Fatigue following pediatric acquired brain injury: Interplay with associated factors in a clinical trial population compared to healthy controls

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Abstract

Objective. The aims of the present study were to compare fatigue levels in children with pABI with healthy controls (HCs), and examine the interplay of fatigue with associated factors. **Method.** We used baseline data from a preregistered randomized controlled trial. Seventy-six children aged 10 to 17 (median 13y) with pABI in the chronic phase (88% with confirmatory cerebral imaging findings) and executive function (EF) complaints were included, most with moderate disability according to The Glasgow Outcome Scale Extended (GOSE-E) categorization. HCs consisted of 60 children aged 10 to 17 (median 13y). All 127 participants completed measures of fatigue and IQ. pABI participants were also assessed for behavioral problems, health-related quality of life (HRQoL) and EF. Nonparametric statistics were employed, in addition to a network analysis to model the unique associations between parent-reported fatigue and related factors. **Results.** Parents reported significantly more fatigue in the pABI-group (75% of scores in clinical range; <70) compared to HCs (11.7% of scores in clinical range). No strong associations were found between fatigue and injury characteristics, but findings indicated more fatigue in the older than younger age-group for pABI participants. Network modeling revealed a central role for HRQoL, behavioral and EF symptoms in relation to fatigue. **Conclusions.** Fatigue is reported to be highly prevalent in the chronic phase of pABI. When addressing fatigue, our findings demonstrate the advantage of including multidimensional measures of fatigue and examining associated psychological and cognitive constructs, such as HRQoL, behavioral problems and EF.

Keywords: Fatigue; brain injury; executive function; quality of life; pediatric.

Question: What is the prevalence and severity of fatigue in children and adolescents with pediatric brain injuries, and is it related to other factors?

Findings: For the majority of children in chronic phase of pABI, parents reported fatigue in the clinical range. Fatigue is associated with health-related quality of life, behavioral problems and executive function.

Importance: Fatigue is a complex symptom that negatively impacts functioning across a range of areas, and needs to be addressed in all phases of brain injury rehabilitation.

Next Steps: Longitudinal studies are needed to confirm the directionality of the relationships between factors associated with fatigue.

Fatigue refers to a set of symptoms common in healthy individuals (Loge et al, 1998; Pawlikowska et al., 1994), as well as in a range of medical conditions, such as cancer, multiple sclerosis, brain injuries and other neurological conditions (Curt et al, 2000; Englander et al, 2010; Kluger et al, 2013; Levine & Greenwald, 2009; Mulhern et al, 2004; Thomas, 2018). While fatigue in the general population is normally transitory and alleviated by rest and sleep, fatigue in the medical sense refers to an enduring, subjective experience of physical, emotional and/or cognitive weariness that interferes with daily functioning, does not recede after rest, and is not proportional to recent activity (Bower, 2014). The etiology of the symptom is complex, influenced by several common factors in a variety of disorders, pertaining to changes in the central and peripheral nervous system and endocrine disturbances (Armstrong et al, 2010; Kluger et al., 2013; Crichton et al, 2015). External factors such as social and academic demands, may exacerbate fatigue symptoms (Ezekiel et al, 2020). Furthermore, acts and processes that require cognitive effort, like revising for an exam, may in general incur a cost on limited cognitive resources, for instance executive function (EF), resulting in a subjective feeling of fatigue (e.g., Gailliot et al., 2007; Kool et al, 2010). These findings underpin the transdiagnostic nature of the construct. Fatigue has been demonstrated to cluster with other symptoms, including physical, psychiatric and cognitive problems, such as reduced activity, sleep and mood disorders, as well as EF impairment (Armstrong et al. 2010; Manoli et al, 2020; van Markus-Doornbosch et al, 2020). Studies find no consistent associations between the prevalence and severity of fatigue and etiology, disease duration and severity or treatment factors (Armstrong et al., 2010; Cantor et al., 2008; Levine & Greenwald 2009; Struik et al., 2009). However, some treatments for brain tumor (BT), e.g., chemo- and radiation therapy, are considered to be significant risk factors (e.g., Bower, 2014). In children with pediatric acquired brain injury (pABI) fatigue has been described as one of the most universal symptoms (Crichton et al., 2015). In a recent review by Wilkinson et al (2018),

pABI survivors reported significantly higher levels of fatigue post-pABI than healthy controls (HCs) (Borg et al, 2009; Palmer et al, 2007), with 58% to 74.6% reporting fatigue across multiple pABI etiologies (i.e., encephalitis, BT, traumatic brain injury (TBI), meningitis) (Eisenberg et al, 2014; Logar et al, 2000; Macartney et al, 2014; Sumpter et al, 2011). There is evidence of greater levels of fatigue in BT survivors than other pABI conditions (Brand et al, 2016; Meeske et al, 2004), possibly due to treatment factors. Importantly, fatigue following pABI interferes with daily function, academic performance and social/school participation, and is linked to poorer health-related quality of life (HRQoL) (Berrin et al., 2006; Dornonville de la Cour et al, 2018; Goretti et al., 2012; Macartney et al., 2014). Despite this, studies of fatigue in pABI are scarce.

The chronic nature of fatigue is not well understood, as few studies have examined this construct over time (Brand et al., 2016). Existing literature suggest that for some pABI-patients, in particular BT survivors, fatigue continues to be a significant and persistent problem years after injury or treatment (Jonsson et al, 2014; Puhr et al., 2019; Câmara-Costa et al 2019). Poor functional long-term outcomes following pABI have been found to be strongly associated with fatigue and executive dysfunction (Puhr, et al., 2019). The association of fatigue and disrupted functional connectivity in the cerebral attentional network has been demonstrated in several studies (Nordin et al., 2016; Finke et al., 2015, Ziino & Ponsford, 2006). The directionality of the association is yet to be established. However, the finding is in keeping with the hypothesis that brain lesions in the neural circuits involved in the regulation of attention, arousal, response speed, and EF may contribute to the development of weariness and aversion to effort leading to fatigue (Kutlubaev & Mead, 2012). Accordingly, the coping hypothesis by van Zomeren and colleagues (1984) and a model presented by Ponsford et al. (2014), ascribe a vital role to attentional impairment as a driving force in fatigue after ABI. Study results from Ponsford and colleagues confirm the

complexity of the fatigue symptomatology and suggest that a self-preserving cycle may exist between fatigue, attention and mood (Ponsford et al, 2015). Nevertheless, there is a knowledge gap concerning fatigue and the above-mentioned factors in pABI.

Fatigue is subjective and multidimensional by nature, and its wide symptomatology and lack of a consensus framework (Chaudhuri & Behan, 2004; Crichton et al., 2015), makes quantification of the construct challenging. The symptom is typically measured using questionnaires. Girls report fatigue more often than boys (van Markus-Doornbosch et al., 2020; Norup et al., 2019), a finding which is in line with epidemiological studies pointing to a female predominance in the prevalence of a variety of self-reported psychosomatic and mental health conditions (Piccinelli & Wilkinson, 2000; Preiss-Farzanegan et al, 2009). Measuring fatigue in the pediatric population involves some additional issues, relating to respondent types and developmental factors (Câmara-Costa et al., 2019; Haines et al, 2005). Thus, there is a need to obtain information from children and parents (Crichton et al., 2017; Eiser & Varni, 2013). However, few studies have included both child- and proxy-reports, as well as HCs (Wilkinson et al, 2018).

Notably, the methodological shortcomings in existing studies on fatigue and pABI limit the generalizability of findings in relation to the prevalence of fatigue, functional consequences and associations to demographic variables and other domains (Crichton et al., 2015; Wilkinson et al., 2018). Hence, there is a persisting need for further investigation of these issues. The present study represents baseline data from a preregistered randomized controlled trial (RCT) on the efficacy of cognitive rehabilitation, including matched healthy controls (HCs) (Hypher et al., 2019). The aim of the present study was threefold:

First, we wanted to compare the severity of fatigue in children and adolescents with pABI with HCs, in addition to examining potential differences in self- and parent reports of fatigue. Second, we wanted to investigate possible associations between fatigue and injury

type, sex, age, time since injury, and general intellectual ability (verbal IQ). Additionally, we explored how the three subdomains of The Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (MFS; Varni & Limbers, 2009) General, Sleep/rest and Cognitive fatigue, differed over time since injury. Our third aim was to investigate how fatigue following pABI is related to indicators of EF, processing speed, behavioral problems, and HRQoL, each of which have been proposed as central constructs in relation to fatigue. In order to model the complex interplay between these constructs and fatigue, we relied on network analysis, which forms a data driven approach to model unique associations between our constructs of interest. The network approach in relation to complex symptomatology postulates that symptoms do not co-occur because they originate from a common underlying disease, but because they are strongly inter-related, activating, intensifying and mutually reinforcing one another. Even though the network approach primarily advocates analyses on item level, the method can be equally interesting to model how latent constructs relate to one another (Faelens et al, 2019; Hoorelbeke et al, 2016; Hoorelbeke et al, 2019). Although the obtained network model is undirected due to the cross-sectional nature of the data, network models allow generation of hypotheses regarding the relation between cognition, HRQoL, behavioral problems, and fatigue, which may be informative for future, confirmatory research in the context of pABI.

Materials and Methods

Setting, design, participants and procedures

This cross-sectional study presents baseline data derived from a national multicenter RCT (Hypher et al., 2019). Participants were recruited from the trauma referral centers from all the regions of Norway. The study was approved by the Regional Committees for Medical and Health Research Ethics, Norway (2017/772/REK), and conducted in accordance with principles of Good Clinical Practice, the Helsinki Declaration and the standards for Ethical

Research Involving Children (ChildWatch International and UNICEF). Clinical Trial Registration No.: NCT03215342.

Participants with acquired brain injury

The study population consists of participants with pABI resulting from traumatic (TBI) and non-traumatic injuries (BT, cerebrovascular accident, hypoxia/anoxia and brain infections/inflammations) aged 10 to 17 years. Inclusion required executive dysfunction in daily life as determined by a semi-structured interview and minimum 12 months since injury/illness or completion of cancer therapy. Exclusion criteria: (i) pABI before 2 years of age; (ii) cognitive or medical impairments affecting the capacity to attend regular school; (iii) pre-injury neurological disease, severe psychiatric disorder and/or use of stimulant medication; (iv) recently detected brain tumor relapse; (v) not fluent in Norwegian.

Procedures

Invitation letters were sent to potential participants ($n = 223$) identified by hospital discharge diagnosis and record information from three university hospitals in Norway: St. Olav's Hospital (SOH) in Trondheim, Oslo University Hospital (OUS), and University Hospital of North Norway (UNN). The invitation letter specifically solicited participants experiencing EF dysfunction in daily life. Following a positive invitation response, written informed consent was required from potential participants (> 16 years) or primary caregivers (participants < 16 years) before conducting a semi-structured screening interview, informed by hospital records, in order to determine whether they were eligible for study inclusion. Participants older than 16 years of age were invited to attend the interview, while parents reported for participants < 16 years of age. Of the 99 individuals who were eligible for screening, ten participants did not meet inclusion criteria and were excluded, and two participants declined to participate. Once the participants had been randomized ($n = 87$), a baseline assessment of 76 participants was completed. Pre-inclusion attrition included 11

participants (after randomization, before baseline), due to worsening of illness, initiation of drug testing or intensification of rehabilitation (9 participants) and information indicating obvious violation of eligibility not previously communicated (2 participants).

Healthy controls

Sixty HCs were recruited from schools in the Oslo and Trondheim area. They were matched for age and sex and had to meet the following inclusion criteria: healthy, normally developed children, between the age of 10 and 17 years. *Exclusion criteria:* (i) previous head injury with loss of consciousness > 5 minutes, stroke, other brain injuries or brain diseases; (ii) severe (neuro)psychiatric disorder or substance abuse; (iii) cognitive, sensory, physical, or language impairment affecting the capacity to attend mainstream school; (iv) not fluent in Norwegian. The HCs were assessed with the Wechsler Intelligence Scale for Children-Fifth edition (WISC-V) subscales (Vocabulary, Similarities, Block Design, Matrix Reasoning) (Wechsler, 2014). Both HCs and their parents completed the PedsQL MFS. Additional information was obtained from parents concerning parental educational level and the child's residence.

Measures

Fatigue

Fatigue was assessed using the 18item PedsQL MFS (self- and parent reports), which consists of three subscales: (1) General Fatigue (6 items, e.g., “I feel tired.”; “I feel too tired to do things that I like to do.”), (2) Sleep/Rest Fatigue (6 items, e.g., “I feel tired when I wake up in the morning.”; “I rest a lot.”), and (3) Cognitive Fatigue (6 items, e.g., “It is hard for me to keep my attention on things.”; “It is hard for me to remember what people tell me.”), in addition to a total fatigue score (Varni & Limbers, 2009). Robust psychometric properties have been reported (Crichton et al., 2015; Crichton et al., 2017), including evidence for the validity of the PedsQL MFS for a wide age-range (2-18 yrs) (Panepinto et al., 2014). Scores $\leq$

70 were defined as being in the clinical range (Varni & Limbers, 2009). In the present study good internal consistency was found for both the parent-report ($\alpha = .93$) and the self-report ($\alpha = .94$).

Health-related quality of life

The 23-item PedsQL Generic Core Scales (GCS, self- and parent reports) is a questionnaire assessing HRQoL that encompasses four subscales, representing physical, emotional, social and school functioning, in addition to a total subscale. Good reliability and validity have been reported, including the pABI population (McCarthy et al., 2005; Varni & Limbers, 2009). In this study, the parent-reported total was employed ($\alpha = .93$), with normative data derived from Upton and colleagues (2005) ($n = 665$, $M = 84.61$, $SD = 11.19$). Cut-off was defined as scores < 65.4 (Varni, Burwinkle, Seid, & al., 2003).

Behavioral problems

Behavioral problems were assessed with the parental report from Achenbach System of Empirically Based Assessment: Child Behavior Checklist for ages 6–18 (CBCL/6-18; Achenbach, 2001). The form yields various subscales and three composite scores, of which Total problems ($T = 50$, $SD = 10$) was employed in the present study. The questionnaire has robust psychometric properties with adequate internal consistency ($\alpha = .82$) (Achenbach, 2001).

Functional outcome

The Glasgow Outcome Scale Extended (GOSE-E). The GOSE-E is a scale with 19 items developed to measure functional outcome in children and adolescents following pABI (Beers et al., 2012). It has 8 levels (minimum score = 1, maximum score = 8): Level 1 = dead, Level 2 = vegetative State, Level 3 = low severe disability, Level 4 = upper severe disability, Level 5 = low moderate disability, Level 6 = upper moderate disability, Level 7 = low good recovery, and Level 8 = upper good recovery.

Cognitive measures

Wechsler Intelligence Scale for Children-Fifth Edition. The WISC-V is an individually administered test battery to assess the general intellectual ability of children from 6 years 0 months to 16 years 11 months (Wechsler, 2014). The Verbal Comprehension Index (VCI), derived from the subtests Vocabulary and Similarities, was used as IQ estimate in our study. The Working Memory (WMI) and Processing Speed (PSI) indexes were included in the network analyses.

The Conner's Continuous Performance Test, 3rd Edition (CPT-III). The CPT-III is a computerized assessment of attention, and evaluates several components of the construct (e.g., selective, divided, and sustained attention) (Conners, 2014). The test is well validated in the assessment of pABI (Ringdahl et al., 2019). We employed Omissions as a measure of sustained attention.

The Delis–Kaplan Executive Function System (D-KEFS). The D-KEFS is a battery of standardized tests designed to measure a wide range of EF abilities (Delis, Kaplan, & Kramer, 2001). In the present study, we included the Color-Word Interference Test subtest 3 (CWIT3), targeting subcomponents of EF pertaining to cognitive control and response inhibition.

The Behavior Rating Scale of Executive Function (BRIEF). The BRIEF is an 86-item standardized questionnaire that captures the informant's perceptions of a child's EF in his or her everyday environment (Gioia, 2000). The questionnaire has been applied to several clinical groups in Norway which reported good validity, high test-retest reliability and internal consistency (Sørensen & Hysing, 2014). Scores >65 were defined as being in the clinical range (Gioia et al, 2000). Here, we relied on the Metacognitive Index score (MI) ($T = 50$, $SD = 10$, parent report, $\alpha = .71$), as a subjective indicator of EF as this score places a strong emphasis on the attentional and metacognitive subdomains.

Statistical analysis

All data analyses were conducted using IBM-SPSS version 25 (SPSS, Inc., Chicago, Illinois), except for the network analyses which were conducted in R version 3.6.1 (for more detailed information on the version of R-packages included in the analyses, see Supplemental materials). Categorical data were summarized by numbers and percentages. Continuous data were summarized by mean and standard deviation if data were normal distributed, and median and interquartile range (IQR) if data were skewed. Bonferroni corrections for multiple comparisons were employed. All statistical testing used an alpha value of .05 (two-tailed). As the majority of variables were non-normally distributed, nonparametric statistics were employed. Between group differences were investigated by Mann–Whitney U-test (continuous variables). Univariate analyses for continuous data and Pearson Chi-square or Kruskal-Wallis Test for categorical data were applied to explore the associative value of demographic variables and injury factors for the fatigue measure (PedsQL MFS, parent report). Spearman rank order correlation (ρ) was used to estimate the association between PedsQL MFS and IQ. A MANCOVA was employed to control for group differences that reached statistical significance between the patient group and the HC group (IQ and level of education). Effect size (ES) is reported as r defining small ES as $r = 0.1–0.3$; medium ES as $r = 0.3–0.5$; large ES as $r > 0.5$ (Field, 2013).

A network analysis was performed to model the unique associations between parent-reported fatigue, HRQoL, level of behavioral problems and multiple indicators of EF, including parent-reported EF symptoms (BRIEF MI) and performance-based measures of inhibition (CWIT3), attention (CPT Omissions), working memory (WISC-V WM), and processing speed (WISC-V PS). For this purpose, the variables of interest were transformed using the *huge* package (nonparanormal transformation) to improve normality (Zhao et al., 2015). The *qgraph* package was used to estimate a Gaussian Graphical Model (GGM)

(Epskamp et al, 2012). In this model, the included variables are represented by nodes, whereas the unique associations (i.e., partial correlations) between these variables are represented by edges. As such, each edge between two given nodes represents the shared variance between these nodes while controlling for the other nodes in the model. Given that the absence of a relation between two psychological constructs will almost never result in (partial) correlations that are exactly zero, we used the Graphical Least Absolute Shrinkage and Selection Operator as a regularization method to remove small, spurious partial correlations from the model (Friedman et al, 2014). The final model was selected based on the Extended Bayesian Information Criterion (EBIC) where the hyperparameter γ was set at 0.5 to maximize specificity of the model. γ can range between 0 and 0.5, where the latter setting reflects a rather conservative approach, erring on the side of parsimony, whereas a value of 0 errs towards discovery (Epskamp & Fried, 2018).

As an indicator of the importance of each node within the obtained network, we estimated Strength Centrality. Strength Centrality reflects the level of connectivity of a node in the model and is calculated as the sum of absolute edge weights connected to each node (Costantini et al., 2015; Epskamp & Fried, 2018). Furthermore, relying on the *mgm package* (Haslbeck & Waldorp, 2015), we used a node-wise regression approach to estimate the proportion of variance of each node that is explained by its neighboring nodes, referred to as node predictability (Haslbeck & Fried, 2017).

In order to assess the accuracy and stability of the obtained GGM, we relied on bootstrapping procedures described by Epskamp et al (2018). In particular, we investigated the sampling variability in edge weights and plotted significant differences between edges. Moreover, stability of Strength Centrality was assessed using a case-dropping subset bootstrap. This procedure allows to assess the extent to which the order of node Strength Centrality remains stable within subsets of the data (i.e., by dropping cases). In this context,

the correlation stability coefficient should not be < 0.25 (Epskamp et al., 2018). The analyses pertaining stability and accuracy of the model were conducted using the *bootnet* package (Epskamp & Fried, 2015).

The obtained GGM was plotted using *qgraph*, where – given our aim to model the direct and indirect associations between fatigue and the constructs of interest – the obtained network structure was plotted as a flow diagram. As such, nodes are positioned based on the order of connectedness to fatigue. In particular, fatigue is placed on top of the model, directly linked nodes in the obtained network are positioned on the first row, followed by the indirectly connected nodes on the following rows. Strength of connectivity is reflected by the thickness of the edges. Positive associations are depicted by blue edges, whereas negative associations are depicted by red edges. In order to foster interpretability of the results of the network model, prior to the network analyses all variables were (re)coded such that a high score reflects being in a more positive state / a higher level of functioning, whereas low scores reflect a lower level of functioning. Note that this is not the case for the other analyses reported in this manuscript (where for behavioral problems [CBCL], subjective EF [BRIEF MI], attention [CPT-III Omissions], and inhibition [CWIT 3] a high score reflects a lower level of functioning).

In addition, each node is plotted with a pie chart in the ring of the node. The blue area of the pie chart reflects the amount of variance that is predicted by the neighboring nodes (Haslbeck & Fried, 2017).

Results

Sample characteristics

Demographic, medical and cognitive characteristics are summarized in Table 1. BT was the dominant cause of the pABIs ($n = 29$), and median time since injury was 5 years ($IQR = 4$ years). The pABI-group displayed cognitive functioning within the normal range relative

to the standardization samples (norms), i.e. the group median was within 1 *SD* from the normative scores on the performance-based cognitive tests (i.e., WISC-V tests, CWIT3, CPT-III subtest). Similarly, the BRIEF (MI group median) scores were within the normal to subclinical range. With regard to PedsQL GCS scores, the group median parent-report score was above cut-off. The median functional outcome (GOSE-E) group score was level 6 (range 3 – 8) corresponding to upper moderate disability, and 33 had pathological neurological findings. Sex was equally distributed, and median age was 13 years in both samples. However, higher levels of maternal education and IQ ($ps < .001$) were detected for the HCs when compared to pABI.

TABLE 1 NEAR HERE

Fatigue in the ABI-group compared to healthy controls

There were significant differences on all PedsQL MFS scales between the pABI-group and the HCs (Table 2). Effect sizes were large for all parent-reports. For the self-reports, the effect sizes were small for the general and sleep/rest fatigue scales, and medium for the cognitive and total fatigue scales. In the ABI group, 75% of the participants obtained scores indicating clinical fatigue (>70) on the total scale (parent-report), compared to 11.7% in the HC-group.

A MANCOVA was performed to control for the group differences on PedsQL MFS between the groups with respect to verbal IQ and level of maternal education (Group 1: Compulsory 1-9 years, Group 2: High School 12 years, and Group 3: University/College >12 years). The adjustments changed the results only marginally and did not reach statistical significance for any of the scales.

TABLE 2 NEAR HERE

There were statistically significant differences between parent-and self-reports on the PedsQL MFS total in both the pABI-group ($z = -2.02, p = .044, r = .24$) and HC-group ($z = -4.45, p < .001, r = .41$), with parents reporting *more* fatigue in the pABI-group and *less* fatigue in the HC-group. Fatigue levels (i.e., PedsQL MFS total scale, parent- and self-reports) did not differ significantly between girls ($Md = 54.17$) and boys ($Md = 56.94$), $\chi^2(1, n = 76) = .004, p = .950$ in the pABI group on the parent-reports. However, for the self-reported data, girls reported more fatigue ($Md = 52.78$) than boys ($Md = 64.58$), $\chi^2(1, n = 75) = 5.79, p = .02$. In the HC-group, no differences were found between girls and boys on the self-reports ($p = .761$) or the parent-reports ($p = .314$).

Fatigue related to injury characteristics

There were no significant relationships between fatigue (PedsQL MFS total scale, parent-report) and time since injury ($p = .61$) or age at injury ($p = .08$). Furthermore, no significant associations were observed for any of the subdomains of PedsQL MFS, parent-report: General fatigue ($p = .42$), Sleep/rest fatigue, ($p = .20$) and Cognitive fatigue ($p = .35$), and time since injury. Although a higher percentage of BT survivors (86%) compared to other pABI etiologies (68%) had scores above the clinical threshold, and a similar trend was seen in the mean differences between the injury types, these differences did not reach statistical significance ($p = .46$). In order to explore the impact of age at assessment on levels of fatigue (PedsQL MFS total, scale, parent-report) (Table 3), participants were divided into groups corresponding to the three levels in the Norwegian school system (elementary, middle and high school). The purpose of the group division was to explore if the affiliation to different school levels had an impact on fatigue symptoms. A statistically significant difference in fatigue scores was observed for the three age groups: $F(2, 73) = 4.1, p = .02$. Post-hoc

comparisons (Tukey HSD test) indicated that the mean score for the age group 12-14 years ($M = 62$, $SD = 18.19$) was significantly different (i.e., more fatigue) from the age group 15-17 years ($M = 47.92$, $SD = 20.01$). The age group 10-11 years ($M = 56.25$, $SD = 16.23$) did not differ significantly from the other age groups. A similar pattern was found in the HC-group, but did not reach statistical significance (PedsQL MFS total scale, parent-report, $\chi^2(2, n = 60) = 5.036$, $p = .08$). There were no significant differences across the three age-groups on self-reported total fatigue in the pABI ($p = .49$) or HC group ($p = .37$).

TABLE 3 NEAR HERE

There was a small, positive correlation between fatigue (PedsQL MFS total scale) and IQ (verbal) on both parent-report ($r = .28$, $n = 74$, $p < .017$) and self-report ($r = .28$, $n = 73$, $p < .015$), with high levels of fatigue (as indicated by low scores) associated with lower IQ.

Modeling the (in)direct associations between fatigue, EF, behavioral problems, and HRQoL

In order to visualize the unique (in)direct associations between fatigue and the constructs of interest, the obtained GGM was plotted as a flow chart (for visualization of the structure of the GGM using a circular layout, see Supplemental Figure 1 and Supplemental Table 1 for the corresponding weight matrix). Our findings suggest no direct pathways between fatigue and the performance-based measures of EF (attention [CPT-III Omissions], working memory [WISC-V WM], inhibition [CWIT 3], and processing speed [WISC-V PS]). Instead, the latter nodes were connected to fatigue indirectly, via subjective EF (BRIEF MI) and HRQoL. While controlling for the impact of each of the other nodes in the model, a higher level of functioning in terms of fatigue following pABI was uniquely related to higher HRQoL and subjective EF. HRQoL and subjective EF were positively related to one another (i.e., higher levels of HRQoL were associated with better subjective EF) and linked fatigue to

behavioral problems. In addition, multiple weaker connections appeared in the model, linking the parent-report measures to the performance-based measures of EF. In particular, HRQoL showed unique associations with processing speed and working memory, where task performance was positively related to higher parent-reported HRQoL. Higher processing speed and working memory task performance were related to better inhibition scores, and positively related to one another. Inhibition was directly related to parent-reported subjective EF, via which it was indirectly connected to fatigue. In particular, higher levels of inhibition (as indicated by a higher value) were associated with higher levels of subjective EF. In addition, inhibition was related to lower levels of behavioral problems (i.e., a higher score on the reverse scored CBCL measure) and better performance on the attention task (CPT-III Omissions, reverse scored). Finally, a better performance on the attention task was related to lower levels of behavioral problems.

FIGURE 1 NEAR HERE

Examination of Strength Centrality (Supplemental Figure 2) suggests that HRQoL emerged as one of the most central and strongly connected nodes in the model, followed by behavioral problems, subjective EF, inhibition and fatigue.¹ Attention was the least central node in the model. This was also reflected by the explained variance for each of the nodes, which was highest for HRQoL ($R^2 = .66$), behavioral problems ($R^2 = .65$), and EF symptoms ($R^2 = .63$). Lowest predictability was observed for Attention ($R^2 = .13$) and working memory ($R^2 = .24$; for an overview of node predictability, see Supplemental Table 2). Importantly, stability of Strength centrality was acceptable (Correlation stability coefficient = .28; Supplemental Figure 3). For the analysis of edge weights accuracy and significant edge differences, we refer to Supplemental Figures 4 – 5. Finally, we conducted a post-hoc sensitivity analysis to

investigate the effect of replacing the parent-reported measures of fatigue, subjective EF, behavioral problems and HRQoL with self-reports in the network model. Using self-report rather than parent report data did not impact our main findings pertaining the role of cognitive functioning in fatigue following pABI, and only had a limited impact on the overall network structure (Supplemental Figure 6).

Discussion

The main findings from the present study revealed significantly higher levels of fatigue in pABI participants compared to HCs. No strong associations were found between fatigue and injury characteristics. Nevertheless, findings indicated *more* fatigue for the pABI participants in the older compared to the younger age-group, as well as girls compared to boys. Finally, the network approach revealed that fatigue symptoms played a less central role in the model, compared to HRQoL, behavioral problems and EF symptoms.

Aim 1: Fatigue in children and adolescents with pABI and healthy controls

In accordance with previous research (e.g., Borg et al., 2009; Hutchison et al., 2009; Palmer et al., 2007), significantly more fatigue was experienced in the pABI-group compared to HC, even when controlling for maternal education and verbal IQ. Of note, 75% of the pABI participants in our sample obtained fatigue scores in the clinical range, representing a high symptom load, even when compared to other pABI studies (Wilkinson et al., 2018). Consistent with previous studies, effect sizes were larger for parent-report than self-report (Crichton et al., 2017). Cognitive fatigue had the highest magnitude of difference for both parent- and self-reports, while the sleep/rest subscale had the smallest magnitude compared to the other subscales, both of which are in accordance with previous findings (e.g., Crichton et al., 2018; Ryan et al., 2016). Indeed, many individuals with ABI primarily experience fatigue as a cognitive phenomenon, and it has also been shown that they experience greater fatigue when performing (demanding) cognitive tasks (Hattori et al., 2009; Pardini et al., 2010;

Wilkinson et al., 2018). This finding may have implications for follow-up and rehabilitation of pABI. That is, unresolved cognitive fatigue may place children at added risk of reduced academic performance after pABI and puts emphasis on the need for additional cognitive support in educational and treatment settings. Moreover, the use of a multidimensional fatigue assessment exposed differences between the domains of fatigue, as well as highlighting the clinical utility of such measures compared to more simplistic assessments of the construct (Crichton et al., 2015). However, it is important to consider that the pABI sample in our study was selected on the presence of EF complaints. As there is an overlap in item content between the questionnaires measuring fatigue (PedsQL MFS, cognitive scale) and EF (BRIEF), which may reflect the relative difference between the cognitive and other subdomains of fatigue in our sample, these findings may not be generalized to all survivors of pABI.

Moreover, girls reported significantly more fatigue symptoms than boys, but only in the pABI group. This finding is in accordance with previous studies where female sex has been found to be a risk factor for fatigue after ABI (Câmara-Costa et al., 2019; Cantor et al., 2008; Kutlubayev et al., 2019), as well as other self-reported psychosomatic and mental health complaints (Piccinelli & Wilkinson, 2000). In line with previous research, children and adolescents reported significantly lower fatigue levels than parents in the ABI group, but not in the HC group, suggesting important differences in parent and child perspectives in the clinical and healthy population (Lloyd et al., 2018; Câmara-Costa et al., 2019). There are several factors to consider when interpreting these differences. Firstly, response bias due to parental anxiety or expectations (Sato et al., 2013) may account for some of the discrepancy between self- and parent reporting. On the other hand, some studies (Wochos et al., 2014) have demonstrated how severe illness in children, like cancer, may lead parents to minimize negative symptoms and lower expectations, in favor of positive personal traits, highlighting the complex nature of self- and parent reporting (de Ruiter et al., 2016). Furthermore, the

discrepancy between self- and parent-report may reflect reduced awareness, both as a function of developmental factors, such as the prolonged development of metacognition and EF (Rothbart et al, 2011) and ABI sequela (Krasny-Pacini et al., 2015). Specifically, EF dysfunction in pABI is associated with lower self-awareness (Wolfe et al., 2015). A study by Lloyd and colleagues (2018) demonstrates how children with TBI tend to overestimate their functioning compared to their parents, while a reversed pattern was observed in healthy peers. Consequently, as the sample in our study was included on the basis of EF complaints, it is possible that the self-ratings were affected by reduced self-awareness. Thus, our results underline the importance of including both HCs as well as self- and parent report in future studies, in order to fully capture the impact of fatigue in pABI. Overall, our findings confirm that fatigue continues to be a considerable problem for the majority of children and adolescents in the chronic phase of pABI.

Aim 2: Fatigue and demographic variables related to injury type, age at injury and intervention, time since injury and IQ in the pABI group

No significant associations were found between the pABI etiologies and fatigue levels. BT survivors did, however, have a higher percentage of scores above the clinical threshold than the other etiologies. As some of the etiology-subgroups had small samples, the result must be interpreted with caution. Results from studies examining fatigue levels in the various pABI etiologies are, however, mixed and highlight the need for long-term follow up for all pABI etiologies (Meeske et al, 2004; van Markus-Doornbosch et al., 2016; Wilkinson et al., 2018). IQ did show a small, significant correlation with fatigue, with lower IQ levels associated with more fatigue symptoms. Although larger longitudinal studies are needed to confirm the directionality of this relationship, limited cognitive resources such as low general intellectual ability may lead to an increased cognitive effort, including the potential use of compensating strategies, which ultimately may reinforce symptoms of fatigue. In our study,

only participants with reported EF complaints were included, which may have contributed to a sample with more fatigue symptoms when compared to the general pABI population. Nevertheless, lower IQ levels being associated with more fatigue symptoms indicate that children and adolescents with pABI and lower intellectual capacity may need special educational measures in order to prevent fatigue complications. Age at injury did not reach statistical significance with regard to parent-reported fatigue, in line with previous findings (Anderson et al., 2011; Crichton et al., 2017). Parents of the participants who were adolescents (15-17 years) at the time of assessment, reported more symptoms of fatigue compared to those who were 12-14 years of age. Although fatigue in the general pediatric population may fluctuate through development, this result has, to our knowledge, not been observed in pABI previously. However, an increase in fatigue with age, especially in adolescent years, has been found in a study in primary care (Haines et al., 2005). Notably, the older age group corresponds with the transition from middle to high school years, a period characterized by physical and cognitive changes, increased independence and academic demands, and more sophisticated social interaction (Anderson, 2002; Chaudhuri & Behan, 2004). The extended demands on several central functional domains in this period may serve to explain the relative difference in fatigue in the older age group compared to the younger age groups. The burden of increased effort may also result in stress by creating an imbalance between perceived demands and resources, which, in turn, may reinforce the experience of being fatigued (Ponsford et al., 2014). Interestingly, there were no significant effects of age in the HC-group (Câmara-Costa et al., 2019; van Markus-Doornbosch et al., 2016). This may reflect a specific vulnerability in adolescents with pABI to experience fatigue complications when responding to the increased demands and expectations (i.e., elevated cognitive load) in the late teenage years (as reported by parents), compared to healthy peers.

None of the fatigue subdomains (General, Sleep/rest and Cognitive fatigue) differed over time since injury in our cross-sectional study. As there are few longitudinal studies on the course of fatigue after pABI (Boonstra et al., 2017; Câmara-Costa et al., 2019; van Markus-Doornbosch et al., 2016), possible differences in fatigue trajectories after pABI needs to be further explored in future studies. Furthermore, it is important to consider that different factors may contribute to fatigue over time. For example, as suggested in a study of adults with post-stroke fatigue, early fatigue may be activated by biological factors and late, chronic fatigue may be ascribed to psychological and behavioral factors (Wu et al 2015). Future longitudinal studies are needed to clarify this relationship.

Aim 3: Associations between fatigue, EF, behavioral problems and HRQoL in a network analysis

The network analytical approach used, examining the unique interplay (i.e., controlling for the other factors in the model) between parent-reported fatigue, subjective EF, behavioral problems, HRQoL and performance-based measures of EF, resulted in a stable model. Two conceptual clusters emerged, one consisting of the performance-based measures, and a second cluster containing the questionnaires. This is in agreement with existing literature, consistently reporting weak associations between performance-based measures and questionnaire ratings of the same domain (i.e., due to method variance), and conversely, strong correlations between questionnaire-based measures, although each individual questionnaire assesses specific constructs (Coutinho et al., 2017; McCarthy et al., 2005; Payne et al, 2011). There were, however, some interesting associations within and between these clusters: HRQoL proved to be the most strongly connected node in the model, followed by behavioral problems, subjective EF, inhibition and fatigue. Worse HRQoL was related to worse subjective level of EF, and linked fatigue to behavioral problems. Furthermore, HRQoL showed unique associations with processing speed and working memory, where task

performance was positively related to higher levels of HRQoL. Distinct associations between HRQoL and other central domains have been demonstrated in previous studies (Anderson et al., 2011; Sumpter et al., 2011), and the present study confirms direct relations to both subjective and objective measures of EF. Interestingly, there were no direct pathways between fatigue and performance-based tests of EF, after taking into account the influence of the other variables in the model. Instead, fatigue was indirectly connected to the behavioral measures of EF via parent reports of EF symptoms and HRQoL. Contrary to previous findings (Ponsford et al., 2015; Ponsford & Ziino, 2003), performance-based attention was the least central node in the model and not directly related to fatigue. In addition, inhibition was directly related to EF symptoms, via which it was indirectly connected to fatigue. However, a challenge in using performance-based tests, such as CPT-III, is that the behavioral outcome represents the end-point of intertwined cognitive processes. In order to achieve a clearer understanding of attentional processes that are associated with fatigue, electrophysiological measures of attention may be an alternative (Duncan & Miller, 2002).

Thus, the network approach examining the complex interaction between fatigue and associated constructs, revealed that fatigue played a less central role in the model than expected, compared to HRQoL, behavioral problems and EF, which emerged as central nodes. As the method is data-driven and does not imply causality, it allows for the opportunity to explore the relationships without implying a central, underlying disease mechanism for the complex, non-specific symptomatology following pABI. Given the heterogeneity of symptoms related to fatigue, and the lack of evidence in previous studies to confirm causal explanations to persisting fatigue complaints, we argue that a broader perspective of fatigue is required. The biopsychosocial perspective to poor outcome after ABI postulates that symptoms can be causally connected through various biopsychosocial mechanisms (Iverson, 2012). Accordingly, it is possible to infer that measures to improve

central symptoms or constructs in the model, such as HRQoL, behavioral problems or EF, will positively affect fatigue complaints, or even lead to improvement across the entire network of symptoms. The most connected nodes in the network model are all functional areas susceptible to treatment and change, i.e., modifiable (Aarnes et al, 2019). We recommend that future intervention studies targeting cognitive or other domains following pABI should include multiple measures of functioning, including fatigue, as improvement in one central area might generate positive changes in other related domains.

As such, in order to move towards effective interventions for fatigue following pABI, it is important to use different theoretical frameworks to inform further empirical research. For example, in 2009 Lerdal and colleagues presented a biopsychosocial model, based on the theory of unpleasant symptoms by Lenz et al. for fatigue after stroke (Lenz et al, 1997; Lerdal et al., 2009). This model, which may serve as a framework for how fatigue is experienced, consists of three components, namely antecedents (e.g., personal factors, biomarkers, ABI characteristics, pre-ABI fatigue, and chronic diseases), fatigue experiences (e.g., intensity, quality, timing, fluctuation, and long-term trajectory), and effects (functioning in daily life and participation in ADLs (e.g., school participation/academic performance)). This model might be useful in order to specify areas of further investigation in relation to fatigue after pABI.

Limitations

Fatigue after pABI is a multifaceted phenomenon associated with many causative mechanisms. In the present study we focused on a limited number of variables when modelling the unique associations between fatigue and constructs of interest. There may be other variables that should be included in future research. Sleep is recognized as an aggravating factor that may have had an impact on study results (Gagner et al, 2015). Other relevant variables are pain, parental health, other aspects of behavioral problems and HRQoL,

clinical/medical variables (e.g., treatment variables, ABI severity, inflammation, neurotransmitter changes and hormonal dysregulation after pABI), social factors and other cognitive functions (e.g., Wu et al., 2015). Another limitation is that many of the measures employed were questionnaires. Several factors (e.g., over/under reporting of symptoms, awareness, cognitive deficits, or social desirability bias) may affect the accuracy and validity of the reports, in addition to potential overlap in item content between the measures of fatigue, EF and HRQoL. Awareness questionnaires should also be considered for future studies. Moreover, the current sample was likely not representative of the entire population of individuals with pABI. In addition to being motivated for a cognitive rehabilitation intervention, only participants with reported executive problems were included. This may have contributed to a sample with a higher load of fatigue symptoms. Furthermore, the clinical sample in our study was a mix of pABI etiologies. Even though existing literature suggest that fatigue is a transdiagnostic phenomenon across conditions affecting the central nervous system, few studies have investigated fatigue in pABI etiologies. A larger sample in future studies may allow for further analyses of possible between- and within-injury differences. Finally, our study has a cross-sectional design, and does not allow for analyses of directionality of associations or changes over time. Longitudinal studies are needed to address these issues.

Conclusions

Our findings confirm that for the majority of children and adolescents in the chronic phase of pABI, fatigue is highly prevalent. In line with previous literature, girls with pABI reported relatively more fatigue symptoms than boys. As the parents were found to report more fatigue than the children and adolescents with pABI, it is recommended to include both self- and parent reports in the clinic. Importantly, our findings suggest that fatigue to a lesser degree is associated with demographic and medical variables. Instead, we observed a central

role for measures of HRQoL, behavioral problems and EF. These are all functional areas susceptible to treatment and change. However, longitudinal studies are needed to confirm the directionality of the relationships between factors associated with fatigue. The present findings also need to be cross-validated in a larger and more representative pABI sample. Finally, a more detailed description of potentially complicating premorbid or comorbid factors, in addition to advanced neuroimaging studies to explore the role of the brain lesion in the development of fatigue, is recommended for future studies.

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Declaration of interest

The authors report no conflict of interest.

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Footnotes:

1. Follow-up analyses using community detection methods suggest the presence of two communities (i.e., subnetworks consisting of closely interrelates nodes), consisting of (a) behavioral measures for EF, and (b) the parent-report measures. Within these communities, Processing Speed and HRQoL emerged as the strongest bridging variables respectively, connecting each of the communities to one another. In line with the main analyses presented in this manuscript, this points to the importance of measures such as HRQoL which indirectly link Fatigue to objective indicators of EF.

Table 1. Demographic, medical and cognitive characteristics of study samples

		ABI (<i>n</i> = 76)	HCS (<i>n</i> = 60)	<i>p</i>	<i>ES</i> ^d (ϕ)
Gender <i>n</i> (%)	Boys	33 (43.4)	30 (50)	.491 ^a	
	Girls	43 (55.6)	30 (50)		
Age	<i>Median (IQR)</i>	13 (4)	13 (3)	.366 ^a	
Maternal education (<i>n</i> = 74)	Comp. school	4	0	<i>p</i> < .001^a	.47
	High school	23	2		
	Uni/College	36	35		
	Master's dgr	10	23		
Diagnosis <i>n</i> (%)	TBI	18 (23.7)			
	Brain tumor	29 (38.2)			
	Anoxia	5 (6.6)			
	Stroke	17 (22.4)			
	Encephalitis	7 (9.2)			
Imaging <i>n</i> (%)		76 (100)			
Confirmatory findings <i>n</i> (%)		67 (88)			
Pathological neurological findings <i>n</i> (%)		33 (43)			
Age at injury	<i>Median (IQR)</i>	8 (6)			
Time since injury (years)	<i>Median (IQR)</i>	5 (4)			
Cognition, HRQoL, and behavioral problems <i>Median (IQR)</i>	Verbal IQ	96.5 (14)	108 (12.32)	<i>p</i> < .001^b	.48
	BRIEF (MI)	61 (14)		<i>p</i> < .001^c	
	CWIT3 (time)	8.5 (5)			
	CPT-III (HRT)	54 (9)		<i>p</i> < .001 ^c	
	WISC-V WMI	94 (20)		<i>p</i> < .001 ^c	
	WISC-V PSI	89 (20)		<i>p</i> < .001 ^c	
	PedsQL GCS	69.6 (23.9)		<i>p</i> < .001 ^c	
	CBCL (<i>n</i> = 71)	58 (15)		<i>p</i> < .001 ^c	
GOSE-E (<i>n</i> = 73)	<i>Median (IQR)</i>	6 (1)			

Note. ABI = acquired brain injury; HCS = healthy controls; Comp. school = compulsory school; Uni = university; dgr = degree; BRIEF (MI) = Behavior Rating Inventory of Executive Function Metacognition Index; CBCL = The Child Behavior Checklist Total problems ($M = 50$, $SD = 10$); CWIT3 = Color-Word Interference Test subtest 3; CPT-III HRT BC = Conners Continuous Performance Test III Hit Reaction Times Block change ($M = 50$, $SD = 10$); HRQoL = Health related quality of life; WISC-V = Wechsler Intelligence Scale for Children - Fifth edition ($M = 100$, $SD = 15$); WMI = Working Memory index ($M = 100$, $SD = 15$); PSI = Processing Speed index ($M = 100$, $SD = 15$); PedsQL GCS = Pediatric Quality of Life Inventory Generic Core Scales parent report; TBI = traumatic brain injury; IQR = Interquartile range; GOSE-E = Glasgow Outcome Scale Extended. All cognitive scores reported are scaled scores. Higher scaled cognition scores represent better performance, except for scores in CPT-III where T-scores between 40 and 60 are in the normal range, and BRIEF and CBCL were higher score represents more daily life difficulties. For PedsQL higher scores indicate better HRQoL. Clinical cutoffs: BRIEF: GEC ≥ 65 ; PedsQL parent report score >65.4 . All participants had received imaging at some point, with 11 children computed tomography (CT) only. Normal imaging findings: TBI ($n=6$), anoxia

($n=1$), and brain infection/inflammation ($n=2$). Three out of 9 participants with normal imaging had conducted a CT only.

^aPearson Chi-square/Fisher's Exact Test, 2-tailed

^bMann-Whitney U test

^cT-test statistics, comparing pABI group and normative scores

^dEffect sizes are reported in Cramer's V for categorical and $r = z / \text{square root of } N$ for continuous variables

Table 2. Fatigue (PedsQL MFS, self- and parent reports) in pABI group compared to healthy controls

Parent-report	ABI (<i>n</i> = 76) <i>Median (IQR)</i>	HCS (<i>n</i> = 60) <i>Median (IQR)</i>	Mann-W <i>p</i>	Effect size <i>r</i>
General Fatigue	58.33 (33.3)	85.42 (16.7)	<.001	.557
Sleep/Rest Fatigue	62.5 (33.3)	83.33 (16.7)	<.001	.532
Cognitive Fatigue	50 (33.3)	91.66 (25)	<.001	.710
Total Fatigue	56.26 (30.2)	86.11 (14.9)	<.001	.686
Self-report	ABI (<i>n</i> = 75) <i>Median (IQR)</i>	HCS (<i>n</i> = 57) <i>Median (IQR)</i>	<i>p</i>	<i>r</i>
General Fatigue	66.66 (37.5)	79.17 (18.8)	.001	.281
Sleep/Rest Fatigue	58.33 (29.2)	70.83 (29.2)	.011	.221
Cognitive Fatigue	58.33 (33.3)	79.17 (25)	<.001	.393
Total Fatigue	61.11 (31.9)	75 (20.8)	<.001	.347

Note. PedsQL MFS = The Pediatric Quality of Life Inventory Multidimensional Fatigue Scale; ABI = acquired brain injury; HCs = healthy controls; IQR = Interquartile range. Higher scores = less fatigue. Clinical cutoff: >70.

Table 3. Associations between fatigue (PedsQL MFS) and injury characteristics

	PedsQL MFS ^a				ANOVA Tukey
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>p</i>	
Primary injury					
TBI	18	58.6	21.1	.462	
Brain tumor	29	50.6	19.8		
Anoxia	5	60.6	18		
Stroke	17	59.4	13.4		
Encephalitis	7	52.6	24		
Age^b					
10-11 years	20	56.3	16.2	.020	
12-14 years	20	62	18.2		
15-17 years	28	47.9	20		.015

^aFatigue levels measured by the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) total score, scale, parent-report. Higher scores = less fatigue. TBI = traumatic brain injury.

^bAge groups correspond roughly to elementary school, middle school and high school in Norway.

Figure caption

Figure 1. Flow chart of connectedness of fatigue in the network model. *Note.* This figure illustrates how each of the variables of interest are (in)directly connected to fatigue. Edges represent unique associations (regularized partial correlations) between each of the nodes. Edge thickness reflects the strength of the association. The explained variance for each of the nodes is represented by a pie chart surrounding the node. To foster interpretability, each of the variables in the network were coded such that a higher score reflects more adaptive processes / a higher level of functioning, whereas lower scores reflect more maladaptive processes / poor functioning.