist-delivered training programs were studied as well. The first one was cognitive and problems-solving training, which targeted broader metacognitive functions through educational therapy, cognitive behavioral and rehabilitation approaches. Post-treatment improvements were specifically significant for reported social skills scores and quality of written expression. Adverse effects were not reported, and drop-out rate amounted 25%[25]. The second one was a survivor's Journey, targeting executive dysfunctions through behavioral problem-solving therapy and metacognitive strategies. A survivor's Journey showed to improve self-reported emotional QoL, parent reported total QoL and physical QoL immediately after the intervention. Furthermore, their exploratory analysis showed that intervention effects varied based on age at diagnosis and pre-intervention IQ. No information was provided regarding adverse events. Only 10.5% dropped-out of the study[32].

Finally, the last cognitive training is neurofeedback training. This training targets specific beta frequencies associated with arousal and attention. Bot the intervention- and placebo- group showed post-intervention improvement, without significant effect of the neurofeedback training. No serious adverse events were reported and drop-out rate amounted 11.3%[16].

Pharmacological interventions

Two pharmacological compounds, methylphenidate (MPH) and donepezil, have been studied in patients with a PBT. MPH was studied in six articles. Immediate neurocognitive response of a single MPH administration showed a significant effect on selective attention, impulsivity, and cognitive flexibility[21]. Immediate improvement in sustained attention was assessed in two studies, but only significant in one study[19,21]. A 3-week crossover trial (placebo, low dose MPH, and high dose MPH), showed improvement of parent- and teacher reported scores on attention and cognitive problems, improved attention deficit/hyperactivity disorder index for low and high dose MPH[20,22]. Additionally, teachers reported improved social and academic competences, less hyperactivity symptoms, and less problem behavior. Though, less problem behavior was only seen in the high-dose MPH group[20,22]. Finally, a 12-month study with individually titrated MPH dose showed improvement in reported measures of attention, hyperactivity, and attention deficit/hyperactivity disorder in both the MPH- and the control group. However, improvement was significantly larger for measures of attention and attention deficit/hyperactivity disorder in the MPH group compared to control[23,24]. Sustained attention and processing speed were also significantly improved, and improvement in attention was already present after 1 month with a rebound after 3 months[23,24] Modest agreement was observed between parent- and teacher- ratings, and poor agreement was observed between reported ratings and performance-based measures[23,24]. Studies reported various adverse events in the MPH group as well as in the control group. Reported adverse events included abdominal pain, appetite loss, wheezing, dizziness, anxious, tearful, and many more[19–21]. The range of reported drop-out rates was between 10.5% and 33.8%[19,20,23,24].

Donepezil, an acetylcholinesterase inhibitor, was described in one study and showed significant improvement on executive functioning immediately post-intervention, and these improvements persisted after a wash-out period of 12-weeks. Additionally, moderate improvements in parent-reported planning/organizing, WM, and memory were seen. The drop-out rate was 27.3%. Several adverse events were reported, 30% of the participants reported gastro-intestinal problems and 17% reported non-specific mood changes and confusion. Nevertheless, 75.0% of patients preferred re-administration after treatment completion because of perceived benefit[39].

**Table 1**
Summary of study characteristics

| **Reference (year)** | **Study design** | **Design of intervention** | **Age at diagnosis (Mean age, years) (Time since treatment (Mean time since diagnosis, years))** | **Experimental Sample (Mean age at pre-intervention)** | **Control sample (Mean age at pre-intervention)** |
|---|---|---|---|---|---|
| Riggs et al. (2017) | Open-label, RCT with crossover | Exercise training (Group setting: 3x 90min/week, 12 weeks Home setting: 2x 90min/week, 2x 30min/week, 12 weeks) | Mean age: Training first group 11.19±2.98 (5.53±2.38) No training first group 12±3 (5.88±3.41) | n=28, all hemispheric or posterior fossa tumors with heterogeneous therapies (Mean age: Training first group 5.61±2.61, No Training first group 6.33±1.56) | n=28, typically developing control |
| Szulc-Lerch et al. (2018) | Open-label, RCT with crossover | Exercise training (Group setting: 3x 90min/week, 12 weeks Home setting: 2x 90min/week, 2x 30min/week, 12 weeks) | Mean age: Training first group 11.19±2.98 (5.53±2.38) No training first group 12±3 (5.88±3.41) | n=28, all hemispheric or posterior fossa tumors with heterogeneous therapies (Mean age: Training first group 5.61±2.61, No Training first group 6.33±1.56) | n=28, typically developing control |
| Cox et al. (2020) | Open-label, RCT with crossover | Exercise training (Group setting: 3x 90min/week, 12 weeks Home setting: 2x 90min/week, 2x 30min/week, 12 weeks) | Mean age: Training first group 5.77±2.75 (5.28±2.40) No training first group 6.56±1.64 (5.86±3.43) | n=25, all hemispheric or posterior fossa tumors with heterogeneous therapies (Mean age: Training first group 11.10±3.19, No Training first group 12.47±2.94) | n=25, typically developing control |

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|---|---|---|---|---|---|
| Rath et al. (2018) | Longitudinal Single-arm, Open-Label | Individually tailored exercise training (3x/week, 24 weeks) | Mean age: 3.9 (11.1) | n=20, heterogeneous cancer, and treatment types (Mean age:19.8) | N.A. |
| Fontana et al. (2021) | Open-Label, RCT with crossover | Purely physical or physical and attentional exercises (60min/week, 10 months) | N.R. | n=20, heterogeneous cancer, and treatment types (Mean age: 10.8) | N.A. |
| Kanitz et al. (2013) | Longitudinal Single-arm, Open-Label | Eurythmy Therapy (25 hours, 6 months) | Mean age: 7.1±3.2 (/) | n=7, all cerebellar tumors with heterogeneous therapies (Mean age: 11.16±4.37) | N.A. |
| Patel et al. (2009) | Longitudinal Single-arm, Open-Label | Cognitive and Problem-solving training (15 weeks, 60-90 min/session) | Mean age 5.96±4.86 (7.23±2.75) | n=12, heterogeneous cancer, and treatment types (Mean age: 11.75±3.77) | N.A. |
| Conklin et al. (2015) | Single-blinded RCT | Cogmed (25 sessions of 30-45 min/session, 5-9 weeks) | Mean age: Cogmed 5.15±2.92 (4.97±3.02) Control 4.62±2.68 (5.04±2.41) | n=34, heterogeneous cancer types treated with RT and/or intrathecal ChT, (Mean age: 12.21±2.47) | n=34, heterogeneous cancer types treated with RT and/or intrathecal ChT, (Mean age: 11.82±2.42) |
| Conklin et al. (2017) | Single-blinded RCT | Cogmed (25 sessions of 30-45 min/session, 5-9 weeks) | Mean age: Cogmed 5.15±2.92 (4.97±3.02) Control 4.62±2.68 (5.04±2.41) | n=34, heterogeneous cancer types treated with RT and/or intrathecal ChT, (Mean age: 12.21±2.47) | n=34, heterogeneous cancer types treated with RT and/or intrathecal ChT, (Mean age: 11.82±2.42) |

**Table 1**
(continued)

| **Reference (year)** | **Study design** | **Design of intervention** | **Age at diagnosis (Mean age, years) (Time since treatment (Mean time since diagnosis, years))** | **Experimental Sample (Mean age at pre-intervention)** | **Control sample (Mean age at pre-intervention)** |
|---|---|---|---|---|---|
| Hardy et al. (2013) | Double-blinded RCT | Cogmed or MegaMemo (25 sessions of 30-45 min/session, 5-8 weeks) | Mean age: Cogmed 4.9±3.54 (6.0±2.98) Control 5.7±2.88 (3.0±1.77) | n=14, heterogeneous cancer, and treatment types, (Mean age: 12.7±2.77) | n=7, heterogeneous cancer, and treatment types, (Mean age: 10.7±1.89) |
| Siciliano et al. (2021) | Single-blinded RCT | Cogmed: adaptive or non-adaptive (25 sessions of 30-45 min/session, 5 weeks) | N.R. | n=20, all brain tumors with heterogeneous therapies, (Mean age: 11.98±2.68) | n=21, all brain tumors with heterogeneous therapies, (Mean age: 11.98±2.68) |
| Carlson-Green et al. (2017) | Longitudinal Single-arm, Open-Label | Cogmed (35 sessions of 30-45 min/session, 8-10 weeks) | Mean age: 6 (5) | n=21, all brain tumors with heterogeneous therapies, (/) | N.A. |
| Peterson et al. (2022) | Longitudinal Single-arm, Open-Label | Cogmed or JumpMath (40 sessions, 30 min./session, 12 weeks) | Mean age: Cogmed 7.87 (5.36), JumpMath 4.49 (6.01), Control 4.70 (5.55) | Cogmed: n=10, (Mean age: 13.71), Jumpmath: n=9, (Mean age: 10.56), all brain tumors with cranial RT | n=9, all brain tumors with cranial RT, (Mean age: 10.28) |
| Palmer et al. (2014) | Open-Label, Single-blinded RCT | Fast ForWord (30 sessions of 48 min/session, 5 sessions/week, 6 weeks) | N.R. | n=43, all medulloblas-toma with CSI and ChT, (Mean age: 9.38) | n=38, all medulloblas-toma with CSI and ChT, (Mean age: 9.27) |

| | | | | | |
|---|---|---|---|---|---|
| Zou et al. (2016) | Open-Label, Single-blinded RCT | Fast ForWord (30 sessions of 48 min/session, 5 sessions/week, 6 weeks) | Mean age: Fast ForWord 10 (2.8), Control 9.5 (2.5) | n=21, all medulloblastoma with CSI and ChT, (Mean age: 11.7) | n=21, all medulloblastoma with CSI and ChT, (Mean age: 12.1); n=21, typically developing children, (Mean age: 12.3) |
| Hardy et al. (2011) | Longitudinal Single-arm, Open-Label | Captain's Log (50 min/week for 12 weeks) | Mean age: N.R. (5.7±3.20) | n=9, heterogeneous cancer, and treatment types, (Mean age: 13.3±2.44) | N.A. |
| Butler et al. (2008) | Open-Label, RCT | Cognitive Remediation Program (20x 120min/week, 4-5 months) | Mean age: CRP 4.9±3.3 (5.8±2.8), Control 5.6±3.4 (5.6±3.2) | n=108, heterogeneous disease, (Mean age: 10.8±3.4) | n=53, heterogeneous disease, (Mean age: 11.1±3.1) |
| Zou et al. (2012) | Open-Label, RCT | Cognitive Remediation Program (20x 120min/week, 4-5 months) | Mean age: CRP 5.0, Control 5.8 | n=8, heterogeneous cancer, (Mean age: 13.36) | n=6, heterogeneous cancer, (Mean age: 10.5) n=28, typically developing children, (Mean age:12.7) |
| Kesler et al. (2011) | Longitudinal Single-arm, Open-Label | Cognitive Rehabilitation Curriculum (40 sessions, 5 sessions/week, 20 min/session, 8 weeks) | Mean age: N.R. (3.1±2.5) | n=23, heterogeneous cancer, and treatment types, (Mean age: 12.6±4.1) | N.A. |
| Wade et al. (2020) | Longitudinal Single-arm, Open-Label | A Survivor's Journey (Independently online modules and weekly therapist session, 2-4 months) | Mean age: 6.83±3 (8.85±4) | n=19, all brain tumors with heterogeneous treatment types, (Mean age: 17.6±3) | N.A. |

**Table 1**
(continued)

| **Reference (year)** | **Study design** | **Design of intervention** | **Age at diagnosis (Mean age, years) (Time since treatment (Mean time since diagnosis, years))** | **Experimental Sample (Mean age at pre-intervention)** | **Control sample (Mean age at pre-intervention)** |
|---|---|---|---|---|---|
| De Ruiter et al. (2016) | Double-Blind RCT | Neurofeedback training (30 sessions, 30 min/session) | Mean age: Neurofeedback group 6.81±3.65 (7.64±4.04) Control sample 7.42±4.09 (6.03±2.99) | n= 34, all brain tumors with heterogeneous therapies (Mean age: 14.45±2.99) | n=37, all brain tumors with heterogeneous therapies (Mean age: 13.45±3.28) |
| Thompson et al. (2001) | Double-Blind RCT with crossover | Methylphenidate (Single does, 0.60 mg/kg) | Mean age: MPH group 3.5, Control 4.8 | n=15, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.3) | n=17, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.8) |
| Conklin et al. (2007) | Double-Blind RCT with crossover | Methylphenidate (Single does, 0.60 mg/kg) | Mean age at cancer treatment: 5.29±2.91 (4.71±2.90) | n=122, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.76±2.30) | N.A. |
| Mulhern et al. (2004) | Double-Blind RCT with crossover | Methylphenidate (5 days MPH administration, LD: 0.30 mg/kg, HD: 0.60 mg/kg, Placebo) | Mean age: 5.4±3.02 (4.9±3.12) | n=83, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.9±3.12) | N.A. |
| Conklin et al. (2010) | Double-Blind RCT with crossover | Methylphenidate (5 days MPH administration, LD: 0.30 mg/kg, HD: 0.60 mg/kg, Placebo) | Mean age: 5.41±2.87 (4.70±2.92) | n=106, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.92±3.00) | N.A. |

| | | | | | |
|---|---|---|---|---|---|
| Conklin, Reddick et al. (2010) | Longitudinal Single-arm, Open-Label | Methylphenidate (Individually titrated MPH dose, 12 months) | Mean age: MPH group 5.21, SE 0.36 (4.26, SE 0.32); Control 5.43, SE 0.43 (4.35, SE 0.36) | n=68, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.11, SE 0.37) | n=54, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.26, SE 0.43) |
| Netson et al. (2011) | Longitudinal Single-arm, Open-Label | Methylphenidate (Individually titrated MPH dose, 12 months) | Mean age: MPH group 5.21, SE 0.36 (4.26, SE 0.32) | n=68, heterogeneous cancer types with ChT +/- RT, (Mean age: 11.11, SE 0.37) | N.A. |
| Castellino et al. (2012) | Longitudinal Single-arm, Open-Label | Donepezil (10 mg/daily, 24 weeks) | Mean age at RT: 5.55 (4.7) | n=11, all brain tumors with whole brain RT (> 23.4 Gy) +/- ChT, (Mean age 11.1) | N.A. |

Abbreviations: RT, radiotherapy; CSI, craniospinal irradiation; ChT, chemotherapy; ±, standard deviation; SE, standard error; MPH, methylphenidate; RCT, randomized controlled trial; N.R., Not Reported; N.A. Not Applicable

**Table 2** Neurocognitive measurements and outcomes

| **Reference (year)** | **Type of intervention** |
|---|---|
| Riggs et al. (2017) | Exercise training |
| Szulc-Lerch et al. (2018) | Exercise training |
| Cox et al. (2020) | Exercise training |
| Rath et al. (2018) | Individually tailored exercise training |

Fontana et al. (2021) Purely physical or physical and attentional exercises

**Table 2** (continued)
**Reference (year) Type of intervention**

Kanitz et al. (2013) Eurythmy Therapy
Patel et al. (2009) Cognitive and Problem-solving training

Conklin et al. (2015) Cogmed

Conklin et al. (2017) Cogmed

**Table 2** (continued)
Reference (year) Type of intervention

Hardy et al. (2013) Cogmed or MegaMemo

Siciliano et al. (2021) Cogmed: adaptive or non-adaptive

Carlson-Green et al. (2017) Cogmed

Peterson et al. (2022) Cogmed or JumpMath
**Table 2** (continued)
**Reference (year) Type of intervention**

Palmer et al. (2014) Fast ForWord
Zou et al. (2016) Fast ForWord
Hardy et al. (2011) Captain's Log

Butler et al. (2008) Cognitive Remediation Program
**Table 2** (continued)
**Reference (year) Type of intervention**

Zou et al. (2012) Cognitive Remediation Program

Kesler et al. (2011) Cognitive Rehabilitation Curriculum
Wade et al. (2020) A Survivor's Journey

De Ruiter et al. (2016) Neurofeedback training
**Table 2** (continued)
Reference (year) Type of intervention

Thompson et al. (2001) Methylphenidate
Conklin et al. (2007) Methylphenidate

Conklin et al. (2010) Methylphenidate
Conklin, Reddick et al. (2010) Methylphenidate

**Table 2** (continued)
**Reference (year) Type of intervention**

Netson et al. (2011) Methylphenidate

Castellino et al. (2012) Donepezil

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; MEG, Magnetoencephalography; WASI

Discussion

In this systematic review 28 articles were identified investigating the potential impact of an intervention on cognitive functioning in pediatric brain tumor patients. The included articles described a variety of lifestyle, cognitive, and pharmacological possibilities.

First, exercise training had a beneficial impact on processing speed and long-term memory, and on anxiety and emotional control[13,40]. However, none of the lifestyle interventions reported on effect size. The positive effects of a exercise intervention were greater if the activities occurred in a group setting, whereas they were not amplified by adding attentional tasks to the exercise training[13,34]. For in-group training, it is unclear whether the social stimulation caused additional improvement of neurocognition or rather it had led to more intensive physical training[35,40]. Overall, the included studies consolidated the idea that exercise training is easily accessible, safe, and that it can be initiated at any moment after diagnosis[13,35,40]. The benefits for patients with a PBT are likely to be even more evident if exercise training is integrated into a sustainable healthy lifestyle, rather than being used as a short-term intervention[34]. Incorporating exercise training in a healthy lifestyle may be crucial, not only for its potential neurocognitive benefits but also for many other health-related factors that may be compromised in patients with a PBT[2,35,40–42].

In contrast to the low number of physical exercise studies, most of the existing studies focused on cognitive interventions. These approaches either aim to target and improve one specific neurocognitive domain, or they are designed to teach compensatory strategies. Based on the reported effect sizes most promising outcomes were found for Cogmed in the domains of WM, executive functioning and symbolic WM; for CRP in the domains of learning strategies, inattention, and attention and hyperactivity symptoms; and for CRC in the domains of processing speed and visual memory [17,26–28,30,37,38]. Other cognitive interventions also showed a positive impact on neurocognition however, their effect sizes were moderate or small, or they were not reported[43]. Except for neurofeedback training, this showed no effect on neurocognition[16]. It is important to critically reflect on how cognitive impact is measured after a cognitive intervention. If the intervention efficacy is assessed using cognitive tests that overlap with the content of the training exercises, the training effect can be limited to the specific tool-specific skill, rather than a generalizable effect[44,45]. Therefore, to increase ecological validity of the intervention results, it is essential to incorporate a more broadened neurocognitive assessment battery as well as patient- or parent-reported outcomes in daily life[46].

Regarding pharmacological possibilities, the current literature described two pharmacological compounds for their potential mitigation of NCI, namely MPH and donepezil. MPH showed to improve attention in pediatric cancer patients with attentional problems. Nevertheless, reported effect sizes are moderate to small and one study did not confirm the improvement of attention[21]. Other domains such as academic achievement and processing speed appeared to improve as well, these results were inconsistent across different studies as well. Disparities in study outcomes may be attributable to different neurocognitive assessment batteries. Furthermore, results may not be generalizable to patients with a PBT that have a NCI in domains other than attention, and long-term safety and duration of effects is still uncertain[20,22,47]. Donepezil was found to be effective in irradiated patients with a PBT for both performance and proxy-reported measures of executive

functioning. However, similar to MPH, there is no indication whether long-term safety can be guaranteed and what neurocognitive effects would be[39]. Notwithstanding the promising results found for the abovementioned psychostimulants, multiple side effects were reported. By contrast, cognitive interventions did not report specific side effects and only one fall was reported in the lifestyle intervention studies, and therefore provide initial good alternatives with limited potential side effects.

Based on the results of the included studies, it may be concluded that a tendency towards positive effects of neurocognitive interventions on NCI in patients with a PBT exists. Nevertheless, some limitations must be considered. A large methodological variability exists across included studies, decreasing comparability and generalizability of the results to the entire population of patients with a PBT. Also, study populations were relatively small and effect size was not always reported. Measurement of long-term effects in the studies is limited and the impact of the intervention on lifestyle and daily-life functioning should be considered. Additionally, each type of intervention comes with their own advantages and disadvantages. For instance, digital interventions are increasingly accessible, hence they are susceptible for technical and ethical problems, and more parental involvement is required[48]. Conversely, therapist-delivered interventions are time-, labor- and cost-intensive[30,35]. Though, in therapist-delivered interventions, a therapist can better estimate how the patient is doing and their progress, in order to adapt the intervention in time. Also, personal contact is highly important in efficacy. Furthermore, even though implementing cognitive interventions during treatment may be particularly challenging for the pediatric patient during this stressful period, early mitigation might yield larger effect sizes than post-treatment interventions[38,49–51].

Altogether, the heterogeneity of intervention results and the inherent variability among patients with a PBT may suggest that a one-size-fits-all cognitive intervention may not be achievable. A patient-tailored implementation of neurocognitive interventions may be more beneficial[4,49]. Therefore, it is advised that these interventions should be contextualized alongside the prevention-based neurocognitive follow-up model[2]. Such model was proposed by Jacola et al. (2021), in which a primary intervention level is intended for all patients with a PBT. This level can encompass interventions like lifestyle- and behavioral interventions, psychoeducation, social engagement, improving school attendance and school engagement[2,4,41]. A second and a third intervention level can target patients with more specific neurocognitive risk factors and with more severe NCI. These patients may need more intense and targeted support, based on individual neurocognitive strengths and weaknesses as well as the patients' resilience, fatigue and mental capacity[2]. Interventions such as school-based accommodations, teaching organizational strategies, time management, planning, cognitive remediation and problem-solving training, may be appropriate for these patients[2,4,6,25].

Limitations

This systematic review comprehensively reviewed the existing intervention studies in pediatric brain tumors. Still, some limitations need to be noted. First, articles were included if PBTs participated, also if other diagnoses were included. This methodological choice increases the extent of literature regarding possible interventions in patients with a PBT. However, it could also contribute to a more heterogeneous outcome and could complicate generalizability to the PBT population in specific (vs. pediatric oncology patients). Furthermore, we were unable to perform a meta-analysis given the large heterogeneity of different study designs and neurocognitive assessment instruments. A consensus on the neurocognitive assessment instruments and the optimal timing of assessments would facilitate comparison between different intervention methods and different studies [2]. Finally, by manual reference tracking, one additional study was identified, We cannot exclude the possibility there may be other remaining articles which were not detected.

## Conclusion

Different studies showed that NCI in patients with a PBT can be mitigated by diverse and multimodal interventions. Nevertheless, results are very heterogeneous both across and among different types of interventions. Therefore, harmonization of study designs and endpoints is essential to enable comparison of different interventions. Furthermore, efforts should be made to provide patient-tailored interventions, addressing individual neurocognitive performance and psychosocial needs of patients with a PBT. Finally,

multimodal interventions, simultaneously targeting the diverse aspects involved in cognitive functioning (i.e. physical health, brain plasticity) from different angles, might be valuable to assess in future trials.

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