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Self- and Parent-reported Fatigue Seven Years after Severe Childhood Traumatic Brain Injury: Results of the TGE (Traumatisme Grave de l'Enfant) Prospective Longitudinal Study

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Running head: Fatigue after severe pediatric TBI

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Abstract

Objective: To investigate presence of and factors associated with self- and parent-reported Fatigue seven years after severe childhood traumatic brain injury (TBI) in the prospective longitudinal study TGE (*Traumatisme Grave de l'Enfant* - severe childhood trauma).

Method: Self- and/or parent-reports on the Multidimensional Fatigue Scale (MFS) were collected for 38 participants (ages 7-22 years) seven years after severe childhood TBI, and 33 controls matched for age, gender and parental educational level. The data collected included socio-demographic characteristics, age at injury and injury severity scores, overall disability (Glasgow Outcome Scale Extended, GOS-E), intellectual outcome (Wechsler scales) and questionnaires assessing executive functions, Health-Related Quality of Life (HRQoL), behavior and participation.

Results: Fatigue levels were significantly worse in the TBI than in the control group, especially for cognitive fatigue. Correlations of reported fatigue with age at injury, gender, TBI severity and intellectual ability were moderate and often not significant. Fatigue was significantly associated with overall level of disability (GOS-E), and with all questionnaires completed by the same informant.

Conclusion: High levels of fatigue were reported by 30 to 50% of patients seven years after a severe childhood TBI. Reported fatigue explained more than 60% of the variance of reported HRQoL by the same informant (patient or parent).

Keywords: Severe traumatic brain injury, child, multidimensional fatigue, health-related quality of life, prospective cohort study.

Self- and Parent-reported Fatigue Seven Years after Severe Childhood Traumatic Brain Injury: Results of the TGE (Traumatisme Grave de l'Enfant) Prospective Longitudinal Study

Severe pediatric Traumatic Brain Injury (TBI) reaches 3% to 7% of overall pediatric TBI incidence,[1] and is among the most prominent causes of child mortality and long-term disability in developed countries. [2] The detrimental impact of childhood TBI on long-term cognitive, social and educational outcomes is consistently reported.[3]The pertinence of investigating fatigue following childhood TBI has been highlighted in recent reviews.[4,5]Post-TBI fatigue may have an important impact on quality of life and participation.[6,7]

Fatigue is commonly defined as the awareness of a sustained state of exhaustion and a lack of the mental and physical availability required to perform an activity.[8] In adult populations, fatigue subjectively reported after TBI has been associated with sleep disturbances,[9] neuroendocrine abnormalities,[10] disruption of striato-thalamo-cortical tracts,[11] attention deficits and slow processing speed leading to higher levels of mental effort to manage a complex task (the coping hypothesis),[12] TBI severity,[13] poor functional outcome,[14] somatic symptoms and situational stress,[15] depression,[16] and female gender.[17] Subjective reports of fatigue assessed with questionnaires have been distinguished from "objective" fatigue, measured with performance tasks extended in time (e.g. decline in performance with the prolongation of a physical or mental task).[18] Also, mental (or cognitive) fatigue has been distinguished from physical fatigue,[19] and central fatigue from peripheral or muscular fatigue.[20] It has been proposed that "awareness of fatigue" might be measured by the discrepancy between self- and proxy-reports.[21]

Fatigue after TBI in children has been less studied. A recent review suggested the presence and persistence of high levels of fatigue several years after pediatric TBI,[22] but the wide range of methodologies employed in previous studies has led to contrasting results pertaining to the precursors and correlates of fatigue in the context of childhood TBI. For instance, in one study, patients 6-weeks after pediatric TBI reported higher levels of fatigue compared with normative data;[7] but another study, which mainly included patients with mild TBI (84%), found no significant difference in fatigue symptoms reported by patients 24 to 30 months following TBI compared to data from healthy

cohorts.[6] Likewise, greater fatigue levels have been associated with greater TBI severity in some studies,[23,24] despite the relatively small number of patients with severe TBI, while other studies did not find an association between severity of TBI and fatigue.[6,24] Older age has also been associated with increased fatigue after childhood TBI.[6,19] In sum, there is a need for additional studies investigating the precursors and correlates of fatigue after pediatric TBI.[22]

Thus, the aims of this study were (1) to investigate the presence and severity of self- and parent-reported levels of fatigue 7 years after severe childhood TBI (taking into account the multidimensional nature of fatigue - general, sleep/rest, and cognitive fatigue), in comparison with a closely matched control group; and (2) to study factors associated with fatigue following childhood TBI.

For the first aim, we hypothesized that (*i*) participants with severe TBI would present increased levels of self- and parent-reported fatigue compared to controls; and (*ii*) that these differences would be observed across the three domains of fatigue. For the second aim, we separated the factors potentially associated with fatigue into two categories. The first category included demographic characteristics, such as age, gender and parental education, as well as "objective" assessments pertaining to injury severity indices, impairment levels at 3, 12 and 24 months, and measures of overall disability and intellectual ability 7-years post-injury. The second category comprised the questionnaire-based measures completed concurrently 7-years post-injury, which assessed executive functions, Health-Related Quality of Life (HRQoL), behavior, and participation.We hypothesized that (*iii*) increased fatigue in participants after severe TBI would be associated with greater injury severity, higher levels of disability, and possibly gender, age and intellectual ability; (*iv*) correlations between fatigue and other questionnaires completed by the same informant would be strong. Increased fatigue levels would be associated with higher rates of impaired executive functioning, lower HRQoL, more behavioral problems and lower participation. The latter hypothesis is based on previous results reported by our research team with clinically different populations[25,26], which examined the differences in the pattern of correlations between questionnaire-based measures obtained through self- and/or parent-reports.

The present work capitalizes on the data of a larger prospective longitudinal study (*Traumatisme Grave de l'Enfant* [TGE] - severe childhood trauma)[27] aiming to examine overall outcomes following severe childhood TBI. Participants who sustained a pediatric TBI were assessed upon admission and

prospectively at 3-months, 1-, 2- and 7-years post-injury. At the 7-year follow-up, the original experimental design of the TGE study included a control group, individually matched by age, gender and parental education, who underwent the same assessments as the TBI group.

METHODS

Participants

Patients with TBI

Participants were children aged under16 years consecutively admitted within 6 hours following severe accidental TBI to the pediatric neurosurgical intensive care unit (ICU) at *Necker-Enfants-Malades* Hospital in Paris, France, between January 2005 and December 2008. Eighty-one children were included at the acute stage of TBI, defined as a Glasgow Coma Scale (GCS) score at admission ≤ 8,[28] and/or an Injury Severity Score (ISS) > 16.[29] The causes of accidental TBI were motor vehicle accidents and falls. The exclusion criteria were: no vital signs upon admission, non-accidental head injury and previous history of diagnosed neurological, psychiatric or learning disorders. Of the 81 children initially enrolled, 16 died in acute care, leaving 65 children available for follow-up. All children received initial treatment according to international guidelines for the management of severe TBI, and most children (83%) required/received multidisciplinary rehabilitation after acute care. Follow-up comprised comprehensive medical and neuropsychological assessments at 3 months, 1- 2- and 7-years post-injury in the Rehabilitation Department for Children with Acquired Neurological Injury in the *Saint Maurice* Hospital.

At 7-years post-TBI, 27 of the 65 patients were lost to follow-up or did not wish to participate, leaving 38 patients (aged 7-22 years) for assessment. The participants assessed 7-years post-injury (n=38) did not differ significantly from those lost to follow-up or non-responders (n=27) neither for socio-demographic and injury severity characteristics, nor for 3-, 12- or 24-months post-injury outcomes (p>.05, in all cases). Thirty-four (90%) participants completed the self-report fatigue questionnaire, 25 (66%) had available data regarding the parental fatigue report and 21 (55%) had data on both self- and parent-report forms. The main reasons for missing or incomplete questionnaires were parental foreign nationality (parents unable to speak or understand French), failure to return questionnaires or refusal to respond to questionnaires.

Controls

A sample of healthy controls was recruited from local schools or via a general medical practice at the 7-year follow-up point. Controls were closely matched to participants in the TBI group for age (±3 months), gender and parental education (± 2 years' education). There were no significant differences between groups for other familial or socio-cultural factors. The exclusion criteria were previous history of diagnosed neurological, psychiatric or learning disorders, and presence of a TBI history. Among the 38 controls recruited for the study, 33 (87%) had available data on the self-report fatigue questionnaire and 20 (61%) had data on both self- and parent-report forms.

Measures

For the first aim, we used the Fatigue scores assessed both for participants with child TBI and controls at the 7-years follow-up. For the second aim, we based our analyses exclusively on the TBI group in order to investigate the association between Fatigue scores assessed 7-years post-injury with the measures referring to baseline demographics, injury severity, overall disability over the first 2-years post-injury, and the concurrent outcomes assessed 7years post-TBI.

Socio-demographic characteristics

Data collection included socio-demographic information regarding children's age, gender and parental educational level, defined as low (neither of the parents had a secondary school diploma ["*baccalauréat*"]) or high (at least one parent had a secondary school diploma).

Injury severity

The medical data was collected at the acute phase in intensive care unit, including cause of TBI, age at injury, initial lowest *Glasgow Coma Scale* (GCS)[28], *Pediatric Trauma Score* (PTS)[30] and *Injury Severity Score* (ISS)[29]. Length of coma was recorded in days by the specialized intensive care unit doctors, with end of coma defined by spontaneous eye opening of the patient.

Overall disability over the first 2-years post-injury

At 3-months, 1- and 2-years post-injury, overall disability was classified in three categories, *good outcome, moderate disability, or severe disability,* according to the Glasgow Outcome Scale modified for children (GOS Peds).[31]

Seven-years post-injury

The following data was collected and analyzed in the present study:

Main outcome

Fatigue: We used self- and parent-report forms of the Pediatric Quality of Life Inventory™ (PedsQL)Multidimensional Fatigue Scale (MFS).[32]This 18-item inventory allows the computation of a Total Score and 3 subscale scores (General, Sleep/Rest, and Cognitive Fatigue). The scores are expressed in a 0 to 100-point scale, with higher scores indicating lower fatigue levels.

Concurrent outcomes

Overall disability: The *GOS-Extended Pediatric* (GOS-E Peds) *and Adult version* (GOS-E)[31,33] qualified outcome scores into 3 categories: *good recovery*, *moderate* or *severe disability*.

Motor deficits were categorized as the absence or presence of hemiplegia/hemiparesis and/or signs of cerebellar dysfunction (ataxia, coordination disorders), defined following medical neurological examination.

Ongoing education was categorized as Mainstream education (with or without help) *versus* special education.

Intellectual ability: Full Scale Intellectual Quotient (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Working Memory Index (WMI) and Processing Speed Index (PSI)were collected using age-appropriate Wechsler Intelligence Scales for children[34] and adults.[35]

Executive Functioning (EF) was measured using age-appropriate self- and parent-report forms of the Behavior Rating Inventory of Executive Functions (BRIEF).[36,37] The total score [Global Executive Composite index (GEC)], expressed as *T*-score (Mean=50, SD=10) was used as the outcome, with higher scores indicating worse executive functioning.

Health-related Quality of Life (HRQoL): We used age-appropriate self- and parent-report forms of the PedsQL.[38] Higher Total Scores indicate better HRQoL (range 0 to 100).

Behavioral problems were assessed using age-appropriate versions of self- and parent-report forms of the Achenbach's Behavior Checklist (Children's Behavior Checklist, Youth Self-Report, Adult Behavior Checklist; Adult Self-report).[39,40] Only the total problems *T*-score is reported here (Mean=50, SD=10); higher scores reflect more pronounced behavior problems.

Participation: We used the summary score of the self- (ages ≥ 11years) and parent-report (whole sample) forms of the Child and Adolescent Scale of Participation (CASP).[41,42] The scores are expressed in a 0 to 100-point scale with lower scores indicating lower levels of participation.

Procedure

This study was approved by the (*Comité de Protection de Personnes d'Île-de-France VI* [CPP IDF VI]) ethics committee. Adult participants or parent/caregivers (for participants under 18 years of age) were asked by the physician who assessed them in the initial phase of the TGE study to participate in the 7-year follow-up and provided informed written consent to participate in the study.

The assessments took place in the Saint Maurice Hospital on two separate occasions. A specialized physician performed the medical assessments, which included information about current medication and rehabilitation therapy, ongoing education and occupation, the GOS-E (Peds), and a neurological examination. On a different day, a trained child psychologist performed the neuropsychological assessment, and proposed the questionnaires to the participant and his/her parents. If they did not answer the questionnaires immediately, they were asked to return them by post. For the control group, the procedures to collect data were the same as for the TBI group, although controls did not undergo the medical examination.

Participants and their parents completed the questionnaires independently. Participants answered them during the neuropsychological assessment session, and whenever they exhibited insufficient reading, oral comprehension and/or cognitive skills to understand the questions, the psychologist helped them by reading the questions aloud and clarifying the items as needed. Parents completed the questionnaires on their own during the assessment session and if their mastery of French was not sufficient, the psychologist helped them clarify any doubts at the end of the session.

Statistical Analyses

Data analyses were performed using SAS© software version 9.[43] For the first aim of the study, we used non parametric tests (Wilcoxon signed rank-tests) to compare the Fatigue scores between participants and controls. In addition, we performed repeated-measures ANOVAs to investigate interaction between domains of fatigue (general, sleep/rest, cognitive) and group (TBI *vs*. controls).

For the second aim of the study, we used non-parametric tests (Spearman rank correlations and partial correlations, Wilcoxon signed rank-tests) to examine the association of the Fatigue scores in the TBI group with demographic characteristics, injury severity, impairment levels at 3, 12 and 24 months, and concurrent outcomes 7-years post-injury.

Statistical significance was 2 tailed, as generally recommended, and set at $p<.05$. Whenever the sample size was relatively small, we discuss some results with significance values >.05, since statistical significance is dependent on the sample size available for each of the analyses presented below.

RESULTS

Socio-demographic and injury severity characteristics of the participants with TBI (Table 1)

Seven-years post-injury, the TBI sample comprised 38 participants (24 males, 63%), among whom 25 (66%) were children or adolescents and 13 were young adults (age ≥ 18 years). Mean age at injury was 7.5 years, mean length of coma 6.6 days, and all participants had GCS scores at admission ≤ 8. Three patients were under 1 year of age (3, 4 and 10 months) at the time of injury.

At 3-months, 1-year and 2-years post-injury, about half of the sample presented "moderate disability" at all-time points (GOS Peds), but the proportion of participants with "good recovery" tended to increase (from 8% at 3 months to 18% at 2-years post-injury), and the proportion of participants with "severe disability" tended to decrease (from 42% at 3 months to 27% at 2-years post-injury).

At 7-years post-injury, the proportion of participants with "good recovery" had increased (55%), but the proportion of participants with "severe disability" showed little change (21%, compared to 27% at 2-years post-injury). Seven participants (18%) had persistent motor deficit; among them, 4 were classified "severe disability", and 3 "good recovery". Eight participants (21%) were enrolled in special education, from which 5 were classified with "severe" and 3 with "moderate disability".

Aim 1: Comparisons between participants 7 years after TBI and controls (Table 2, Figure 1)

All fatigue scores, except self-reported sleep/rest fatigue, were significantly lower (greater fatigue) in the TBI group than in the control group (Table 2). High levels of fatigue (*i.e*. in the first deciles of the control group or lower) were observed for 30% and 50% of the TBI group in self-report and parent-report, respectively (Figure 1).

For self-report, a repeated-measures ANOVA with domain of fatigue (general, sleep/rest and cognitive) as the within-subjects factor and group (TBI, control) as the between-subject factor, showed a significant group (F(1,65)=14.96, p=.0003) and domain effect (F(2,64)=10.04, p=.0002), as well as a group by domain interaction (F(2,130)=7.53, p=.0008). Cognitive fatigue was more pronounced (lower score) than general and sleep/rest fatigue in the TBI group, but not in the control group. The same analysis for parent-reports showed only a significant group effect (F(1,43)=15.23, p=.0003). The inter-correlations between the three domains of fatigue (general, sleep/rest, cognitive) were all significant both for self-reports (Spearman's r_s from .36 to .67; Cronbach's α=.75) and for parent-report (r_s from .42 to .75; Cronbach's α =.83). However, correlations between sleep/rest fatigue and cognitive fatigue were moderate (r_s= .36 and .42, for self- and parent-reports, respectively). Correlations between self- and parent-reports of fatigue in the group of participants with TBI were significant, but moderate for cognitive fatigue (general fatigue r_s=.67; sleep/rest fatigue r_s=.79; cognitive fatigue r_s=48; and total fatigue r_s=.65). In the control group, the correlations were moderate for general fatigue (r_s=.50) and total fatigue (r_s=.51), and non-significant for sleep/rest (r_s=.01, p=.95) and cognitive fatigue (r_s=.39, p=.09).

Aim 2: Factors associated with Fatigue in participants 7 years after severe TBI

Baseline demographics, initial severity and overall disability over the first 2-years post-injury **(Table 3)**

Self-reported fatigue (Total score) was more pronounced in females (p<.05, but an important effect size [Cohen's d=.92]), in participants who were older at injury (and marginally at assessment, r_s=-.33, p=.06), who sustained a longer coma (more severe TBI), and had increased levels of disability at 3-months, 1- and 2-years post-injury according to the GOS-Peds scale. Of note, the tendency of increased self-reported fatigue in older children was also observed in the control group (r_s=-.32, p=.07).

Parent-reported fatigue (total score and cognitive fatigue) was mainly linked to overall level of disability 1-year post-injury. Cognitive fatigue was also associated to the injury severity score (ISS) and overall disability at 3-months and 1-year post-injury.

***Fatigue and 7-years post-injury concurrent TBI outcomes* (Table 4)**

Overall disability and intellectual ability

Self-reported fatigue (Total score) was significantly higher in patients with severe disability (GOS-E/GOS-E Peds; p=0.01, see Figure 2), but it was not significantly related to full-scale intellectual ability. Self-reported cognitive fatigue correlated with the WMI, and sleep/rest fatigue was associated with the PSI (Table 4).

Parent-reported fatigue (Total score and cognitive fatigue) was associated with overall level of disability (GOS-E) 7-years post-injury (Figure 2), and cognitive fatigue was associated with FSIQ. No other associations with self- and parent-reported fatigue were significant, except an increased level of parent-reported Cognitive fatigue in case of specialized education (p = .03).

Questionnaire-based measures

Self-reported fatigue correlated significantly with all self-completed questionnaires assessing executive functions, HRQoL, behavior, and participation, and these correlations remained significant when age and injury severity indices were taken into account.

Parent-reported fatigue correlated significantly with all questionnaires (executive functions, HRQoL, behavior, or participation) completed by the same parent.

The strongest correlations of self- and parent-reported fatigue with the questionnaires completed 7-years post-injury were observed with HRQoL (.78 and .83, for self- and parent-report, respectively). These correlations remained significant when overall disability (GOS at 7-years) was taken into account. Crossed correlations between questionnaires (self-reported fatigue with parental questionnaires, and parent-reported fatigue with self-completed questionnaires) were generally moderate and often significant.

DISCUSSION

The objective of the present study was twofold. First, we aimed to compare self-and parent-reported multidimensional fatigue between participants 7-years after severe childhood TBI and a closely matched control group. Our results evidenced that fatigue 7-years post-injury is a significant and persistent problem. Second, we sought to uncover the factors associated with fatigue in participants who sustained severe childhood TBI. Overall, fatigue was moderately associated with initial injury

severity, overall disability over the first 2-years post-injury, and concurrent outcomes assessed 7-years post-injury. Strong correlations were found between levels of fatigue 7-years post-injury and questionnaire-based measures completed by the same informant. This particular finding questions the specificity of the questionnaires aimed at assessing different domains and justifies the separation of factors associated with parent- and self-reported fatigue into two categories: "objective" (performance-based) and subjective (questionnaire-based) assessments.

Aim 1: TBI and control group comparisons

Seven-years after severe childhood TBI self- and parent-reported levels of fatigue were high, with 30% to 50% of participants reporting higher fatigue levels than matched controls. These results are in line with those from previous reports describing greater fatigue among patients with TBI 6-weeks and 5-years post-injury,[7,44] and with the conclusions of recent reviews [22,24] suggesting that fatigue can be a very long-lasting problem following severe childhood TBI.

The three dimensions of the multidimensional scale of fatigue (general, sleep/rest, and cognitive fatigue) were sufficiently inter-correlated to allow the computation and use of a total score. However, among the fatigue domains assessed, the levels of cognitive fatigue were more pronounced than general and sleep/rest fatigue, especially in self-reports. This finding is coherent with the common complaints by patients following severe TBI in clinical practice, and consistent with earlier studies reporting greater cognitive fatigue among patients with more severe injuries.[23,44] A similar finding was reported in a study on self-reported HRQoL, where the most problematic areas mentioned by patients 13-years post-childhood TBI were concentration and fatigue problems.[24]

Aim 2: Factors associated with Fatigue in participants 7 years after severe TBI

Fatigue and baseline demographics, initial severity and overall disability over the first 2-years post-injury

The tendency of female participants to self-report more fatigue post-TBI, compared to males, is in accordance with previous studies.[17,45,46] Likewise, self-reported fatigue tended to be more pronounced in older participants, similar to the results of one previous report after pediatric TBI.[6] A plausible explanation for this association may be related to under-report of fatigue in young children compared to older children and young adults, possibly related to diminished awareness of fatigue (or imperfect

understanding of the "fatigue" questions) in younger children. The marginally significant association between self-reported fatigue and age at assessment observed in the control group provides some support to this argument. In the present study, performed 7-years post-injury, the youngest participants were very young at injury (under 5 years) and had probably not integrated a "normal" feeling of fatigue pre-injury, as opposed to the oldest patients who were aged up to 15 years at injury. Younger children might under report their fatigue levels or, alternatively, might be especially at risk for developing awareness deficits when assessing some aspects of their cognitive or behavioral functioning, as suggested in a previous study with a sample of patients with TBI.[47]

It is important to note, however, that self-reported fatigue levels were not low when compared to the parent-reported fatigue levels, and a relatively strong correlation between self- and parent-reported total fatigue was observed. In addition, the discrepancy between self- and parent-reports of fatigue was not higher in the TBI group than in the control group, as in the study by Chiou et al.[21]

Injury severity indices, such as length of coma, were moderately correlated with self-reported fatigue, but not related to parental reports. Length of coma can be considered an indicator of the extent of brain lesions, and consequently of TBI severity. We estimate that self-reports of fatigue may be more closely related to brain dysfunction, which underlies the association between self-reported fatigue and length of coma, whereas parent-reports may be more influenced by personal and environmental factors, such as the extra effort and resources allocated to their child's needs.[6] After acquired pediatric brain injury, fatigue is linked to severity, according to a recent review,[48] and 12-months after pediatric TBI, fatigue was worse after moderate/severe than after mild TBIs.[23] In another study, the course of fatigue during the first year after TBI decreased in mild TBIs, but increased in severe TBIs.[13]

Overall disability assessed 1-year post-injury was associated with self- and parent-reported fatigue 7-years post-injury. Overall disability is based on the presence or absence of specific symptoms, such as motor deficits and/or cognitive impairment. We estimate that the relation observed in the present study is due to the presence of symptoms pertaining to physical and cognitive health, in accordance with previous findings evidencing an association between physical/motor symptoms at 6-months post-injury and reports of fatigue 12-months post-injury among patients with TBI.[23]

Fatigue and 7-years post-injury outcomes: overall disability and intellectual ability

Overall outcome assessed with the GOS-E 7-years post-injury was related to fatigue. Fatigue levels were significantly increased in case of severe disability, both in self- and parents-reports. In a previous study [14], increases in fatigue over the first two years was associated with general functioning. Overall, correlations of fatigue scores with the Wechsler scales were not significant, except for FSIQ with parent-reported cognitive fatigue. This result is in accordance with a previous report, suggesting that parents tend to report cognitive fatigue on the basis of the extra efforts required to help children with schoolwork, probably in relation to their child's intellectual limitations.[6] Our findings were moderately in favor of the "coping hypothesis".[12] We found a moderate but significant positive correlation of self-reported cognitive fatigue with the working memory index: participants who evidenced preserved working memory skills reported less cognitive fatigue 7 years following child TBI. The same tendency was observed in parent-reports, although it failed to reach statistical significance due to the small sample size. These associations were expected taking into account that difficulties in working memory skills require additional cognitive resources to perform a particular task, which in turn might contribute to increased levels of self- and parent-perceived fatigue. Despite the link observed between fatigue and working memory, its association with the processing speed index was not significant.

The sleep/rest dimension was only moderately correlated with the other two dimensions. Fatigue and sleep disturbances have been considered as key sequelae of moderate to severe TBI.[9,49] One previous study found weak-to-absent associations between sleep disturbances and fatigue,[50] but the majority of previous investigations reported either that sleep disturbances contribute to fatigue,[51,52] or that fatigue causes daytime sleepiness.[53,54]

Fatigue and 7-years post-injury outcomes: questionnaire-based measures

The present results show relatively strong correlations between questionnaires assessing fatigue, and questionnaires assessing HRQoL, executive functions, behavior and participation, especially when questionnaires are completed by the same informant (self or parent). These findings are in line with previous investigations highlighting the associations of post-TBI fatigue with other questionnaire-based measures assessing depression,[17,53,54] chronic situational stress,[15] reported cognitive difficulties

and somatic symptoms,[13,15] or participation[55], although specific measures of some of the previously mentioned dimensions (e.g. depression) were not used in the present study.

The strong correlations observed among questionnaire-based measures remained strong even after controlling for possible confounding factors such as age, overall disability or intellectual ability. All the items of all the questionnaires used in the present study, assessing fatigue (PedsQL MFS), HRQoL (PedsQL), executive functions (BRIEF), behavior (CBCL) and participation (CASP), have a clear consensual positive/negative polarity. We hypothesized elsewhere[25,26] that this "polarity", associated with an overlapping of the items among questionnaires, can create correlations between measures completed by the same informant. For instance, both the MFS and the PedsQL ask about sleep disturbances, attention-concentration or memory problems.[56]

Limitations

The current results should be interpreted taking certain limitations into account. Despite the large sample size of severe childhood TBI participants, specific comparisons between participants with fatigue scores in the upper and lower subcategories were impracticable because of the small numbers of cases in the extremes. In addition, our analyses were based on the total number of observations available for the primary outcome, which differed across informants completing the questionnaires, and may have contributed to the differences in the patterns of associations between self- and parent-reported fatigue, although the comparative analyses were based on a comparable number of observations for each. Indeed, both self- and parent-reports of fatigue were available only for 25 and 20 participants, which could have impacted the findings. The control group proved very challenging to recruit, especially those participants from very low socio-economic backgrounds, and if we managed most of the time to perform the direct assessments, it was more difficult to obtain the questionnaires responses. Further, a number of univariate comparisons were performed, which could have led to some significant results to have occurred by chance. Given the sample size, we did not perform multivariate analyses. Also, the control group was recruited only at the 7-year follow-up, and fatigue was only assessed at this time point, rather than prospectively since the early stages post-injury, which did not allow assessing change over time. To our knowledge, the multidimensional fatigue index scale was not available in French at the time of the study start. Fatigue had been assessed on several

occasions in the form of one of the items of the Paediatric Injury Functional Outcome Scale (Physical Change subscale). However, it was difficult to link this one item collected serially to a whole scale performed several years later. Further, fatigue has been reported to be linked to presence and severity of anxiety and depression symptoms, and those were not assessed specifically in our study, which did not allow assessing the role of those symptoms in the perception of fatigue. Finally, fatigue was assessed using a questionnaire allowing assessment of subjective fatigue, which should be distinguished from objective and specific measures of fatigue using performance tasks. However, patients' subjective views on this aspect are fundamental and cannot be ignored.

Future directions

Although the following suggestions are not directly drawn from the study results, they arise from the high levels of fatigue reported in this paper, combined with our extensive clinical experience in follow-up of children and youth who sustained severe TBI. Those suggestions and future directions are directly aimed at researchers and clinicians dealing with those patients in the long-term. Fatigue is a multidimensional construct associated with different factors influencing its onset and course over time. Taking into account the growing evidence that fatigue symptoms are frequent and persistent following childhood TBI,[22,24] further research is needed, in order (1) to investigate more closely the different components of fatigue; (2) to better understand the determinants of fatigue, especially cognitive fatigue, which is extremely disabling in everyday life and liable to compromise integration; (3) to develop interventions to reduce fatigue post-TBI. These should explore several avenues. First, when patients or parents report sleep/rest difficulties, more in-depth assessments of sleep should be provided, in order to characterize the disturbances and propose suitable interventions combining self-care and lifestyle advice (e.g. regular routines, reduced use of screens in the evening) and medication in some cases (e.g. melatonin). Second, when cognitive fatigue arises from cognitive limitations, such as slow processing speed, attention or working memory deficits, adaptations should be provided in the classroom in order to reduce the load of information handled by the child. Third, when children are slow and fatigued, they could also benefit from a reduction in homework, so that they can get the rest they need, and maintain leisure and sports activities, which greatly contribute to their wellbeing and

overall participation, especially because there is evidence that severe TBI is predictive of poor participation in school and leisure activities.[57]

Conclusion

In accordance to the present results and previous reports, reported fatigue several years after severe childhood TBI is considerable, and closely linked to reported HRQoL, as well as to other self- or proxy-reported behavioral, cognitive symptoms, or sleep problems. It is overall moderately linked to indices of injury severity and overall outcome, such as the level of disability. These findings are highly coherent with findings from other studies and current clinical practice, where fatigue emerges as one of the most frequent and disabling symptoms after TBI.[7] Fatigue often is an obstacle to optimal participation in school, leisure, and later professional activities. This is supported by our results evidencing the relatively strong associations between the levels of fatigue and participation.

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Table 1. Socio-demographic, early severity characteristics and outcomes of the participants in the TBI group

	Severe TBI ***n* = 38**
	Mean (SD) [Range]
Socio-demographic characteristics	
Age at follow-up	15.27 (4.45) [7.42 - 22.67]
Sex, male *n (%)*	24 (63.16)
Parental education level, *n (%)*	
Medium-high	19 (50)
Injury Severity	
Age at injury (years)	7.46 (4.58) [.25 - 14.7]
Lowest Glasgow Coma Scale Score	5.84 (1.70) [3 - 8]
Paediatric Trauma Score	3.92 (2.33) [-1 - +9]
Injury Severity Score	27.50 (9.71) [4 - 50]
Length of coma (days)	6.58 (4.93) [1 - 22]
Overall disability over the first 2 years post-injury	
3-monthsGOS Peds, n (%)	
Good Recovery	3 (8)
Moderate Disability	19 (50)
Severe Disability	16 (42)
1-yearGOS Peds, n (%)	
Good Recovery	5 (13)
Moderate Disability	21 (55)
Severe Disability	12 (32)
2-yearsGOS Peds, n (%)	
Good Recovery	7 (18)
Moderate Disability	21 (55)
Severe Disability	10 (27)
7-years post-injury outcomes	
GOS-E/GOS-E Peds, n (%)	
Good Recovery	21 (55)
Moderate Disability	9 (24)
Severe Disability	8 (21)
Motor deficits	
Presence, n (%)	7 (18)
Ongoing education	
Mainstream, n (%)	30 (79)
Specialized, n (%)	8 (21)

TBI: Traumatic Brain Injury; SD: Standard Deviation; GOS Peds: Pediatric Glasgow Outcome Scale; GOS-E/GOS-E Peds: Glasgow Outcome Scale-Extended; Glasgow Outcome Scale-Extended, Pediatric version.

Table 2. Self- and parent-reported mean scores on the PedsQL Multidimensional Fatigue Scales for the TBI group 7-years post-injury and for the control group

	Severe TBI			Controls			
	n	**Mean**	**SD**	***n***	**Mean**	**SD**	***p*** [†]
Self-report							
General Fatigue	34	66.68	22.65	33	82.33	16.99	.004
Sleep/Rest Fatigue	34	64.13	21.10	33	71.35	15.39	.239
Cognitive Fatigue	34	53.70	22.83	33	78.53	19.35	<.0001
Total Fatigue	34	61.11	18.76	33	77.39	15.33	. 0006
Parent-report							
General Fatigue	25	67.47	22.13	20	88.55	11.13	.001
Sleep/Rest Fatigue	25	71.52	22.82	20	86.88	12.20	.024
Cognitive Fatigue	25	64.36	26.06	20	87.50	20.27	.005
Total Fatigue	25	67.78	20.34	20	87.62	11.38	.0006

[†] Two-tailed Wilcoxon signed-rank test; TBI: Traumatic Brain Injury; SD: Standard deviation.

Table 3. Spearman correlations of self- and parent-reported scores in the PedsQL Multidimensional Fatigue Scale with sociodemographic characteristics, injury severity, overall disability over the first 2-years post-injury, and 7-years post-injury outcomes

	Multidimensional Fatigue Scale							
	Self-report *n*=34				Parent-report *n*= 25			
	General	Sleep/ Rest	Cognitive	Total	General	Sleep/ Rest	Cognitive	Total
Sociodemographic								
Age at injury	-.29	-.36*	-.26	-.37*	-.19	-.35	-.13	-.24
Gender[†] (*es*)	(.94)*			(.92)*				
Initial Injury Severity								
Lowest GCS Score	.31	.10	-.04	.14	.33	.37	.29	.33
Pediatric Trauma Score	-.03	-.24	-.08	-.11	-.14	-.13	-.04	-.17
Injury Severity Score	-.36*	-.02	-.40*	-.30	-.12	.02	-.46*	-.21
Length of coma	-.47**	-.16	-.45**	-.42*	-.14	-.11	-.26	-.19
Overall disability								
3-months GOS Peds	-.26	-.24	-.45**	-.44*	-.20	-.24	-.51*	-.42
1-year GOS Peds	-.30	-.21	-.46**	-.46**	-.30	-.38	-.51*	-.48*
2-yearsGOS Peds	-.41*	-.24	-.40*	-.46**	-.16	-.28	-.42	-.34
7-years post-injury outcomes								
Overall disability								
GOS-E/GOS-E Peds	-.10	-.15	-.22	-.20	-.37	-.32	-.64***	-.52**
Intellectual ability								
FSIQ	-.09	-.23	.26	.01	-.01	-.17	.41*	.16
VIQ	-.06	-.10	.18	.06	-.05	-.13	.29	.11
PIQ	-.12	-.33	.17	-.09	-.15	-.38	.35	.03
WMI	-.16	.01	.38*	.25	.20	.04	.39	.29
PSI	-.23	-.36*	.14	-.16	-.11	-.23	.30	.05

[†] Two-tailed Wilcoxon signed-rank test (*Z*); *es*: effect size (Cohen's *d*); * $p < .05$, ** $p < .01$, *** $p < .001$; GCS: Glasgow Coma Scale; GOS Peds: Pediatric Glasgow Outcome Scale GOS-E/GOS-E Peds: Glasgow Outcome Scale-Extended; Glasgow Outcome Scale-Extended, Pediatric version; FSIQ: Full Scale Intellectual Quotient; VIQ: Verbal Intellectual Quotient; PIQ: Performance Intellectual Quotient; WMI: Working Memory Index; PSI: Processing Speed Index.

Table 4. Spearman correlations of self- and parent-reported scores in the PedsQL Multidimensional Fatigue Scale with 7-years post-injury questionnaire-based outcomes

	Multidimensional Fatigue Scale							
	Self-report *n*=34				Parent-report *n*= 25			
	General	Sleep/ Rest	Cognitive	Total	General	Sleep/ Rest	Cognitive	Total
Executive Function								
BRIEF GEC (Self)	-.63*	.21	-.63*	-.70*	-	-	-	-
BRIEF GEC (Parent)	-.31	-.11	-.20	-.24	-.67***	-.32	-.64**	-.69***
Health-Related Quality of Life								
PedsQL Total score (Self)	.78***	.47**	.68***	.78***	.59**	.35	.47*	.52*
PedsQL Total score (Parent)	.53*	.61**	.34	.56**	.78***	.67***	.61**	.83***
Behavior								
CBCL Total score (Self)	-.66***	-.26	-.60**	-.66***	-.33	-.18	-.49	-.47
CBCL Total score (Parent)	-.52**	-.19	-.22	-.40**	-.48*	-.28	-.59**	-.55**
Participation								
CASP Total score (Self)	.49**	.18	.40*	.48*	.55*	.54*	.49	.53*
CASP Total score (Parent)	.60***	.31	.43*	.59***	.60**	.44*	.58**	.63***

* $p < .05$, ** $p < .01$, *** $p < .001$; BRIEF: Behavior Rating Inventory of Executive Functions; GEC: Global Executive Composite; PedsQL: Pediatric Quality of Life Inventory; CBCL: Child Behavior Checklist; CASP: Child and Adolescent Scale of Participation.

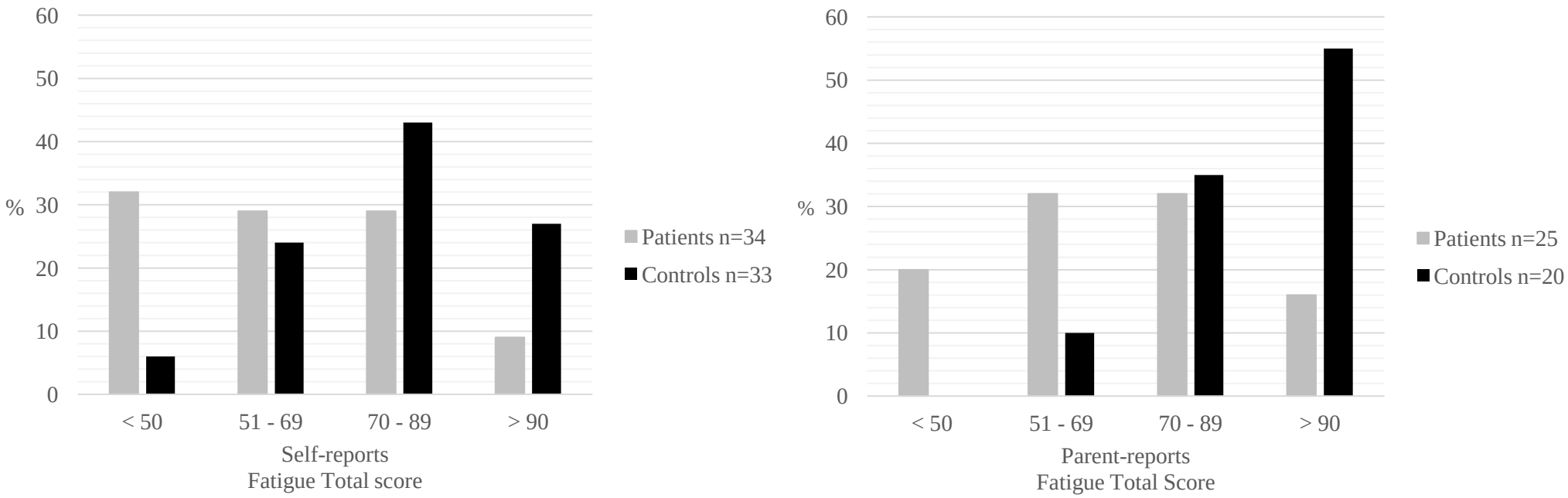

Figure 1. Distribution of the Fatigue Total Score for participants with TBI and controls according to self- and parents-reports.

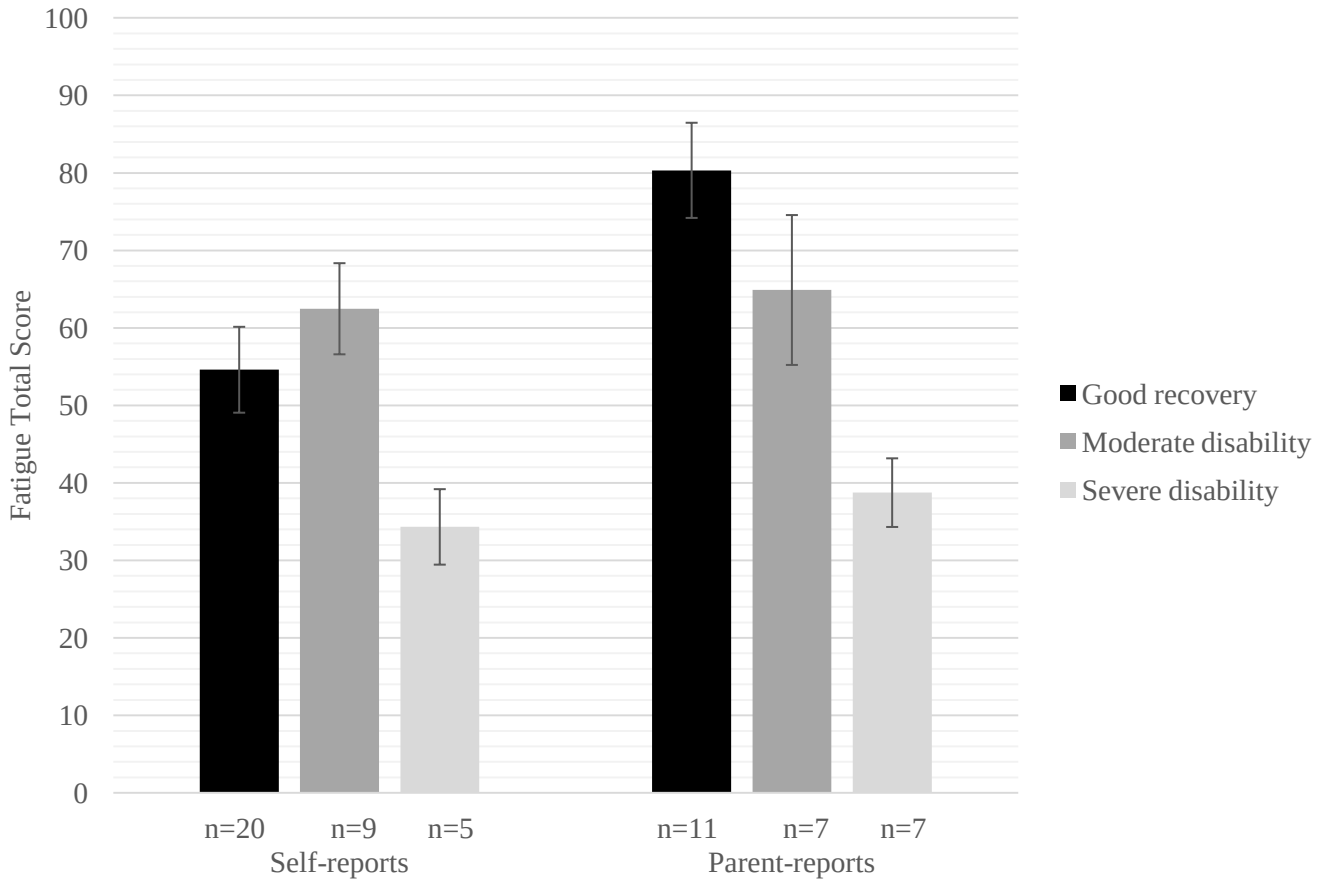

Figure 2. Distribution of the self- and parent-reported Cognitive Fatigue scores for participants with TBI according to the clinician-rated degree of overall disability (GOS-E/GOS-E Peds) 7-years post-injury.