Fig 1. Flow Diagram

Figure 1. Study Selection Flow Diagram

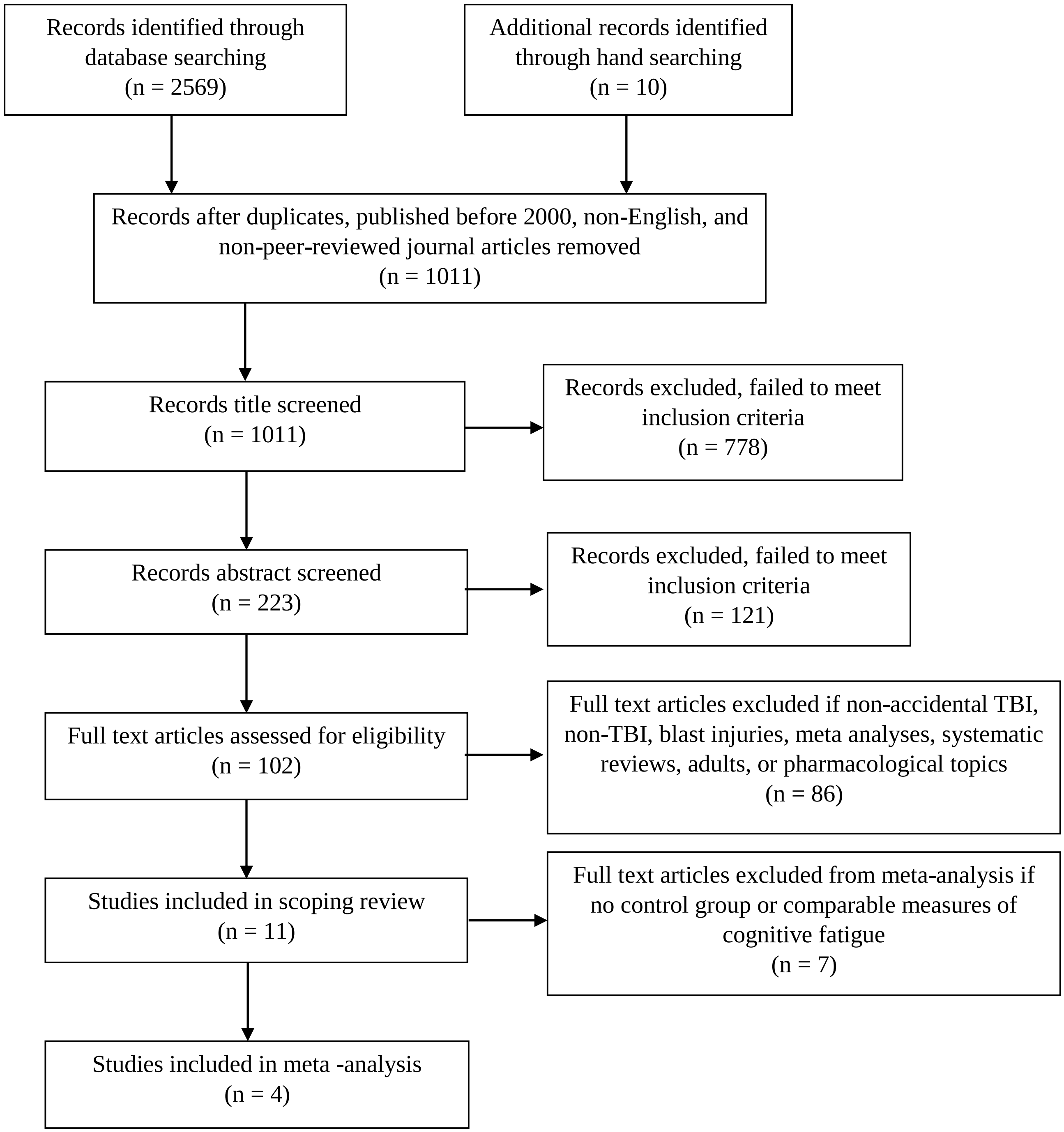
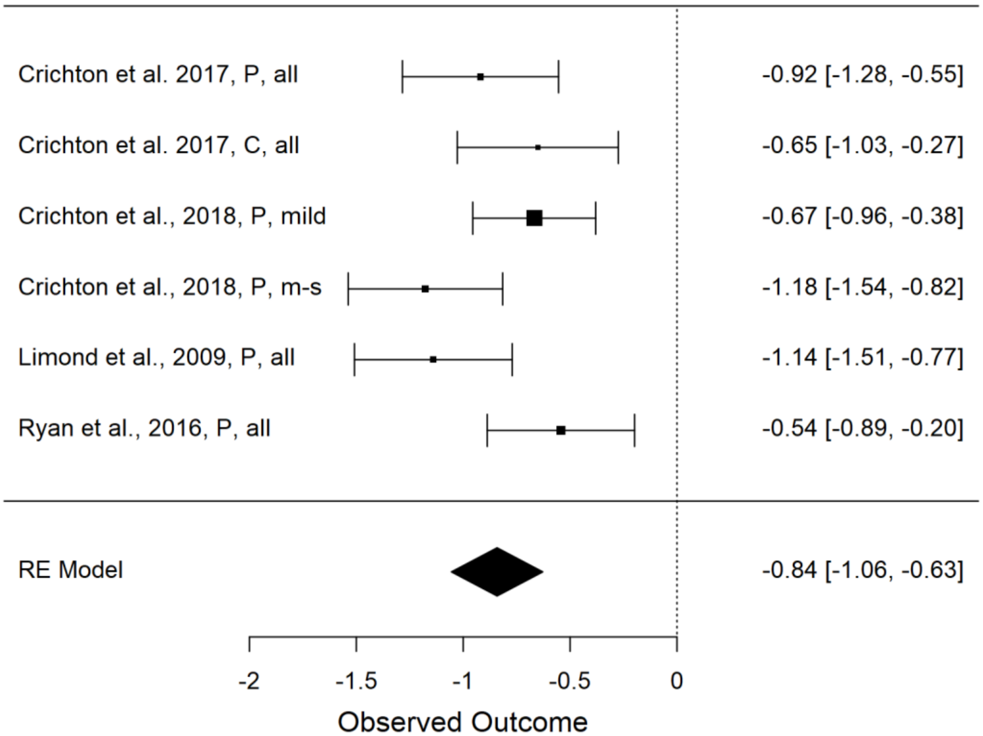
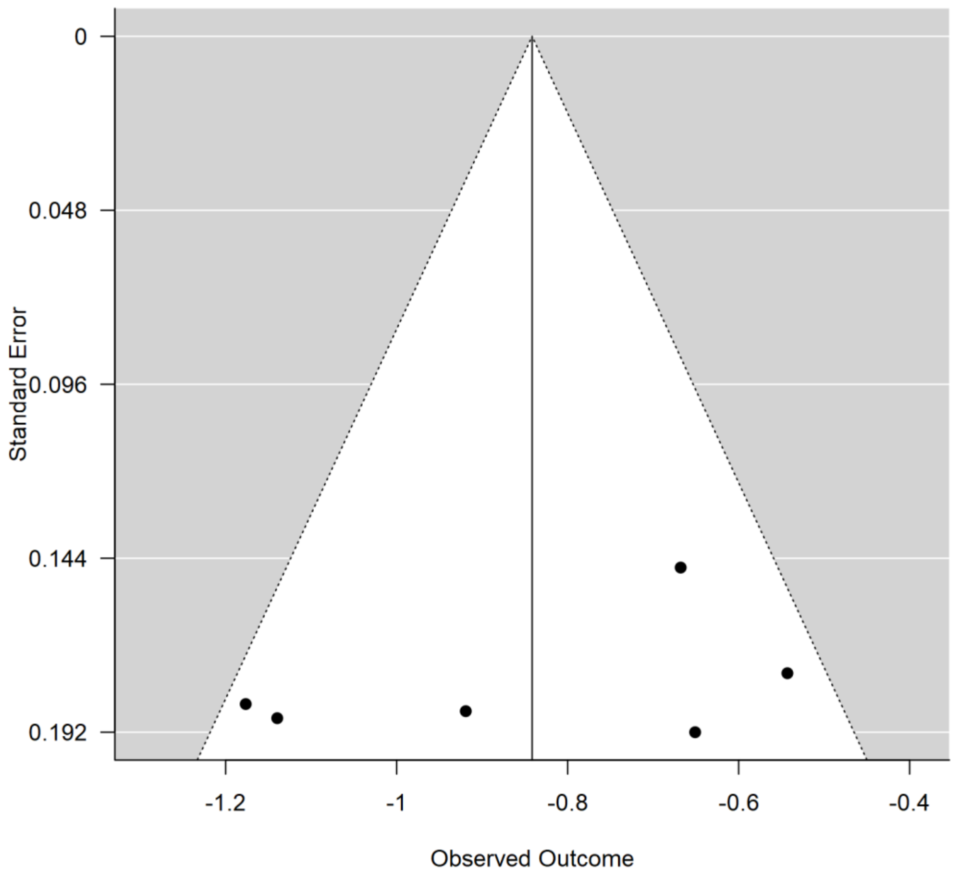


Figure 2. Forest Plot of Cognitive Fatigue Scores



P= parent report; C= child self-report; all= all severities of injuries; mild= only mild injuries; m-s= moderate-severe injuries

Figure 3. Funnel Plot of Publication Bias



Title: Cognitive fatigue in pediatric TBI: A meta analysis and scoping review

Abstract

Objective To review the evidence available on cognitive fatigue (i.e., increase in mental exhaustion after prolonged cognitive activity) in childhood TBI, including rates, associated factors and effects, and management strategies

Methods A meta analysis and scoping review of the literature were conducted following the PRISMA guidelines. Terms were searched in relevant databases and through hand-searching. Articles were included and excluded based on specific criteria and methods were evaluated for risk of bias.

Results Of 2579 initially eligible articles, four studies with six effect sizes (due to reporting of data by group in two studies) were included for a meta-analysis and 11 for a scoping review. Cognitive fatigue was a common symptom in children after TBI of varying severities and times post-injury. Few studies investigated factors or effects associated with cognitive fatigue, although emerging evidence indicates some relations with family and injury factors and post-injury functioning. Active rehabilitation was investigated by two studies and could be a safe management strategy for cognitive fatigue, but additional investigation is needed on this and other possible assessment and treatment approaches.

Conclusions Cognitive fatigue is a common symptom in children who experience a TBI of any severity. Additional research is needed to determine the course of cognitive fatigue, elucidate the relations between cognitive fatigue and secondary factors, and to build clinically-useful assessment and treatment methods.

Keywords: (3-5)

Pediatric traumatic brain injury, cognitive fatigue, fatigue

Introduction

Traumatic brain injury (TBI) in childhood is known to cause acute and chronic changes in development and functioning.[1] Up to 60% of children with TBI experience the symptom of fatigue chronically post-injury when attempting to participate in daily life.[2–6] Fatigue has been defined as "the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (p. 46).[7] Fatigue can be challenging to measure, particularly in individuals with TBI, due to its subjective nature.[7,8] To best understand fatigue after TBI, the influence of neuro-biological and personal-contextual factors on multiple fatigue dimensions must be considered.[4,7,8]

The neurological and biological changes occurring chronically and acutely after a TBI are often associated with decreased physical, cognitive, emotional, and sleep functioning.[4,8] Individuals with TBI than must exert increased effort to complete daily life tasks, ultimately evoking fatigue more quickly and more often than individuals without TBI.[8] When self-reporting fatigue, various factors appear related to higher rates of fatigue including: higher pre-injury functioning, greater mental health needs, lower resiliency, and higher academic and social demands (e.g., expectations for work completion).[4,8–10] Although the exact causes of fatigue and relations amongst factors are unclear, children are at a particularly high risk for experiencing fatigue after TBI due to neuro-biological and personal development and unique expectations for academic and social participation.[5]

Fatigue is typically conceptualized as multi-dimensional including physical, emotional, sleep/rest, and cognitiveelements.[7,8] One previous review paper in pediatric acquired brain injury (ABI) addressed general fatigue (i.e., consideration of all fatigue dimensions).[5] Wilkinson et al. (2018) found fatigue to be prevalent following childhood ABI, affecting functional participation in daily life, but failure to consider the multidimensional nature of fatigue limits the understanding and management of fatigue. Based on these findings and those of other studies, the consideration of cognitive fatigue appears particularly important in childhood TBI.[10,11]

Post-TBI, children commonly experience deficits in cognition and executive functioning.[12–14] In light of these deficits, children often report feeling mentally or cognitively fatigued when attempting to participate in typical academic and social activities; this is sometimes referred to as feeling “mentally foggy”.[2,15] Cognitive fatigue, as defined by Wylie & Flashman,[8] is a “transient increase in mental exhaustion resulting from prolonged periods of cognitive activity” (p. 4). When experiencing cognitive fatigue, other cognitive symptoms (e.g., slower processing time) might be exacerbated, increasing the child’s frustration and decreasing their motivation to participate.[16,17] Ultimately, the child disengages academically and socially.[16,17] Although cognitive fatigue co-occurs with other fatigue dimensions, the presentation and persistence of cognitive fatigue appears unique but under-investigated.[5,10] Due to the lack of discussion of cognitive fatigue in experimental studies and review papers, it remains difficult for researchers and clinicians to draw conclusions about the prevalence of and assessment and management strategies for cognitive fatigue after childhood TBI.

The primary aim of this meta-analysis and scoping review was to review the evidence available in published literature on reports of cognitive fatigue after childhood (i.e., 0-18 years) TBI. Secondary aims were 1) to identify factors and effects associated with cognitive fatigue, and 2) to determine implications for clinical practice and future directions for practice and research related to cognitive fatigue in childhood TBI. To the best of the authors' knowledge, this is the first review paper focusing on cognitive fatigue in childhood TBI. Previous systematic reviews in this area have not specifically analyzed cognitive fatigue in childhood TBI, rather focusing on the broad multidimensional construct of fatigue post-TBI while noting the necessity of separately considering different fatigue dimensions in future studies.[4-6]

Methods

To comprehensively assess the available literature, a meta analysis and scoping review were conducted to account for studies with and without control groups. Both the meta analysis and scoping review were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the extension for Scoping Reviews.[18,19] Initially, a meta analysis was intended to be conducted due to its methodological rigor. After the literature search yielded a small number of peer-reviewed articles with non-injured control groups, a scoping review was also included as a broad and preliminary evaluation of existing literature, including articles without non-injured control groups, specifically to highlight gaps in the literature for future investigation.

Search Strategy & Identification

In July 2019, four databases relevant to cognition and TBI were searched for peer-reviewed journal articles published in the English language between 2000 and July 1, 2019. Additional articles were identified by hand-searching citations of articles that met criteria and from authors' knowledge of relevant publications. Table 1 provides the keywords and databases used during the search. The search results were available to all reviewers via Rayyan QCRI.[20]

Articles were reviewed in three stages (i.e., title screen, abstract screen, and full text screen) based on the inclusion and exclusion criteria listed in Table 2.

Data Extraction & Risk of Bias Assessment

Articles that met criteria were available to all authors via a group folder in Google Drive. Two masters students in speech-language pathology extracted preliminary data (i.e., study design, participant characteristics, prevalence of cognitive fatigue, findings on related outcomes) from included studies using a standardized data collection form, shared via a Google sheet with all researchers. Review of and feedback on the literature search, themes, and manuscript was also shared via e-mail and at three in-person meetings.

Risk of bias of the included articles was assessed by two masters students in speech language pathology using an adapted version of guidelines proposed by Hayden et al..[21] The following domains were evaluated for risk of bias: study participation, attrition, outcome measurement, confound measurement, and analysis. Each reviewer assessed each domain, rating each item as “yes”, “no”, “partly”, “unsure”, or “not applicable. The ratings were summarized using an adapted version of a method proposed by the Scottish Intercollegiate Guidelines Network.[22] Articles were classified as “high quality” (+++), “moderate quality” (++), or “fair quality” (+). No study with a retrospective design received a “high” or “moderate” classification, since this is a weak study design.[22]

Data Analysis

Studies with a control group that reported a cognitive fatigue score were included for meta-analysis. Cohen’s d effect sizes and standard errors were calculated based on the data available in the articles. A model of random effect sizes was used to combine effect sizes.[23] Statistical heterogeneity was calculated with Q and I^2. Visual and statistical inspection (i.e., rank correlation test) of publication bias was made with a funnel plot. All analyses were conducted with - and the forest and funnel plots were derived from - JASP 0.9.2.0. All studies meeting inclusion criteria, with or without a control group, were included for a scoping review.

Results

Search Results & Data Extraction

The initial search generated 2569 results, with 10 additional articles being identified from hand-searching. A total of 11 articles met inclusion criteria for this study. The flow diagram of study selection is depicted in Figure 1. Interrater agreement for all levels of review and data extraction is presented in Table 3. All discrepancies were resolved through discussion between the two reviewers/extractors and the first author.

Study Characteristics

A summary of the 11 included studies is presented in Table 4. Of note, one research group (i.e., Crichton et al. and Ryan et al.) published four of the included articles, and, although it is not explicitly stated in the studies, there is likely overlap in the samples based on study timelines and locations. Average age at the time of study participation ranged from 4.8- 16.3 years. Sample size of TBI groups ranged from 10 to 136 participants. Four studies[24–27] examined mild injuries and seven studies[3,28–33] examined multiple severities or grouped severities (e.g., mild, moderate, and severe; moderate/severe). Time post-injury ranged from two days to 2.7 years. Four studies measured fatigue at multiple time points, all less than seven months post-injury.[3,24,27,28] Two studies investigated the efficacy of a treatment approach,[25,26] and all other studies were descriptive.

Reports of Cognitive Fatigue

Scoping Review

Two types of measures were used to quantify levels of cognitive fatigue: the Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL MFS)[34] (N= 7) or symptom rating scales including item reporting for "feeling in a fog" (i.e., symptom questionnaire from ImPACT test battery[24]; Post-Concussion Symptom Scale (PCSS)[26]; Post-Concussion Symptom Inventory (PCSI)[27]; ACE Parent Questionnaire[32]) (N= 4). One study included both types of measures.[24] These measures are described in Table 5.

Five studies used parent report, four studies used child self-report, and two studies used both parent and child self-report. The average scaled rating of cognitive fatigue on the PedsQL MFS ranged from 63.7 to 83.3 for children with TBI, including the baseline ratings in the treatment studies. The symptom "feeling in a fog" was endorsed by 0% to 41.4% of children with TBI, and was rated between 1.0 to 1.6 on 0 to 6 severity scales (0= no symptoms, 6= most severe) or in the mild-moderate range.

Meta-Analysis

Six measures of cognitive fatigue from four studies[28–31] with non-injured control groups and adequate data for effect size calculations were included for meta-analysis. As two manuscripts[28-29] presented data based on groups (i.e., parent vs child report; mild vs moderate-severe injury severity), multiple effect sizes were calculated, yielding six effect sizes from four articles. Of note, all control groups were previously published controls (i.e., published normative samples, published healthy sample from a study of a different clinical sample). Although Ryan et al.[31] included an experimental control group, data for this group was not reported, and an effect size could not be calculated.

All studies used the PedsQL MFS. Five measures[28–31] were parent-reported and one measure[28] was child-reported. Four measures[29–31] included all severities of TBI, one measure[28] included only mild TBI, and one [28] included moderate-severe TBI. At the time of study participation, children with TBI were on average 11.22 years old (9.90-13.30 years) and 13.93 months post-injury (1.6-32.40 months). Studies reported average scores for children with TBI between 65.70 to 77.18, and children who are typically developing between 82.40 and 90.70. Meta-analysis revealed a statistically significant negative effect, d = -.84, 95% CI [-1.06, -0.63], indicating that children with TBI had significantly lower fatigue scores (i.e., experienced higher levels of cognitive fatigue) than control groups. The forest plot in Figure 2 depicts these results. Heterogeneity across studies was significant, $Q_{(5)} = 11.2$, $p = 0.047$, and moderate, $I^2 = 55.67$.[35] Visual and statistical inspection of the funnel plot depicted in Figure 3 did not indicate publication bias, $\tau = -0.20$, $p = 0.719$.

Scoping Review: Associated Factors and Effects

Many studies discussed or hypothesized effects associated with cognitive fatigue, but only three studies measured and ran analyses to explore the relations. Crichton et al.[3] found bivariate relations between cognitive fatigue and post-injury sleep, physical/motor functioning, and emotional functioning. Ryan et al.[31] observed smaller brain volumes with greater levels of cognitive fatigue. Van Markus-Doornbosch et al.[33] found older age at onset (>11 yo), single parent household status, greater limitations in activities and participation, and lower ratings of quality of life to be associated with worse ratings of cognitive fatigue.

Scoping Review: Management Strategies

Although most studies discussed assessment and treatment recommendations based on their findings, only two studies[25,26] directly examined management strategies, both investigating the effect of active rehabilitation on children with mild TBI and persistent symptoms. Both studies implemented the same active rehabilitation program (described in detail by Gagnon et al.[26]). Active rehabilitation was defined and conceptualized as a slow return to physical activity post-mild TBI that does not exacerbate symptoms.[26] Both studies used the PedsQL MFS to measure cognitive fatigue pre- and post- treatment, with Gagnon et al.[26] also reporting the PCSI item of “feeling mentally foggy” pre- and post-treatment. Chan et al.[25] did not conduct statistical analyses on the pre- and post- treatment data, but, based on the data reported and analysis by the authors of this paper, no significant differences were observed in cognitive fatigue from pre- to post- treatment. Gagnon et al.[26] found significant improvement in cognitive fatigue when comparing pre- and post- treatment PedsQL MFS scores. In addition, fewer participants endorsed “feeling mentally foggy” post-treatment (N= 0) compared to pre-treatment (N= 2). Both studies recommended the use of active rehabilitation treatment for children with mild TBI, noting that the treatment approach appears safe (i.e., limited to no exacerbation of symptoms)[25,26] and potentially supports improvement of a range of common post-concussive symptoms including cognitive fatigue.[26]

Risk of Bias

Based on the risk of bias domains, three studies were identified as “high quality”.[24,28,29] Four studies were identified as “moderate quality”,[25,28,31,33] and four studies were identified as “fair quality”.[26,27,30,32] Table 6 presents the risk of bias assessment results.

Discussion

This meta-analysis and scoping review appraised the available evidence on cognitive fatigue after childhood TBI. The results from 11 studies support the main study aim, indicating that children with TBI, when examined in cohorts that vary in severity, can experience cognitive fatigue, even years after injury. Limited experimental evidence was available to address the secondary aims of this study - factors and effects associated with cognitive fatigue and management strategies. These findings suggest that cognitive fatigue is a significant symptom following childhood TBI, and further research is warranted, particularly to identify effective assessment and treatment approaches.

Ratings of Cognitive Fatigue

It is challenging to generalize findings of cognitive fatigue scores due to inconsistencies in methodologies and reporting across studies. Of studies that used control groups,[25,28–31,33] four used previously published control scores (i.e., published normative samples, published healthy sample from a study of a different clinical sample), all of which were included in the meta analysis where demographic differences were not controlled for or not mentioned in the report.[28–31] All four studies reported that children with TBI had significantly worse levels of cognitive fatigue compared to controls who were typically developing, as observed in the meta-analysis of the data. Ryan et al.[31] also included a control group specific to their study, with no significant demographic differences from the TBI group, but did not find significant differences in cognitive fatigue levels between groups. Unfortunately, data for the experimental control group was not reported, and therefore could not be included in the meta analysis. Two studies'[25,33] control groups included individuals with TBI, and were not included in the meta analysis. Chan et al.[25] utilized children with similar injuries to compare treatment effects, while Van Markus et al.[33] studied children with non-traumatic brain injuries and found that children with non-TBI presented with worse levels of cognitive fatigue than children with TBI. Without the use of a non-injured control group in which demographic and external variables can be accounted for and in the absence of standardized assessments of fatigue, cognitive fatigue scores can be difficult to interpret.[6]

All measures of cognitive fatigue were subjective, potentially biasing results. Five studies[3,28,30–32] used exclusively parent reports, and four studies[24–27] used exclusively child self-reports. The two studies that used both parent and child-self reports did not find a significant difference between parent and child-self ratings.[29,33] Studies on general fatigue following childhood TBI suggest using both parent and child-self report forms to improve the validity of the findings, while recognizing the subjective nature of experiencing fatigue. Most measures, including the PedsQL MFS and post-concussion scales, are validated for both parent and child report, making multiple scores from multiple reporters feasible.[29] To the best of the authors' knowledge, objective or standardized fatigue measures have not been developed or utilized in childhood TBI but are emerging for adult TBI and other populations.[36–39] Pairing subjective and objective measures would likely provide a more robust picture of cognitive fatigue post-childhood TBI, elucidate the relationship (e.g., discrepancies) between subjective and objective reports to support assessment practices, help determine clinically-significant levels and changes in cognitive fatigue, and better inform management strategies.[5]

Because no studies included pre-injury measures of cognitive fatigue, comparisons of pre- and post-injury or typical vs atypical levels were not possible. Unfortunately, all measures from studies included in this review demonstrated limited utility in measuring cognitive fatigue, largely due to their lack of standardized items and ability to differentiate between typical or healthy fatigue levels and atypical fatigue levels.[5] Symptom rating scales using the item related to "mental fog" are less reliable and were extrapolated to represent cognitive fatigue for the purpose of this review, given literature supporting the representativeness of this item.[15,40]

The PedsQL MFS does include a valid and reliable sub-scale specific to cognitive fatigue.[34] Of the studies with available comparisons between fatigue dimensions (i.e., general, sleep/rest, cognitive), five studies[3,28,30,31,33] found that cognitive fatigue was the dimension with the worst ratings. Three studies[25,26,29] found mixed results (i.e., cognitive fatigue was worse than some and better than other dimensions). Interestingly, studies that found cognitive fatigue to have the worst rating included younger participants (8-11 years old at injury; 8-13 years old at study participation), compared to the other studies (14-18 years old at injury; 13-18 years old at study participation). Consistent with a previous review on general fatigue,[5] these findings demonstrate the importance of considering fatigue dimensions separately to advance the understanding of fatigue and provide tailored treatment and management strategies specific to the child's needs. Developmental stages and academic and social expectations should also be considered when determining the salience of cognitive fatigue post-TBI.[33]

With respect to age at injury, most studies examined children who experienced a TBI in later childhood and early adolescence (i.e., about 8 to 18 years old). Only one study examined earlier childhood TBI with an average age of injury at 4.8 years old.[32] Due to a limited number of studies in each age group, differences in the presentation of cognitive fatigue based on age were difficult to elucidate. Studies suggested that adolescence is a particularly important time to evaluate and consider fatigue, due to the natural increase of fatigue during that developmental period.[3,33] In addition, early childhood presents with the highest rates of TBI across childhood with major cognitive and developmental changes shortly after injury, although Suskauer et al.[32] did not find notable ratings of cognitive fatigue in their sample. This could be due to adults' inability to readily observe "feeling mentally foggy" in children who cannot accurately convey their symptoms;[32] this possibility warrants additional investigation and development of measures that could accurately capture cognitive fatigue in this age group.

When examining cognitive fatigue levels based on severity, most studies that included multiple severities did not report cognitive fatigue levels separately for severity groups, limiting comparisons. Generally, children with milder injuries were over-represented compared to those with moderate or severe injuries, but tended to present with lower levels of cognitive fatigue.[3,24,27,28] This trend becomes less clear when considering children with persistent symptoms following a mild injury, potentially appearing more similar to moderate-severe injuries.[25,26] Future investigations should consider assessing cognitive fatigue symptoms longitudinally in children with chronic mild TBI to better our understanding of the course of symptoms and to inform management strategies.

Studies included in this review reveal multiple trajectories for the presence of cognitive fatigue throughout recovery. Studies conducted in the chronic stages of recovery, about two years post-injury, indicated that cognitive fatigue can persist at clinically-significant levels for all severities of TBI.[30,31,33] Changes in cognitive fatigue over time were inconsistent when examined multiple times in the acute stages of recovery. One study[28] found that cognitive fatigue at one year post-TBI was significantly worse than at six months post-TBI. Three studies,[24,26,27] including a treatment efficacy study, saw improvement within five months of injury with and without intervention. One study,[25] a treatment efficacy study, found no change, and one study[3] observed an increase in clinically-significant fatigue scores for individuals with mild injuries, but improvement for those with moderate-severe injuries. Multiple factors could be influencing levels of cognitive fatigue including: developmental stages, social and academic expectations or involvement, and personal or environmental characteristics.[3,28]

Associated Factors & Effects

Post-injury functioning (e.g., sleep, physical, emotional, daily participation), brain volume, age at onset, parental marriage status, and quality of life appear to be associated with cognitive fatigue, but the directions of these relations remain unclear.[3,31,33] Other studies hypothesized or presented additional data that could support or warrant further investigation of potential relations with other factors. Children with more significant levels of cognitive fatigue would likely experience greater difficulties in academics and general functioning and lower quality of life.[27,28,30] Psycho-social and mental health needs and sleep disturbances could be exacerbated by and/or contribute to acute levels of cognitive fatigue.[24,29] These hypothesized relations would not be unexpected, given literature indicating the general association of these factors (i.e., academic and social functioning, quality of life, psycho-social and mental health, sleep) with childhood TBI.[3] Although evidence is limited, given the subjective nature of fatigue, personal, injury, and post-injury functioning factors are essential to the understanding of cognitive fatigue and to tailor management strategies to individual needs.

Management Strategies

Suggestions for assessment of cognitive fatigue in childhood TBI included: regular and systematic screenings for symptoms into the chronic stages of recovery to track progress and ongoing needs;[24,27,29,30] multidimensional fatigue assessments with multiple reporters;[3,28,29,33] structural imaging of biomarkers to identify and predict cognitive fatigue;[41] and self-report assessments specific to the child's developmental stage (e.g., including more concrete language regarding cognitive fatigue for younger children).[32] From the two studies that evaluated treatment efficacy, active physical rehabilitation did not appear to exacerbate general post-concussion or fatigue symptoms following childhood TBI and could improve cognitive fatigue, but additional investigation is needed.[25,26] Many additional management strategies were suggested in the included articles but did not include empirical evidence. Recommendations for interventions included: treat both the cognitive fatigue symptoms and areas of functioning associated with greater fatigue (e.g., physical skills);[3] support functional improvements for participation and quality of life through cognitive rehabilitation, behavior management, and academic supports;[27,29,30,33] and consider external demands based on age when designing supports and implementing services.[32] One study[30] reported that children who experienced cognitive fatigue did not receive specialty supports at school, reinforcing the potential broader impact of unmet need in children with TBI.[42,43] Evidence-based management strategies for cognitive fatigue after childhood TBI are limited and need additional attention to support positive outcomes.

Future Directions

Future research in cognitive fatigue after childhood TBI should utilize more robust methodologies such as pairing objective and subjective measures of cognitive fatigue, measuring cognitive fatigue at multiple time points, and controlling for confounding factors. Additional attention is needed on younger children with TBI including monitoring symptoms into later childhood and adolescence. Research in the neuro-biological mechanisms underlying cognitive fatigue and changes in fatigue with overall development could provide valuable information to inform management. Translational research investigating the feasibility and efficacy of assessment and treatment methods is essential to support long-term outcomes for children with TBI. Establishing a program, such as TBI Model Systems, for children could support longitudinal and clinical research to better inform management of cognitive fatigue after TBI.

Limitations

Although our literature search reached the point of duplication, some relevant studies might have been missed. Overall, limited evidence was available on cognitive fatigue after childhood TBI. Of the available research, few studies used control groups; therefore results of the meta-analysis should be interpreted with caution. In addition, multiple studies published by the same research group likely included overlapping samples, potentially decreasing the efficacy of the meta analysis due to correlation amongst samples. Comparisons across studies were difficult due to differences in methodology (e.g., time since injury, severity of injury, measures of course of fatigue, parent vs child-self report), limiting the generalizability of results. Despite these limitations, results of this study provide a comprehensive summary of the available evidence on cognitive fatigue after childhood TBI and highlight areas in need of further investigation.

Conclusions & Clinical Implications

Specific consideration of cognitive fatigue is necessary for effective assessment and treatment after childhood TBI. Additional investigation is needed to better inform clinical services. Based on the current literature, children with any severity of TBI should be continuously assessed for cognitive fatigue through the chronic stages of recovery, with special focus on children with associated factors including lower general post-injury functioning and lower quality of life. Treatment approaches should include direct management of cognitive fatigue and reduction of the secondary effects, such as academic and social engagement, to improve long-term quality of life in children with TBI.

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Tables

Table 1. Search Terms and Databases

Search Terms (searched in each database)	Cogn* and fatigue and child* and brain injury Cogn* and fatigue and pediatric and brain injury Cogn* and fatigue and child* and acquired brain injury Cogn* and fatigue and pediatric and acquired brain injury Cogn* and fatigue and child* and traumatic brain injury Cogn* and fatigue and pediatric and traumatic brain injury Mental and fatigue and child* and brain injury Mental and fatigue and pediatric and brain injury Mental and fatigue and child* and acquired brain injury Mental and fatigue and pediatric and acquired brain injury Mental and fatigue and child* and traumatic brain injury Mental and fatigue and pediatric and traumatic brain injury
Databases	Pubmed, PSYCINFO, ERIC, ScienceDirect

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Fatigue with some mention of cognitive and/or mental fatigue; child/pediatric/adolescents; brain injury
Exclusion Criteria	non-ABI; Non-accidental ABI or child abuse; blast injuries; meta analyses, systematic reviews, or non-peer reviewed papers; adults

Table 3. Interrater Agreement for Study Selection, Data Extraction, & Risk of Bias

Review	**Agreement Prior to Resolution** (proportion of items review)
Title Screen	90.5% (915/1011)
Abstract Screen	84.98% (191/223)
Full Text Screen	94.2%

	(96/102)
Data Extraction	98.8% (543/550)
Risk of Bias Assessment	96.4% (53/55)

Table 4. Summary of Included Summaries

Study (Author, Year Location)	**Level of Evidence Study Design** no studies using published controls received a rating higher than a III	**TBI Group Characteristics** (N severity; % male; Age at study participation (AS) (M (SD)); Time post injury (TPI) (M (SD))	**Control Group Characteristics** (N type; Age at survey (AS) (M (SD))	**Reporter; Measure**	**Results for Cognitive Fatigue**
Blinman, 2009 Pennsylvania, USA	III Prospective cohort without controls	63 mild; 69.8% male; AS: 14.1 (SD not reported) yrs; TPI: 2 days and 2-3 wks	n/a	Self-report; Symptom questionnaire of the ImPACT neurocognitive test battery (item: “feeling mentally foggy”) rated 0=no symptoms to 6= severe	41.4% (2.7 average rating) reported “feeling mentally foggy” at initial visit; 19.1% (1.6 average rating) reported at follow-up visits
Chan, 2018 British Columbia, Vancouver, Canada	I Single-site, parallel, open-label, randomized control	10 mild, PCS; 40% male; AS: 15.9 (1.66) yrs; TPI: 132 (52.0) days for initial assessment and post-treatment	9 mild, PCS; AS: 15.1 (1.42) yrs	Self-report; PedsQL MFS	Children who participated in a closely monitored, active rehabilitation treatment program did not experience more adverse effects than those receiving treatment as usual. No significant changes were observed between physical activity, symptom exacerbation, and clinical outcomes. Chan et al. did not perform statistical analysis of fatigue data, due to its exploratory nature in this study. The authors of this meta analysis conducted paired sample t-tests to compare pre- and post-treatment fatigue scores. No significant differences were found in the cognitive fatigue ratings for the active rehabilitation group. *Management Strategies:* Active rehabilitation, when closely monitored, could be beneficial for adolescents with persistent symptoms, such as cognitive fatigue, post-TBI.

Crichton, 2017 Melbourne, Australia	III Prospective with published controls	27 mild, 5 mod, 3 severe; 34 parent proxies; % male not reported; AS: not reported (age at injury: 13.3 (2.4) yrs (mild), 13.2 (2.6) yrs (mod/severe)); TPI: 7.3 (1.6) wks	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample[1] and demographic differences could not be controlled	Self-report and parent-report; PedsQL MFS	Children and parents reported significantly greater levels of cognitive fatigue for the TBI group than the control sample.
Crichton, 2018a Australia and Canada	III Longitudinal prospective with published controls	59 mild, 36 mod/severe; 77% male; AS: not reported (age at injury: 9.9 (5.0) yrs); TPI: 6 and 12 mos	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample[1] and demographic differences could not be controlled	Parent-report; PedsQL MFS	Cognitive fatigue was significantly worse for children with moderate-severe TBI than mild TBI. Cognitive fatigue worsened significantly from 6 months to 12 months post-injury.
Crichton, 2018b Australia and Canada	III Prospective, non-randomized cohort without controls	52 mild, 27 mod/severe; 82.69% male (mild), 85.19% (male mod/severe); AS: 11.73 (4.42) yrs (mild), 9.72 (5.17) yrs (mod/severe); TPI: 6 and 12 months	n/a	Parent-report; PedsQL MFS	At 6 and 12 months post-TBI, 10% and 17%, of children with mild TBI and 27% and 19% of children with mod-severe TBI were rated in the clinical range for total fatigue, respectively (cognitive fatigue levels were not individually reported). Cognitive fatigue was the dimension with the worst ratings compared to sleep/rest and general fatigue. *Associated Effects:* General post-injury physical functioning significantly predicted cognitive fatigue 12 mos post-TBI (child factors and injury severity did not). Relationships with pre and post injury functioning might be bi-directional.
Gagnon, 2016 Montreal, Canada	III Clinical series without controls	10 sport-related concussion (slow to recover); 70% male; AS: 14-18 yrs; TPI: 7.9 wks for initial assessment and post-6 week treatment	n/a	Self-report; PedsQL MFS and PCSS (item: "feeling mentally foggy")	Cognitive fatigue and all fatigue measures improved significantly post-treatment in an active rehabilitation program. "Feeling mentally foggy" was endorsed by 2 participants pre-treatment and no participants post-treatment. *Management Strategies:* Low-levels of active rehabilitation might be beneficial for children who are slow-to-recover from concussion. Active rehabilitation appears to support improvement

					across different symptoms, particularly fatigue dimensions.
Limond, 2009 United Kingdom	III Retrospective, cross-sectional study compared to published normative data	47 mild, moderate, and severe (hospitalized for at least 48 hrs); % male not reported; AS: 10.5 (3.6) yrs; TPI: 2.7 (1.2) yrs	105 healthy; 68.6% male; AS: 13.70 (9.47) yrs parent report: 157 healthy; 62.4% male; AS: 11.63 (8.59) years *controls are from a published normative sample[2] and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI were reported to have significantly greater levels of fatigue for all injury severities compared to the control sample. Cognitive fatigue was the dimension with the worst rating compared to sleep/rest and general fatigue. Less than half (47%) of children with TBI had ratings of "normal" levels of cognitive fatigue, while 15% were considered "borderline" and 38% were considered "abnormal", based on cut-off scores.
Macartney, 2018 Ontario, Canada	III Retrospective chart review without controls	136 mild; 45.6% male; AS: 15.4 (median); TPI: 5.4 (3-10.8) days for initial assessment then 28 days, 56 days, and 84 days *participants were discharged when symptoms returned to baseline therefore not all participants required assessment at all time points	n/a	Self-report; PCSI (item: "feeling in a fog") rated 0 to 6 (higher scores= more severe)	The median rating of "feeling in a fog" was 2.9 (1.0-5.8); 1.4 (0.1-5.2); 1.0 (0.4-5.0), at 28; 56; and 84 days, respectively.
Ryan, 2016 Melbourne, Australia	III Prospective, non-randomized cohort with experimental controls and published controls	67 mild, 24 moderate, 12 severe; 67.96% male; AS: 10.54 (2.39) yrs (mild), 10.37 (2.58) yrs (moderate), 10.41 (3.10) yrs (severe); TPI: 24 months	Experimental: 34 healthy; 21% male; AS: 10.41 (2.76) *no demographic differences between groups Published: 157 healthy; 47.1% male; AS: 13.68 (2.17) yrs *controls are from a published normative sample[3] and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI had significantly greater levels of cognitive fatigue compared to the published control sample, but, when compared with experimental controls, no differences were observed. *Associated Effects:* Cognitive fatigue was significantly associated with smaller brain volumes. This finding could indicate disruptions of neural pathways cause an imbalance in effort-reward experiences which is subjectively reported as cognitive fatigue.

Suskauer, 2018 Maryland, USA	III Retrospective medical record review	28 mild/moderate/severe; 50% male; AS: not reported (age at injury: 4.8 yrs); TPI: 38 days	n/a	Parent-report; ACE Parent Questionnaire (item: "feeling mentally foggy") classified as "ever experienced post-TBI" or "currently experiencing post-TBI"	No parents (0%) reported their child ever or was currently experiencing "feeling mentally foggy".
van Markus-Doornbosch, 2016 Netherlands	III Prospective review and follow-up study without controls	58 mild, 11 moderate/severe; 46% male; AS: not reported (age at injury:11 (6) yrs (median, IQR)); TPI: 24-30 mos	19 non-traumatic BI (NTBI); 11% male; AS: 14 (7); TPI: 24-30 mos	Parent-report and self-report; PedsQL MFS	Children with NTBI were parent- and self-reported to have significantly greater levels of cognitive fatigue compared to children with TBI. No significant difference was observed between parent and child self- report for cognitive fatigue. *Associated Effects:* Greater levels of cognitive fatigue was significantly associated with older age at onset (>11 yo); single parent household; greater limitations in activities and participation; and lower quality of life.

Table 5. Measures used to quantify levels of cognitive fatigue	
Measure	Description
PedsQL Multidimensional Fatigue Scale (PedsQL MFS)[34]	- parent and child self-report forms for ages 2-18 years old - 3 subscales (i.e., general fatigue, sleep, cognitive fatigue) are rated on a Likert scale (0= never a problem to 4= almost always a problem over the past month). Items are then reverse scored and transformed to a 0- to 100-point scale, such that higher scores indicate less fatigue.[a] - shown good internal consistency reliability, test-retest reliability, and inter-observer reliability[34]
Immediate Post-Concussion Assessment and Cognitive Test (ImPACT)[44]	- FDA endorsed online tool for baseline and post-injury testing for ages 12-59 years old - assesses visual and verbal memory, reaction time, and processing speed through 8 tasks and includes a series of symptom-related questions rated on a 7-point Likert scale (0= no symptom, 6= severe symptom) - validity and reliability are unclear and highly dependent on time administered post-injury, area assessed, and other factors[45,46]
Post-Concussion Symptom Scale (PCSS)[47]	- self-report for individuals over 11 years old - 22-items of symptom-related questions rated from 0 (not endorsed) to 6 (severe) - shown good test-retest reliability and internal consistency reliability and reliable to detect change over time[48]
Post-Concussion Symptom Inventory (PCSI)[49]	- parent and child self-report for ages 5-18 years old - 27-items of symptom-related questions rated from 0-6 with higher scores representing more severe symptoms - shown good internal consistency[50]
Acute Concussion Evaluation (ACE)[51]	- parent and child self-report for ages 4 years old-adult - shown good internal consistency reliability, content validity, predictive validity, convergent/divergent validity, and construct validity[52]
[a]Chan et al.[25] did not appear to calculate the scaled score in reporting results	

Table 6. Risk of Bias Summary						
Author, Year	**Study Participation**	**Attrition**	**Outcome Measurement**	**Confound Measurement**	**Analysis**	**Assessment Summary**
Blinman et al., 2009	no	party	no	no	no	+++
Chan et al., 2018	no	no	partly	partly	no	++
Crichton et al., 2017	no	no	partly	no	no	+++
Crichton, Anderson, et al., 2018	no	no	no	no	no	+++
Crichton, Oakley, et al., 2018	partly	no	partly	no	no	++
Gagnon et al., 2015	no	no	partly	yes	partly	+
Limond et al., 2009	no	no	partly	no	no	+
Macartney et al., 2018	no	no	partly	no	no	+
Ryan et al., 2016	no	no	yes	no	no	++
Suskauer et al., 2017	no	no	partly	partly	no	+
van Markus-Doornbosch et al., 2016	no	partly	partly	no	no	++

Note: no= no to little potential bias; partly= some bias; yes= likely bias

Title: Cognitive fatigue in pediatric TBI: A meta analysis and scoping review

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Abstract

Objective To review the evidence available on cognitive fatigue (i.e., increase in mental exhaustion after prolonged cognitive activity) in childhood TBI, including rates, associated factors and effects, and management strategies

Methods A meta analysis and scoping review of the literature were conducted following the PRISMA guidelines. Terms were searched in relevant databases and through hand-searching. Articles were included and excluded based on specific criteria and methods were evaluated for risk of bias.

Results Of 2579 initially eligible articles, four studies with six effect sizes (due to reporting of data by group in two studies) were included for a meta-analysis and 11 for a scoping review. Cognitive fatigue was a common symptom in children after TBI of varying severities and times post-injury. Few studies investigated factors or effects associated with cognitive fatigue, although emerging evidence indicates some relations with family and injury factors and post-injury functioning. Active rehabilitation was investigated by two studies and could be a safe management strategy for cognitive fatigue, but additional investigation is needed on this and other possible assessment and treatment approaches.

Conclusions Cognitive fatigue is a common symptom in children who experience a TBI of any severity. Additional research is needed to determine the course of cognitive fatigue, elucidate the relations between cognitive fatigue and secondary factors, and to build clinically-useful assessment and treatment methods.

Keywords: (3-5)

Pediatric traumatic brain injury, cognitive fatigue, fatigue

Introduction

Traumatic brain injury (TBI) in childhood is known to cause acute and chronic changes in development and functioning.[1] Up to 60% of children with TBI experience the symptom of fatigue chronically post-injury when attempting to participate in daily life.[2–6] Fatigue has been defined as "the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (p. 46).[7] Fatigue can be challenging to measure, particularly in individuals with TBI, due to its subjective nature.[7,8] To best understand fatigue after TBI, the influence of neuro-biological and personal-contextual factors on multiple fatigue dimensions must be considered.[4,7,8]

The neurological and biological changes occurring chronically and acutely after a TBI are often associated with decreased physical, cognitive, emotional, and sleep functioning.[4,8] Individuals with TBI than must exert increased effort to complete daily life tasks, ultimately evoking fatigue more quickly and more often than individuals without TBI.[8] When self-reporting fatigue, various factors appear related to higher rates of fatigue including: higher pre-injury functioning, greater mental health needs, lower resiliency, and higher academic and social demands (e.g., expectations for work completion).[4,8–10] Although the exact causes of fatigue and relations amongst factors are unclear, children are at a particularly high risk for experiencing fatigue after TBI due to neuro-biological and personal development and unique expectations for academic and social participation.[5]

Fatigue is typically conceptualized as multi-dimensional including physical, emotional, sleep/rest, and cognitiveelements.[7,8] One previous review paper in pediatric acquired brain injury (ABI) addressed general fatigue (i.e., consideration of all fatigue dimensions).[5] Wilkinson et al. (2018) found fatigue to be prevalent following childhood ABI, affecting functional participation in daily life, but failure to consider the multidimensional nature of fatigue limits the understanding and management of fatigue. Based on these findings and those of other studies, the consideration of cognitive fatigue appears particularly important in childhood TBI.[10,11]

Post-TBI, children commonly experience deficits in cognition and executive functioning.[12–14] In light of these deficits, children often report feeling mentally or cognitively fatigued when attempting to participate in typical academic and social activities; this is sometimes referred to as feeling “mentally foggy”.[2,15] Cognitive fatigue, as defined by Wylie & Flashman,[8] is a “transient increase in mental exhaustion resulting from prolonged periods of cognitive activity” (p. 4). When experiencing cognitive fatigue, other cognitive symptoms (e.g., slower processing time) might be exacerbated, increasing the child’s frustration and decreasing their motivation to participate.[16,17] Ultimately, the child disengages academically and socially.[16,17] Although cognitive fatigue co-occurs with other fatigue dimensions, the presentation and persistence of cognitive fatigue appears unique but under-investigated.[5,10] Due to the lack of discussion of cognitive fatigue in experimental studies and review papers, it remains difficult for researchers and clinicians to draw conclusions about the prevalence of and assessment and management strategies for cognitive fatigue after childhood TBI.

The primary aim of this meta-analysis and scoping review was to review the evidence available in published literature on reports of cognitive fatigue after childhood (i.e., 0-18 years) TBI. Secondary aims were 1) to identify factors and effects associated with cognitive fatigue, and 2) to determine implications for clinical practice and future directions for practice and research related to cognitive fatigue in childhood TBI. To the best of the authors' knowledge, this is the first review paper focusing on cognitive fatigue in childhood TBI. Previous systematic reviews in this area have not specifically analyzed cognitive fatigue in childhood TBI, rather focusing on the broad multidimensional construct of fatigue post-TBI while noting the necessity of separately considering different fatigue dimensions in future studies.[4-6]

Methods

To comprehensively assess the available literature, a meta analysis and scoping review were conducted to account for studies with and without control groups. Both the meta analysis and scoping review were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the extension for Scoping Reviews.[18,19] Initially, a meta analysis was intended to be conducted due to its methodological rigor. After the literature search yielded a small number of peer-reviewed articles with non-injured control groups, a scoping review was also included as a broad and preliminary evaluation of existing literature, including articles without non-injured control groups, specifically to highlight gaps in the literature for future investigation.

Search Strategy & Identification

In July 2019, four databases relevant to cognition and TBI were searched for peer-reviewed journal articles published in the English language between 2000 and July 1, 2019. Additional articles were identified by hand-searching citations of articles that met criteria and from authors' knowledge of relevant publications. Table 1 provides the keywords and databases used during the search. The search results were available to all reviewers via Rayyan QCRI.[20]

Articles were reviewed in three stages (i.e., title screen, abstract screen, and full text screen) based on the inclusion and exclusion criteria listed in Table 2.

Data Extraction & Risk of Bias Assessment

Articles that met criteria were available to all authors via a group folder in Google Drive. Two masters students in speech-language pathology extracted preliminary data (i.e., study design, participant characteristics, prevalence of cognitive fatigue, findings on related outcomes) from included studies using a standardized data collection form, shared via a Google sheet with all researchers. Review of and feedback on the literature search, themes, and manuscript was also shared via e-mail and at three in-person meetings.

Risk of bias of the included articles was assessed by two masters students in speech language pathology using an adapted version of guidelines proposed by Hayden et al..[21] The following domains were evaluated for risk of bias: study participation, attrition, outcome measurement, confound measurement, and analysis. Each reviewer assessed each domain, rating each item as “yes”, “no”, “partly”, “unsure”, or “not applicable. The ratings were summarized using an adapted version of a method proposed by the Scottish Intercollegiate Guidelines Network.[22] Articles were classified as “high quality” (+++), “moderate quality” (++), or “fair quality” (+). No study with a retrospective design received a “high” or “moderate” classification, since this is a weak study design.[22]

Data Analysis

Studies with a control group that reported a cognitive fatigue score were included for meta-analysis. Cohen’s d effect sizes and standard errors were calculated based on the data available in the articles. A model of random effect sizes was used to combine effect sizes.[23] Statistical heterogeneity was calculated with Q and I^2. Visual and statistical inspection (i.e., rank correlation test) of publication bias was made with a funnel plot. All analyses were conducted with - and the forest and funnel plots were derived from - JASP 0.9.2.0. All studies meeting inclusion criteria, with or without a control group, were included for a scoping review.

Results

Search Results & Data Extraction

The initial search generated 2569 results, with 10 additional articles being identified from hand-searching. A total of 11 articles met inclusion criteria for this study. The flow diagram of study selection is depicted in Figure 1. Interrater agreement for all levels of review and data extraction is presented in Table 3. All discrepancies were resolved through discussion between the two reviewers/extractors and the first author.

Study Characteristics

A summary of the 11 included studies is presented in Table 4. Of note, one research group (i.e., Crichton et al. and Ryan et al.) published four of the included articles, and, although it is not explicitly stated in the studies, there is likely overlap in the samples based on study timelines and locations. Average age at the time of study participation ranged from 4.8- 16.3 years. Sample size of TBI groups ranged from 10 to 136 participants. Four studies[24–27] examined mild injuries and seven studies[3,28–33] examined multiple severities or grouped severities (e.g., mild, moderate, and severe; moderate/severe). Time post-injury ranged from two days to 2.7 years. Four studies measured fatigue at multiple time points, all less than seven months post-injury.[3,24,27,28] Two studies investigated the efficacy of a treatment approach,[25,26] and all other studies were descriptive.

Reports of Cognitive Fatigue

Scoping Review

Two types of measures were used to quantify levels of cognitive fatigue: the Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL MFS)[34] (N= 7) or symptom rating scales including item reporting for "feeling in a fog" (i.e., symptom questionnaire from ImPACT test battery[24]; Post-Concussion Symptom Scale (PCSS)[26]; Post-Concussion Symptom Inventory (PCSI)[27]; ACE Parent Questionnaire[32]) (N= 4). One study included both types of measures.[24] These measures are described in Table 5.

Five studies used parent report, four studies used child self-report, and two studies used both parent and child self-report. The average scaled rating of cognitive fatigue on the PedsQL MFS ranged from 63.7 to 83.3 for children with TBI, including the baseline ratings in the treatment studies. The symptom "feeling in a fog" was endorsed by 0% to 41.4% of children with TBI, and was rated between 1.0 to 1.6 on 0 to 6 severity scales (0= no symptoms, 6= most severe) or in the mild-moderate range.

Meta-Analysis

Six measures of cognitive fatigue from four studies[28–31] with non-injured control groups and adequate data for effect size calculations were included for meta-analysis. As two manuscripts[28-29] presented data based on groups (i.e., parent vs child report; mild vs moderate-severe injury severity), multiple effect sizes were calculated, yielding six effect sizes from four articles. Of note, all control groups were previously published controls (i.e., published normative samples, published healthy sample from a study of a different clinical sample). Although Ryan et al.[31] included an experimental control group, data for this group was not reported, and an effect size could not be calculated.

All studies used the PedsQL MFS. Five measures[28–31] were parent-reported and one measure[28] was child-reported. Four measures[29–31] included all severities of TBI, one measure[28] included only mild TBI, and one [28] included moderate-severe TBI. At the time of study participation, children with TBI were on average 11.22 years old (9.90-13.30 years) and 13.93 months post-injury (1.6-32.40 months). Studies reported average scores for children with TBI between 65.70 to 77.18, and children who are typically developing between 82.40 and 90.70. Meta-analysis revealed a statistically significant negative effect, d = -.84, 95% CI [-1.06, -0.63], indicating that children with TBI had significantly lower fatigue scores (i.e., experienced higher levels of cognitive fatigue) than control groups. The forest plot in Figure 2 depicts these results. Heterogeneity across studies was significant, $Q_{(5)} = 11.2$, $p = 0.047$, and moderate, $I^2 = 55.67$.[35] Visual and statistical inspection of the funnel plot depicted in Figure 3 did not indicate publication bias, $\tau = -0.20$, $p = 0.719$.

Scoping Review: Associated Factors and Effects

Many studies discussed or hypothesized effects associated with cognitive fatigue, but only three studies measured and ran analyses to explore the relations. Crichton et al.[3] found bivariate relations between cognitive fatigue and post-injury sleep, physical/motor functioning, and emotional functioning. Ryan et al.[31] observed smaller brain volumes with greater levels of cognitive fatigue. Van Markus-Doornbosch et al.[33] found older age at onset (>11 yo), single parent household status, greater limitations in activities and participation, and lower ratings of quality of life to be associated with worse ratings of cognitive fatigue.

Scoping Review: Management Strategies

Although most studies discussed assessment and treatment recommendations based on their findings, only two studies[25,26] directly examined management strategies, both investigating the effect of active rehabilitation on children with mild TBI and persistent symptoms. Both studies implemented the same active rehabilitation program (described in detail by Gagnon et al.[26]). Active rehabilitation was defined and conceptualized as a slow return to physical activity post-mild TBI that does not exacerbate symptoms.[26] Both studies used the PedsQL MFS to measure cognitive fatigue pre- and post- treatment, with Gagnon et al.[26] also reporting the PCSI item of “feeling mentally foggy” pre- and post-treatment. Chan et al.[25] did not conduct statistical analyses on the pre- and post- treatment data, but, based on the data reported and analysis by the authors of this paper, no significant differences were observed in cognitive fatigue from pre- to post- treatment. Gagnon et al.[26] found significant improvement in cognitive fatigue when comparing pre- and post- treatment PedsQL MFS scores. In addition, fewer participants endorsed “feeling mentally foggy” post-treatment (N= 0) compared to pre-treatment (N= 2). Both studies recommended the use of active rehabilitation treatment for children with mild TBI, noting that the treatment approach appears safe (i.e., limited to no exacerbation of symptoms)[25,26] and potentially supports improvement of a range of common post-concussive symptoms including cognitive fatigue.[26]

Risk of Bias

Based on the risk of bias domains, three studies were identified as “high quality”.[24,28,29] Four studies were identified as “moderate quality”,[25,28,31,33] and four studies were identified as “fair quality”.[26,27,30,32] Table 6 presents the risk of bias assessment results.

Discussion

This meta-analysis and scoping review appraised the available evidence on cognitive fatigue after childhood TBI. The results from 11 studies support the main study aim, indicating that children with TBI, when examined in cohorts that vary in severity, can experience cognitive fatigue, even years after injury. Limited experimental evidence was available to address the secondary aims of this study - factors and effects associated with cognitive fatigue and management strategies. These findings suggest that cognitive fatigue is a significant symptom following childhood TBI, and further research is warranted, particularly to identify effective assessment and treatment approaches.

Ratings of Cognitive Fatigue

It is challenging to generalize findings of cognitive fatigue scores due to inconsistencies in methodologies and reporting across studies. Of studies that used control groups,[25,28–31,33] four used previously published control scores (i.e., published normative samples, published healthy sample from a study of a different clinical sample), all of which were included in the meta analysis where demographic differences were not controlled for or not mentioned in the report.[28–31] All four studies reported that children with TBI had significantly worse levels of cognitive fatigue compared to controls who were typically developing, as observed in the meta-analysis of the data. Ryan et al.[31] also included a control group specific to their study, with no significant demographic differences from the TBI group, but did not find significant differences in cognitive fatigue levels between groups. Unfortunately, data for the experimental control group was not reported, and therefore could not be included in the meta analysis. Two studies'[25,33] control groups included individuals with TBI, and were not included in the meta analysis. Chan et al.[25] utilized children with similar injuries to compare treatment effects, while Van Markus et al.[33] studied children with non-traumatic brain injuries and found that children with non-TBI presented with worse levels of cognitive fatigue than children with TBI. Without the use of a non-injured control group in which demographic and external variables can be accounted for and in the absence of standardized assessments of fatigue, cognitive fatigue scores can be difficult to interpret.[6]

All measures of cognitive fatigue were subjective, potentially biasing results. Five studies[3,28,30–32] used exclusively parent reports, and four studies[24–27] used exclusively child self-reports. The two studies that used both parent and child-self reports did not find a significant difference between parent and child-self ratings.[29,33] Studies on general fatigue following childhood TBI suggest using both parent and child-self report forms to improve the validity of the findings, while recognizing the subjective nature of experiencing fatigue. Most measures, including the PedsQL MFS and post-concussion scales, are validated for both parent and child report, making multiple scores from multiple reporters feasible.[29] To the best of the authors' knowledge, objective or standardized fatigue measures have not been developed or utilized in childhood TBI but are emerging for adult TBI and other populations.[36–39] Pairing subjective and objective measures would likely provide a more robust picture of cognitive fatigue post-childhood TBI, elucidate the relationship (e.g., discrepancies) between subjective and objective reports to support assessment practices, help determine clinically-significant levels and changes in cognitive fatigue, and better inform management strategies.[5]

Because no studies included pre-injury measures of cognitive fatigue, comparisons of pre- and post-injury or typical vs atypical levels were not possible. Unfortunately, all measures from studies included in this review demonstrated limited utility in measuring cognitive fatigue, largely due to their lack of standardized items and ability to differentiate between typical or healthy fatigue levels and atypical fatigue levels.[5] Symptom rating scales using the item related to "mental fog" are less reliable and were extrapolated to represent cognitive fatigue for the purpose of this review, given literature supporting the representativeness of this item.[15,40]

The PedsQL MFS does include a valid and reliable sub-scale specific to cognitive fatigue.[34] Of the studies with available comparisons between fatigue dimensions (i.e., general, sleep/rest, cognitive), five studies[3,28,30,31,33] found that cognitive fatigue was the dimension with the worst ratings. Three studies[25,26,29] found mixed results (i.e., cognitive fatigue was worse than some and better than other dimensions). Interestingly, studies that found cognitive fatigue to have the worst rating included younger participants (8-11 years old at injury; 8-13 years old at study participation), compared to the other studies (14-18 years old at injury; 13-18 years old at study participation). Consistent with a previous review on general fatigue,[5] these findings demonstrate the importance of considering fatigue dimensions separately to advance the understanding of fatigue and provide tailored treatment and management strategies specific to the child's needs. Developmental stages and academic and social expectations should also be considered when determining the salience of cognitive fatigue post-TBI.[33]

With respect to age at injury, most studies examined children who experienced a TBI in later childhood and early adolescence (i.e., about 8 to 18 years old). Only one study examined earlier childhood TBI with an average age of injury at 4.8 years old.[32] Due to a limited number of studies in each age group, differences in the presentation of cognitive fatigue based on age were difficult to elucidate. Studies suggested that adolescence is a particularly important time to evaluate and consider fatigue, due to the natural increase of fatigue during that developmental period.[3,33] In addition, early childhood presents with the highest rates of TBI across childhood with major cognitive and developmental changes shortly after injury, although Suskauer et al.[32] did not find notable ratings of cognitive fatigue in their sample. This could be due to adults' inability to readily observe "feeling mentally foggy" in children who cannot accurately convey their symptoms;[32] this possibility warrants additional investigation and development of measures that could accurately capture cognitive fatigue in this age group.

When examining cognitive fatigue levels based on severity, most studies that included multiple severities did not report cognitive fatigue levels separately for severity groups, limiting comparisons. Generally, children with milder injuries were over-represented compared to those with moderate or severe injuries, but tended to present with lower levels of cognitive fatigue.[3,24,27,28] This trend becomes less clear when considering children with persistent symptoms following a mild injury, potentially appearing more similar to moderate-severe injuries.[25,26] Future investigations should consider assessing cognitive fatigue symptoms longitudinally in children with chronic mild TBI to better our understanding of the course of symptoms and to inform management strategies.

Studies included in this review reveal multiple trajectories for the presence of cognitive fatigue throughout recovery. Studies conducted in the chronic stages of recovery, about two years post-injury, indicated that cognitive fatigue can persist at clinically-significant levels for all severities of TBI.[30,31,33] Changes in cognitive fatigue over time were inconsistent when examined multiple times in the acute stages of recovery. One study[28] found that cognitive fatigue at one year post-TBI was significantly worse than at six months post-TBI. Three studies,[24,26,27] including a treatment efficacy study, saw improvement within five months of injury with and without intervention. One study,[25] a treatment efficacy study, found no change, and one study[3] observed an increase in clinically-significant fatigue scores for individuals with mild injuries, but improvement for those with moderate-severe injuries. Multiple factors could be influencing levels of cognitive fatigue including: developmental stages, social and academic expectations or involvement, and personal or environmental characteristics.[3,28]

Associated Factors & Effects

Post-injury functioning (e.g., sleep, physical, emotional, daily participation), brain volume, age at onset, parental marriage status, and quality of life appear to be associated with cognitive fatigue, but the directions of these relations remain unclear.[3,31,33] Other studies hypothesized or presented additional data that could support or warrant further investigation of potential relations with other factors. Children with more significant levels of cognitive fatigue would likely experience greater difficulties in academics and general functioning and lower quality of life.[27,28,30] Psycho-social and mental health needs and sleep disturbances could be exacerbated by and/or contribute to acute levels of cognitive fatigue.[24,29] These hypothesized relations would not be unexpected, given literature indicating the general association of these factors (i.e., academic and social functioning, quality of life, psycho-social and mental health, sleep) with childhood TBI.[3] Although evidence is limited, given the subjective nature of fatigue, personal, injury, and post-injury functioning factors are essential to the understanding of cognitive fatigue and to tailor management strategies to individual needs.

Management Strategies

Suggestions for assessment of cognitive fatigue in childhood TBI included: regular and systematic screenings for symptoms into the chronic stages of recovery to track progress and ongoing needs;[24,27,29,30] multidimensional fatigue assessments with multiple reporters;[3,28,29,33] structural imaging of biomarkers to identify and predict cognitive fatigue;[41] and self-report assessments specific to the child's developmental stage (e.g., including more concrete language regarding cognitive fatigue for younger children).[32] From the two studies that evaluated treatment efficacy, active physical rehabilitation did not appear to exacerbate general post-concussion or fatigue symptoms following childhood TBI and could improve cognitive fatigue, but additional investigation is needed.[25,26] Many additional management strategies were suggested in the included articles but did not include empirical evidence. Recommendations for interventions included: treat both the cognitive fatigue symptoms and areas of functioning associated with greater fatigue (e.g., physical skills);[3] support functional improvements for participation and quality of life through cognitive rehabilitation, behavior management, and academic supports;[27,29,30,33] and consider external demands based on age when designing supports and implementing services.[32] One study[30] reported that children who experienced cognitive fatigue did not receive specialty supports at school, reinforcing the potential broader impact of unmet need in children with TBI.[42,43] Evidence-based management strategies for cognitive fatigue after childhood TBI are limited and need additional attention to support positive outcomes.

Future Directions

Future research in cognitive fatigue after childhood TBI should utilize more robust methodologies such as pairing objective and subjective measures of cognitive fatigue, measuring cognitive fatigue at multiple time points, and controlling for confounding factors. Additional attention is needed on younger children with TBI including monitoring symptoms into later childhood and adolescence. Research in the neuro-biological mechanisms underlying cognitive fatigue and changes in fatigue with overall development could provide valuable information to inform management. Translational research investigating the feasibility and efficacy of assessment and treatment methods is essential to support long-term outcomes for children with TBI. Establishing a program, such as TBI Model Systems, for children could support longitudinal and clinical research to better inform management of cognitive fatigue after TBI.

Limitations

Although our literature search reached the point of duplication, some relevant studies might have been missed. Overall, limited evidence was available on cognitive fatigue after childhood TBI. Of the available research, few studies used control groups; therefore results of the meta-analysis should be interpreted with caution. In addition, multiple studies published by the same research group likely included overlapping samples, potentially decreasing the efficacy of the meta analysis due to correlation amongst samples. Comparisons across studies were difficult due to differences in methodology (e.g., time since injury, severity of injury, measures of course of fatigue, parent vs child-self report), limiting the generalizability of results. Despite these limitations, results of this study provide a comprehensive summary of the available evidence on cognitive fatigue after childhood TBI and highlight areas in need of further investigation.

Conclusions & Clinical Implications

Specific consideration of cognitive fatigue is necessary for effective assessment and treatment after childhood TBI. Additional investigation is needed to better inform clinical services. Based on the current literature, children with any severity of TBI should be continuously assessed for cognitive fatigue through the chronic stages of recovery, with special focus on children with associated factors including lower general post-injury functioning and lower quality of life. Treatment approaches should include direct management of cognitive fatigue and reduction of the secondary effects, such as academic and social engagement, to improve long-term quality of life in children with TBI.

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Tables

Table 1. Search Terms and Databases	
Search Terms (searched in each database)	Cogn* and fatigue and child* and brain injury Cogn* and fatigue and pediatric and brain injury Cogn* and fatigue and child* and acquired brain injury Cogn* and fatigue and pediatric and acquired brain injury Cogn* and fatigue and child* and traumatic brain injury Cogn* and fatigue and pediatric and traumatic brain injury Mental and fatigue and child* and brain injury Mental and fatigue and pediatric and brain injury Mental and fatigue and child* and acquired brain injury Mental and fatigue and pediatric and acquired brain injury Mental and fatigue and child* and traumatic brain injury Mental and fatigue and pediatric and traumatic brain injury
Databases	Pubmed, PSYCINFO, ERIC, ScienceDirect

Table 2. Inclusion and Exclusion Criteria	
Inclusion Criteria	Fatigue with some mention of cognitive and/or mental fatigue; child/pediatric/adolescents; brain injury
Exclusion Criteria	non-ABI; Non-accidental ABI or child abuse; blast injuries; meta analyses, systematic reviews, or non-peer reviewed papers; adults

Table 3. Interrater Agreement for Study Selection, Data Extraction, & Risk of Bias

Review	**Agreement Prior to Resolution** (proportion of items review)
Title Screen	90.5% (915/1011)
Abstract Screen	84.98% (191/223)
Full Text Screen	94.2%

	(96/102)
Data Extraction	98.8% (543/550)
Risk of Bias Assessment	96.4% (53/55)

Table 4. Summary of Included Summaries

Study (Author, Year Location)	**Level of Evidence Study Design** no studies using published controls received a rating higher than a III	**TBI Group Characteristics** (N severity; % male; Age at study participation (AS) (M (SD)); Time post injury (TPI) (M (SD))	**Control Group Characteristics** (N type; Age at survey (AS) (M (SD))	**Reporter; Measure**	**Results for Cognitive Fatigue**
Blinman, 2009 Pennsylvania, USA	III Prospective cohort without controls	63 mild; 69.8% male; AS: 14.1 (SD not reported) yrs; TPI: 2 days and 2-3 wks	n/a	Self-report; Symptom questionnaire of the ImPACT neurocognitive test battery (item: "feeling mentally foggy") rated 0=no symptoms to 6= severe	41.4% (2.7 average rating) reported "feeling mentally foggy" at initial visit; 19.1% (1.6 average rating) reported at follow-up visits
Chan, 2018 British Columbia, Vancouver, Canada	I Single-site, parallel, open-label, randomized control	10 mild, PCS; 40% male; AS: 15.9 (1.66) yrs; TPI: 132 (52.0) days for initial assessment and post-treatment	9 mild, PCS; AS: 15.1 (1.42) yrs	Self-report; PedsQL MFS	Children who participated in a closely monitored, active rehabilitation treatment program did not experience more adverse effects than those receiving treatment as usual. No significant changes were observed between physical activity, symptom exacerbation, and clinical outcomes. Chan et al. did not perform statistical analysis of fatigue data, due to its exploratory nature in this study. The authors of this meta analysis conducted paired sample t-tests to compare pre- and post-treatment fatigue scores. No significant differences were found in the cognitive fatigue ratings for the active rehabilitation group. *Management Strategies:* Active rehabilitation, when closely monitored, could be beneficial for adolescents with persistent symptoms, such as cognitive fatigue, post-TBI.

Crichton, 2017 Melbourne, Australia	III Prospective with published controls	27 mild, 5 mod, 3 severe; 34 parent proxies; % male not reported; AS: not reported (age at injury: 13.3 (2.4) yrs (mild), 13.2 (2.6) yrs (mod/severe)); TPI: 7.3 (1.6) wks	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample[1] and demographic differences could not be controlled	Self-report and parent-report; PedsQL MFS	Children and parents reported significantly greater levels of cognitive fatigue for the TBI group than the control sample.
Crichton, 2018a Australia and Canada	III Longitudinal prospective with published controls	59 mild, 36 mod/severe; 77% male; AS: not reported (age at injury: 9.9 (5.0) yrs); TPI: 6 and 12 mos	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample[1] and demographic differences could not be controlled	Parent-report; PedsQL MFS	Cognitive fatigue was significantly worse for children with moderate-severe TBI than mild TBI. Cognitive fatigue worsened significantly from 6 months to 12 months post-injury.
Crichton, 2018b Australia and Canada	III Prospective, non-randomized cohort without controls	52 mild, 27 mod/severe; 82.69% male (mild), 85.19% (male mod/severe); AS: 11.73 (4.42) yrs (mild), 9.72 (5.17) yrs (mod/severe); TPI: 6 and 12 months	n/a	Parent-report; PedsQL MFS	At 6 and 12 months post-TBI, 10% and 17%, of children with mild TBI and 27% and 19% of children with mod-severe TBI were rated in the clinical range for total fatigue, respectively (cognitive fatigue levels were not individually reported). Cognitive fatigue was the dimension with the worst ratings compared to sleep/rest and general fatigue. *Associated Effects:* General post-injury physical functioning significantly predicted cognitive fatigue 12 mos post-TBI (child factors and injury severity did not). Relationships with pre and post injury functioning might be bi-directional.
Gagnon, 2016 Montreal, Canada	III Clinical series without controls	10 sport-related concussion (slow to recover); 70% male; AS: 14-18 yrs; TPI: 7.9 wks for initial assessment and post-6 week treatment	n/a	Self-report; PedsQL MFS and PCSS (item: “feeling mentally foggy”)	Cognitive fatigue and all fatigue measures improved significantly post-treatment in an active rehabilitation program. “Feeling mentally foggy” was endorsed by 2 participants pre-treatment and no participants post-treatment. *Management Strategies:* Low-levels of active rehabilitation might be beneficial for children who are slow-to-recover from concussion. Active rehabilitation appears to support improvement

					across different symptoms, particularly fatigue dimensions.
Limond, 2009 United Kingdom	III Retrospective, cross-sectional study compared to published normative data	47 mild, moderate, and severe (hospitalized for at least 48 hrs); % male not reported; AS: 10.5 (3.6) yrs; TPI: 2.7 (1.2) yrs	105 healthy; 68.6% male; AS: 13.70 (9.47) yrs parent report: 157 healthy; 62.4% male; AS: 11.63 (8.59) years *controls are from a published normative sample[2] and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI were reported to have significantly greater levels of fatigue for all injury severities compared to the control sample. Cognitive fatigue was the dimension with the worst rating compared to sleep/rest and general fatigue. Less than half (47%) of children with TBI had ratings of "normal" levels of cognitive fatigue, while 15% were considered "borderline" and 38% were considered "abnormal", based on cut-off scores.
Macartney, 2018 Ontario, Canada	III Retrospective chart review without controls	136 mild; 45.6% male; AS: 15.4 (median); TPI: 5.4 (3-10.8) days for initial assessment then 28 days, 56 days, and 84 days *participants were discharged when symptoms returned to baseline therefore not all participants required assessment at all time points	n/a	Self-report; PCSI (item: "feeling in a fog") rated 0 to 6 (higher scores= more severe)	The median rating of "feeling in a fog" was 2.9 (1.0-5.8); 1.4 (0.1-5.2); 1.0 (0.4-5.0), at 28; 56; and 84 days, respectively.
Ryan, 2016 Melbourne, Australia	III Prospective, non-randomized cohort with experimental controls and published controls	67 mild, 24 moderate, 12 severe; 67.96% male; AS: 10.54 (2.39) yrs (mild), 10.37 (2.58) yrs (moderate), 10.41 (3.10) yrs (severe); TPI: 24 months	Experimental: 34 healthy; 21% male; AS: 10.41 (2.76) *no demographic differences between groups Published: 157 healthy; 47.1% male; AS: 13.68 (2.17) yrs *controls are from a published normative sample[3] and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI had significantly greater levels of cognitive fatigue compared to the published control sample, but, when compared with experimental controls, no differences were observed. *Associated Effects:* Cognitive fatigue was significantly associated with smaller brain volumes. This finding could indicate disruptions of neural pathways cause an imbalance in effort-reward experiences which is subjectively reported as cognitive fatigue.

Suskauer, 2018 Maryland, USA	III Retrospective medical record review	28 mild/moderate/severe; 50% male; AS: not reported (age at injury: 4.8 yrs); TPI: 38 days	n/a	Parent-report; ACE Parent Questionnaire (item: “feeling mentally foggy”) classified as “ever experienced post-TBI” or “currently experiencing post-TBI”	No parents (0%) reported their child ever or was currently experiencing “feeling mentally foggy”.
van Markus-Doornbosch, 2016 Netherlands	III Prospective review and follow-up study without controls	58 mild, 11 moderate/severe; 46% male; AS: not reported (age at injury:11 (6) yrs (median, IQR)); TPI: 24-30 mos	19 non-traumatic BI (NTBI); 11% male; AS: 14 (7); TPI: 24-30 mos	Parent-report and self-report; PedsQL MFS	Children with NTBI were parent- and self-reported to have significantly greater levels of cognitive fatigue compared to children with TBI. No significant difference was observed between parent and child self- report for cognitive fatigue. *Associated Effects:* Greater levels of cognitive fatigue was significantly associated with older age at onset (>11 yo); single parent household; greater limitations in activities and participation; and lower quality of life.

Table 5. Measures used to quantify levels of cognitive fatigue	
Measure	Description
PedsQL Multidimensional Fatigue Scale (PedsQL MFS)[34]	- parent and child self-report forms for ages 2-18 years old - 3 subscales (i.e., general fatigue, sleep, cognitive fatigue) are rated on a Likert scale (0= never a problem to 4= almost always a problem over the past month). Items are then reverse scored and transformed to a 0- to 100-point scale, such that higher scores indicate less fatigue.[a] - shown good internal consistency reliability, test-retest reliability, and inter-observer reliability[34]
Immediate Post-Concussion Assessment and Cognitive Test (ImPACT)[44]	- FDA endorsed online tool for baseline and post-injury testing for ages 12-59 years old - assesses visual and verbal memory, reaction time, and processing speed through 8 tasks and includes a series of symptom-related questions rated on a 7-point Likert scale (0= no symptom, 6= severe symptom) - validity and reliability are unclear and highly dependent on time administered post-injury, area assessed, and other factors[45,46]
Post-Concussion Symptom Scale (PCSS)[47]	- self-report for individuals over 11 years old - 22-items of symptom-related questions rated from 0 (not endorsed) to 6 (severe) - shown good test-retest reliability and internal consistency reliability and reliable to detect change over time[48]
Post-Concussion Symptom Inventory (PCSI)[49]	- parent and child self-report for ages 5-18 years old - 27-items of symptom-related questions rated from 0-6 with higher scores representing more severe symptoms - shown good internal consistency[50]
Acute Concussion Evaluation (ACE)[51]	- parent and child self-report for ages 4 years old-adult - shown good internal consistency reliability, content validity, predictive validity, convergent/divergent validity, and construct validity[52]
[a]Chan et al.[25] did not appear to calculate the scaled score in reporting results	

Table 6. Risk of Bias Summary

Author, Year	Study Participation	Attrition	Outcome Measurement	Confound Measurement	Analysis	Assessment Summary
Blinman et al., 2009	no	party	no	no	no	+++
Chan et al., 2018	no	no	partly	partly	no	++
Crichton et al., 2017	no	no	partly	no	no	+++
Crichton, Anderson, et al., 2018	no	no	no	no	no	+++
Crichton, Oakley, et al., 2018	partly	no	partly	no	no	++
Gagnon et al., 2015	no	no	partly	yes	partly	+
Limond et al., 2009	no	no	partly	no	no	+
Macartney et al., 2018	no	no	partly	no	no	+
Ryan et al., 2016	no	no	yes	no	no	++
Suskauer et al., 2017	no	no	partly	partly	no	+
van Markus-Doornbosch et al., 2016	no	partly	partly	no	no	++

Note: no= no to little potential bias; partly= some bias; yes= likely bias