

Cognitive Fatigue and Processing Speed in Children Treated for Brain Tumours

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Abstract

Objective: The relationship between fatigue and cognition has not been fully elucidated in children and adolescent survivors of brain tumours. The aim of the present study was to investigate the potential relationship between fatigue and cognitive impairments in these survivors, as this group is at risk for both types of deficits. **Methods:** Survivors of paediatric brain tumours ($n = 45$) underwent a neuropsychological testing on average 4 years after diagnosis. Mean age at follow-up was 13.41 years. Cognition was assessed with neuropsychological tests, and fatigue with the Pediatric Quality of Life (PedsQL™) Multidimensional Fatigue Scale. Regression analysis, adjusted for cranial radiotherapy and age at diagnosis, was used to investigate the associations between cognitive variables and fatigue subscales. Cognitive variables associated with fatigue were subsequently exploratively assessed. **Results:** Significant associations were found for cognitive fatigue and measures of cognitive processing speed; Coding: $p = .003$, $r = .583$, 95% CI [9.61; 22.83] and Symbol Search: $p = .001$, $r = .585$, 95% CI [10.54; 24.87]. Slower processing speed was associated with poorer results for cognitive fatigue. Survivors with the largest decrease in processing speed from baseline to follow-up also experienced the most cognitive fatigue. Survivors expressed more cognitive fatigue compared to other types of fatigue. **Conclusions:** The association between cognitive fatigue and cognitive processing speed in children and adolescents treated for brain tumours is in concordance with the results previously reported in adults. Some survivors experience fatigue without impairment in processing speed, indicating the need for comprehensive assessments. Moreover, the study supports that fatigue is a multidimensional concept which should be measured accordingly.

Keywords: Survivorship, Neuropsychology, Neurosurgery, Questionnaires, Follow-up studies, Psycho-oncology

INTRODUCTION

Cognitive fatigue (also referred to as mental fatigue or brain fatigue) includes a spectrum of deficits affecting motivation, emotion, cognition, and behaviour. Mental exhaustion caused by sensory stimulation and/or prolonged cognitive tasks is a characteristic symptom (Johansson & Ronnback, 2014; Moller, Nordin, Bartfai, Julin, & Li, 2017; Moller, Nygren de Boussard, Oldenburg, & Bartfai, 2014), as well as a specific diurnal pattern where performance decreases continuously during the day (Johansson, Berglund, & Ronnback, 2009; Johansson & Ronnback, 2013; Johansson, Starmark, Berglund, Rodholm, & Ronnback, 2010). Amongst adults, cognitive fatigue is commonly associated with decreased processing speed (Ashman

et al., 2008; Johansson et al., 2009; Johansson, Wentzel, Andrell, Mannheimer, & Ronnback, 2015; Jonasson, Levin, Renfors, Strandberg, & Johansson, 2018), as well as impairments in attention, memory, and executive functions (Boksem, Meijman, & Lorist, 2005; Cheung et al., 2017; Lindqvist & Malmgren, 1993; Puhr et al., 2019). Cognitive fatigue in adults is associated with acquired brain injuries, cancer, inflammatory or infectious diseases, and degenerative neurological disorders (Asher, Fu, Bailey, & Hughes, 2016; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2005; Friedman et al., 2007; Huang et al., 2019; Johansson & Ronnback, 2014; Shah, 2009).

Cognitive fatigue in children has been investigated in relation to multiple sclerosis (Goretti et al., 2012), traumatic brain injuries (de Kloet et al., 2015), cancer (Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002), sickle cell disease (Panepinto et al., 2014), and rheumatic diseases (Varni, Burwinkle, & Szer, 2004). Survivors of

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paediatric brain tumours have been shown to suffer from more cognitive fatigue compared to survivors of leukaemia (Irestorm, Tønning Olsson, Johansson, & Ora, 2020; Meeske et al., 2004; Mulrooney et al., 2008). While most follow-up protocols after cancer treatment do not yet include measurements of fatigue, there is an increased demand for including it in follow-up protocols for survivors of both paediatric and adult cancer (Berger, Mitchell, Jacobsen, & Pirl, 2015; Irestorm et al., 2020; Limond et al., 2020; Tomlinson et al., 2013). Cancer-related fatigue has consistently been found to be one of the most prevalent and distressing symptoms in childhood cancer survivors (Kanellopoulos, Hamre, Dahl, Fossa, & Ruud, 2013; Meeske, Patel, Palmer, Nelson, & Parow, 2007; Spathis et al., 2015). Despite this, cognitive fatigue is frequently overlooked as a long-term sequela to paediatric cancer diagnosis and treatment (Spathis et al., 2015; Walter, Nixon, Davey, Downie, & Horne, 2015). Self-reported outcomes, such as questionnaires, are commonly used and recommended when assessing fatigue after both traumatic and non-traumatic brain injuries (Asher et al., 2016; Johansson & Ronnback, 2013). Additionally, a multi-dimensional approach has been recommended in order to facilitate discrimination between different types of fatigue and comorbidities (Berger, Mitchell, et al., 2015; Berger, Mooney, et al., 2015; Cramp & Byron-Daniel, 2012).

In contrast to adults, little is known about the relationship between fatigue and cognition in children and adolescents. Cognitive deficits after treatment for paediatric brain tumours are common and well documented. Cranial radiotherapy is the most common risk factor for cognitive impairments (Brinkman et al., 2016; Ellenberg et al., 2009; Scantlebury et al., 2016; Tønning Olsson, Perrin, Lundgren, Hjorth, & Johanson, 2014), but younger age at diagnosis has also been reported as a predictor for long-term deficits (Mulhern et al., 2001; Palmer et al., 2013; Palmer et al., 2003; Ris et al., 2013; Tønning Olsson et al., 2014). Impairment in processing speed is especially common (Kahalley et al., 2013; Palmer et al., 2013; Scantlebury et al., 2016; Tønning Olsson et al., 2014), but survivors usually perform significantly poorer than controls or age-adjusted norms on most neuropsychological tests. Impaired performance has been reported regarding attention, working memory, long-term memory, executive functions, and full-scale intelligence quotient (Brinkman et al., 2016; Ehrstedt et al., 2016; Krull et al., 2008; Palmer et al., 2013; Tønning Olsson et al., 2014). The relationship between fatigue and neurocognitive impairments in adult long-term survivors of childhood cancer has been investigated (Cheung et al., 2017; Clanton et al., 2011; Meeske, Siegel, Globe, Mack, & Bernstein, 2005; Pühr et al., 2019), but the same associations in children and adolescents have not previously been studied. The aim of the present study was to investigate the relationship between fatigue and impairments in cognition in a paediatric sample of survivors of brain tumours, as this patient group is at risk for both types of deficits.

For clinical neuropsychologists, it is of importance to better understand the association and overlap between fatigue and cognition, in order to avoid misdiagnosis and to offer appropriate interventions.

In line with previous studies on adult survivors of childhood leukaemia (Cheung et al., 2017), we hypothesised general and cognitive fatigue, but not sleep/rest fatigue, to be associated with cognitive measures. Likewise, we expected poorer scores on neurocognitive measures to be associated with more fatigue.

METHODS

Participants

Data were collected as part of a larger clinical project aiming to identify survivors with cognitive impairments to investigate the impact of late effects, and to engage the child and the family with rehabilitative services. All patients were diagnosed with and treated for paediatric brain tumours at Skåne University Hospital in southern Sweden (serving 1.8 million inhabitants). The clinical project includes a baseline testing before the start of treatment and a neuropsychological follow-up assessment.

Inclusion and Exclusion Criteria

Data were extracted from the registry for survivors who completed the neuropsychological follow-up between 2017 and 2019, and survivors 8–18 years of age at assessment were included in the study. A total of 56 survivors in the age group underwent a follow-up testing during that time period. Survivors diagnosed with either autism ($n = 1$) or intellectual disability ($n = 2$) prior to treatment were excluded, likewise if they had severe visual impairment ($n = 1$) or were on cancer therapy for relapse ($n = 5$). Candidates for epilepsy surgery ($n = 2$) were also excluded, due to assessment with a different test battery. No survivors were excluded because of low verbal skills nor low full-scale intelligence quotient at follow-up. A total of 45 survivors were eligible for inclusion in the study. The neuropsychological protocol for this patient group includes a baseline testing whenever possible. If a baseline testing was available, it was included in the study, but the lack of baseline cognitive measurements was not an exclusion criterion.

Neuropsychological Tests

Four different cognitive domains were assessed, and nine different cognitive variables were registered. Executive function was measured with the subtests Tower and Trail-Making-Test (TMT) from the Delis–Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001). For TMT, the scale score equivalent for Item 4 (Number-Letter Switching), time to completion was used. For the Tower test, the total achievement score was used. Processing speed was measured with the Coding and Symbol Search subtests, and the composite Processing Speed Index (PSI) from the age-appropriate Wechsler scale (Wechsler, 2008, 2014). Working memory was measured with the Digit Span subtest from the age-appropriate Wechsler scale. Executive function,

processing speed, and working memory were assessed at both baseline and follow-up. Additionally, the computer-based Conners' Continuous Performance Test 3rd Edition (CPT-3) (Conners, 2014) was used to measure attention deficits. Due to time constraints before surgery, it was administered only at follow-up.

Measures of Fatigue

The Pediatric Quality of Life (PedsQL™) self-report and parent-proxy versions of the Multidimensional Fatigue Scale were used as a measurement of fatigue and administered at follow-up. The questionnaire provides three different subscales: (1) the general fatigue subscale covers problems due to lack of energy (including specific executive difficulties); (2) the sleep/rest fatigue subscale focuses on quality and amount of sleep; and (3) the cognitive fatigue subscale focuses on problems with memory, attention, and processing speed. This instrument measures fatigue in children and teenagers, and high validity and reliability have been demonstrated across age groups from 2 to 25 years (Varni, Beaujean, & Limbers, 2013; Varni et al., 2002; Varni & Limbers, 2008). The questions cover the frequency of different symptoms of fatigue and are scored on a 5-point Likert scale from 0 to 4 (i.e., 0 = 'never', 1 = 'almost never', 2 = 'sometimes', 3 = 'often', 4 = 'almost always'). The answers are reversed and linearly transformed into a scale from 0 to 100, where higher scores indicate less problems. As the impact of fatigue is individual and a subjective experience, it is recommended to use self-reports for the assessment of fatigue in cancer patients (Asher et al., 2016; Berger, Mooney, et al., 2015). Only the self-reports were therefore used in order to explore the hypothesis.

Statistical Analysis

SPSS Version 26 was used for statistical analyses. All scores were transformed to Z scores ($M = 0$, $SD = 1$) using national norms and the scores from CPT-3 were reversed, so that higher scores on all scales indicated less problems. Regression analysis, adjusted for cranial radiotherapy and age at onset, were used to investigate the associations between the nine cognitive variables and the three self-report fatigue subscales. Cranial radiotherapy and younger age at diagnosis are known risk factors for cognitive impairments in survivors of paediatric brain tumours (Brinkman et al., 2016; Ellenberg et al., 2009; Mulhern et al., 2001; Palmer et al., 2013; Palmer et al., 2003; Ris et al., 2013; Scantlebury et al., 2016; Tønning Olsson et al., 2014), and these variables were therefore adjusted for in the regression analysis, with age at diagnosis in years and radiotherapy coded as yes or no. *P*-values were adjusted using the Benjamini–Hochberg procedure, with the false discovery rate set to 0.05. The partial correlation coefficient was used to denote the strength of significant associations between neuropsychological variables and fatigue measures. Cognitive variables with a significant association with fatigue

were subsequently exploratively examined through graphs and visual analysis. A score of more than 1.5 *SD* below the normative mean was applied as an indicator of impairment. The main analysis was cross-sectional, with a focus on data from follow-up visits, while baseline data were included in the explorative evaluation. A majority of the survivors (82.2%, $n = 37$) had undergone a pretreatment neuropsychological assessment, and the difference in test scores between pretreatment tests and follow-up were examined in this analysis. The purpose of the explorative analysis was to investigate symptom manifestation and to identify clinical profiles in survivors with and without fatigue. Furthermore, one-sample *t* tests were used to compare the results from these cognitive variables with the national norms, in order to determine the magnitude of the impairment.

RESULTS

Participant Demographics

The clinical characteristics of the study group are presented in Table 1. Mean age at diagnosis was 9.40 years ($SD = 3.56$), and mean age at follow-up was 13.41 ($SD = 2.74$), which means that the participants were assessed on average 4 years after diagnosis. Treatment had included cranial radiotherapy for 12 (26.7%) of the participants. Tumour types were classified in accordance with the World Health Organization: International Classification of Childhood Cancer, 3rd Edition (Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005). The distribution of tumour types in the sample was as expected when considering the national incidence and survival rates for each type (Lannering et al., 2009). Astrocytoma was the most frequent tumour type (44.67%).

Neurocognitive Variables and Measures of Fatigue

The results from the neurocognitive tests are shown in Table 2. The subtests with the largest group of impaired survivors (defined as a score of more than 1.5 *SD* below the normative mean) were coding, TMT, and hit reaction time from CPT-3. The results from the questionnaires together with internal consistency are shown in Table 3. Survivors rated themselves to have more cognitive fatigue as compared to general fatigue and sleep/rest fatigue ($M = 48.43$, $SD = 26.80$). Cognitive fatigue scores were poor when compared to those reported in healthy controls in Swedish ($M = 76.04$, $SD = 14.75$) and Dutch ($M = 76.46$, $SD = 14.53$) samples (Gordijn, Cremers, Kaspers, & Gemke, 2011; Irestorm et al., 2020). Impairment on the fatigue subscales was defined as a score below the 10th percentile of healthy children and adolescents. Out of the fatigue subscales, cognitive fatigue was the one affecting the largest group of survivors, with 68.89% scoring below this cut-off. The parent-proxy reports showed a similar profile, with cognitive fatigue being the most affected fatigue domain. Internal consistency was similar to what has previously been

Table 1. Study cohort characteristics ($n = 45$)

| | |
|--|------------|
| Age at diagnosis, years | |
| Mean | 9.40 |
| (SD) | (3.56) |
| Range | 1.53–14.20 |
| Age at follow-up, years | |
| Mean | 13.41 |
| (SD) | (2.74) |
| Range | 8.10–18.01 |
| Time since diagnosis, years | |
| Mean | 4.01 |
| (SD) | (2.20) |
| Range | 1.84–7.02 |
| Relapse, n (%) | 11 (24.44) |
| Treatment | |
| Surgery only, n (%) | 27 (60.00) |
| Radiotherapy, n (%) | 12 (26.67) |
| Chemotherapy, n (%) | 15 (33.33) |
| Primary cancer diagnosis distribution, n (%) | |
| IIIa. Ependymomas and choroid plexus tumours | 2 (4.44) |
| IIIb. Astrocytomas | 21 (46.67) |
| IIIc. Embryonal tumours | 5 (11.11) |
| IIId. Other gliomas | 4 (8.89) |
| IIIe. Other specified neoplasms | 11 (24.44) |
| III f. Unspecified intracranial neoplasms | 1 (2.22) |
| Xa. Germ cell tumours | 1 (2.22) |
| Gender, n (%) | |
| Female | 21 (46.67) |
| Male | 24 (53.33) |

Tumour types were classified in accordance with the World Health Organization: International Classification of Childhood Cancer, 3rd Edition (Steliarova-Foucher et al., 2005).

reported for the instrument (Gordijn et al., 2011; Irestorm et al., 2020; Varni et al., 2002).

Associations Between Neurocognition and Fatigue

The results from the regression analysis of the associations between neurocognitive outcomes and self-report fatigue measures are presented in Table 4, with confidence intervals and Benjamini–Hochberg-adjusted p -values. Significant associations were found for measures of cognitive processing speed and the cognitive fatigue self-rate subscale; Coding: $p = .003$, $r = .583$, 95% CI [9.61; 22.83] and Symbol Search: $p = .001$, $r = .585$, 95% CI [10.54; 24.87]. A slow processing speed was associated with more fatigue. An increase with 1 Z score in processing speed indicates that the survivors rate their quality of life for cognitive fatigue 16.22 scores higher, which corresponds to more than 1 SD for healthy children and adolescents. Non-significant associations were also found between D-KEFS TMT and cognitive fatigue, $p = .126$, $r = .348$, 95% CI [1.89; 16.52], and CPT-3 hit reaction time, $p = .278$, $r = .301$, 95% CI [0.33; 15.15]. More fatigue was associated with slower performance on TMT as well as slower hit reaction time.

Table 2. Test results at follow-up

| | Mean | SD | Range | Proportion impaired |
|--------------------------------------|-------|------|--------------|---------------------|
| Cognitive speed | | | | |
| Wechsler Coding | −0.59 | 1.07 | −3.00 – 1.33 | 22.22% |
| Wechsler Symbol Search | −0.41 | 1.00 | −2.67 – 1.33 | 13.33% |
| Executive functions | | | | |
| D-KEFS Tower Test | −0.21 | 0.91 | −3.00 – 1.00 | 10.26% |
| D-KEFS TMT 4 | −0.81 | 1.11 | −3.00 – 1.00 | 25.00% |
| Working memory | | | | |
| Wechsler Digit Span | −0.41 | 0.73 | −2.00 – 1.00 | 6.67% |
| Attention | | | | |
| CPT-3 Detectability | −0.37 | 0.74 | −2.20 – 0.90 | 7.14% |
| CPT-3 Commissions | −0.23 | 0.69 | −1.70 – 1.10 | 7.14% |
| CPT-3 Hit Reaction Time | −0.41 | 1.18 | −3.20 – 1.20 | 21.43% |
| CPT-3 Hit Reaction Time Block Change | −0.43 | 1.08 | −3.00 – 1.30 | 19.05% |

D-KEFS, Delis–Kaplan Executive Function System; TMT, Trail-Making Test; CPT-3, The Conners' Continuous Performance Test 3rd Edition. Results for neurocognitive outcomes are presented with Z scores (normative $M = 0$, $SD = 1$). Results for fatigue subscales are on a scale of 0–100. Higher results on both fatigue subscales and neurocognitive tests indicate less problems. Impairment was defined as a score of more than 1.5 SD below the normative mean for neuropsychological subtests.

Table 3. Fatigue measurements at follow-up

| | α | Mean | SD | Range | Proportion impaired |
|----------------------|----------|-------|-------|-----------|---------------------|
| Self-reports | | | | | |
| Cognitive fatigue | .90 | 48.43 | 27.84 | 0.00–100 | 68.89% |
| Sleep/rest fatigue | .75 | 57.59 | 20.78 | 16.67–100 | 35.56% |
| General fatigue | .86 | 65.56 | 22.09 | 12.50–100 | 40.00% |
| Parent-proxy reports | | | | | |
| Cognitive fatigue | .92 | 56.12 | 26.80 | 8.33–100 | 66.67% |
| Sleep/rest fatigue | .76 | 66.38 | 18.94 | 16.67–100 | 28.89% |
| General fatigue | .80 | 60.94 | 19.81 | 16.67–100 | 46.67% |

α , Cronbach's coefficient alpha. Impairment was defined as a score below the 10th percentile of healthy children and adolescents for fatigue subscales.

Explorative Analysis

As both Wechsler processing speed subtests were associated with cognitive fatigue, the composite score PSI ($M = 100$, $SD = 15$) was used for the explorative analysis when plotting performance against cognitive fatigue (Figure 1). For PSI, a score of more than 1.5 SD below the normative mean was used as an indicator of impairment. For cognitive fatigue, a score below 55, corresponding to the 10th percentile for healthy children and adolescents, was used as an indicator of fatigue (Irestorm et al., 2020). All survivors with impaired processing speed also indicated substantial problems with cognitive fatigue, with no survivor in this group scoring above 55. The survivors experiencing the least cognitive

Table 4. Cognition related to fatigue in children and adolescents after treatment for brain tumours

| | Cognitive fatigue | | | | Sleep/rest fatigue | | | | General fatigue | | | |
|--------------------------------------|-------------------|---------------|-------------|----------|--------------------|---------------|----------|----------|-----------------|---------------|----------|----------|
| | B | 95% CI | <i>p</i> | <i>r</i> | B | 95% CI | <i>p</i> | <i>r</i> | B | 95 %CI | <i>p</i> | <i>r</i> |
| Cognitive speed | | | | | | | | | | | | |
| Wechsler Coding | 16.22 | 9.61 – 22.83 | .003 | .583 | 1.53 | –4.56 – 7.62 | .765 | .073 | 1.28 | –5.16 – 7.71 | .818 | –.016 |
| Wechsler Symbol Search | 17.70 | 10.54 – 24.87 | .001 | .585 | 4.93 | –1.54 – 11.41 | .456 | .217 | –0.38 | –7.38 – 6.63 | .951 | .058 |
| Executive functions | | | | | | | | | | | | |
| D-KEFS Tower Test | 6.24 | –3.44 – 15.92 | .466 | .198 | 1.22 | –6.31 – 8.75 | .845 | .051 | –5.51 | –12.71 – 1.68 | .513 | –.234 |
| D-KEFS TMT 4 | 9.20 | 1.89 – 16.52 | .126 | .348 | –0.33 | –6.20 – 5.53 | .985 | –.017 | –4.33 | –10.43 – 1.76 | .489 | –.206 |
| Working memory | | | | | | | | | | | | |
| Wechsler Digit Span | 9.27 | –1.80 – 20.35 | .454 | .238 | –5.94 | –14.33 – 2.44 | .405 | –.203 | –2.79 | –11.80 – 6.21 | .733 | –.090 |
| Attention | | | | | | | | | | | | |
| CPT-3 Detectability | 4.78 | –5.79 – 15.35 | .535 | .135 | 4.33 | –3.70 – 12.36 | .491 | .161 | –0.20 | –8.50 – 8.10 | .964 | –.007 |
| CPT-3 Commissions | 8.28 | –3.39 – 19.94 | .443 | .210 | 7.83 | –0.96 – 16.61 | .437 | .260 | 5.29 | –3.86 – 14.43 | .463 | .172 |
| CPT-3 Hit Reaction Time | 7.74 | 0.33 – 15.15 | .278 | .301 | –3.06 | –8.91 – 2.79 | .534 | –.156 | 3.00 | –8.97 – 2.99 | .489 | –.150 |
| CPT-3 Hit Reaction Time Block Change | 4.55 | –3.00 – 12.12 | .457 | .179 | –1.70 | –7.54 – 4.13 | .729 | –.088 | –3.58 | –9.46 – 2.30 | .482 | –.181 |

D-KEFS, Delis–Kaplan Executive Function System; TMT, Trail-Making Test; CPT-3, The Conners’ Continuous Performance Test 3rd Edition. Non-standardised coefficients for all the neurocognitive outcomes with the self-rating fatigue subscales as dependent variables were adjusted for age at diagnosis and radiotherapy. Results on neurocognitive tests are in Z scores (Mean = 0, SD = 1) and scores on fatigue subscales are on a scale of 0–100. Higher results on both fatigue subscales and neurocognitive tests indicate better performance and less fatigue. Benjamini–Hochberg-adjusted significant *p*-values are indicated in boldface font.

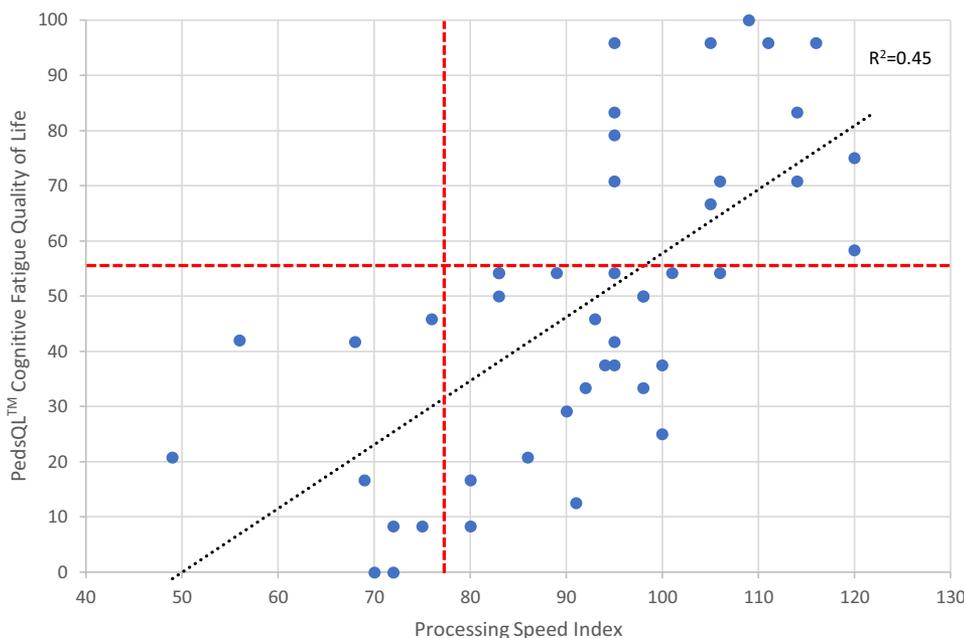


Fig. 1. Scatterplot of processing speed in standard scores ($M = 100$, $SD = 15$) against Pediatric Quality of Life (PedsQL) cognitive fatigue quality of life scores ($n = 45$). Higher scores indicate better performance and less fatigue. The dotted lines indicate impaired performance with impairment defined as cognitive scores more than 1.5 SD below the normative mean and cognitive fatigue scores below 55, corresponding to the 10th percentile of healthy controls.

fatigue had the best processing speed ($r^2 = 0.45$). While some survivors expressed problems with cognitive fatigue with no impairment in processing speed, the opposite was not observed in this study.

PSI scores (standard scores, $M = 100$, $SD = 15$) from the baseline testing were included in the explorative analysis

(Figure 2). Mean PSI was 95.78 ($SD = 11.61$) at baseline and 91.93 ($SD = 16.19$) at follow-up. One-sample *t* tests were used to compare these results to the national norms, and were significant for both the baseline testing, $p = .034$, 95% CI [–0.35; –8.09], and the follow-up, $p = .002$, 95% CI [–3.20; –12.93] The change in PSI between baseline and

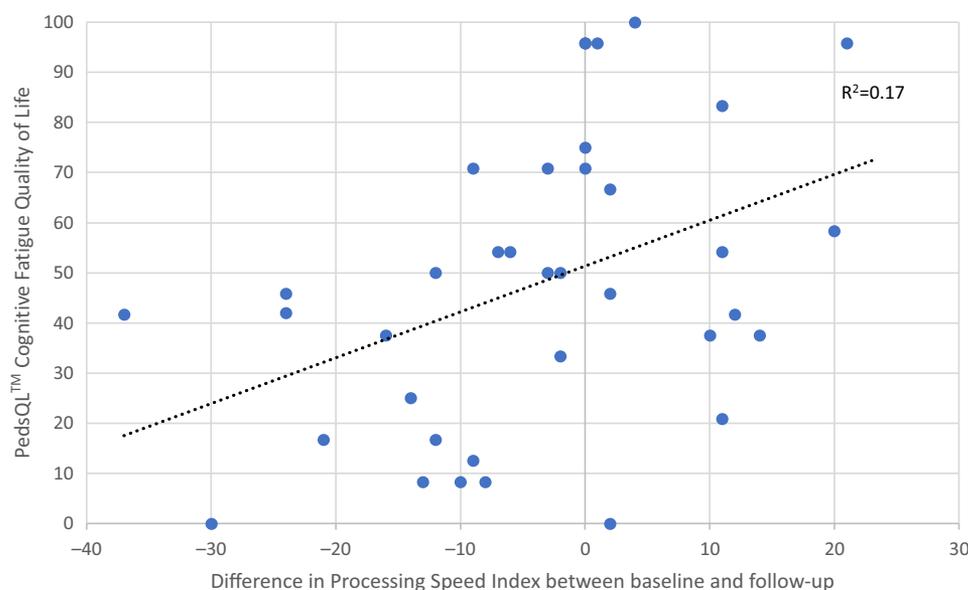


Fig. 2. Comparisons between cognitive fatigue (higher scores indicate less problems) and change in Processing Speed Index (PSI) ($M = 100$, $SD = 15$) from baseline to follow-up (sub-cohort, $n = 37$).

follow-up was plotted against the score in cognitive fatigue and shows that survivors with the largest decrease in processing speed also experienced more cognitive fatigue ($r^2 = 0.17$). Mean difference between the test at baseline and follow-up was -3.03 ($SD = 14.32$), and the median difference was -2.00 .

DISCUSSION

We here present, to our knowledge, the first study investigating the association between fatigue and cognition in children and adolescents treated for paediatric brain tumours. Several studies have investigated the relationship between cognition and fatigue in adults, but the area is understudied in children and adolescents. We found an association between cognitive processing speed and cognitive fatigue, but no associations with the other two measures of fatigue nor between fatigue and other measures of cognition. In the explorative analysis, we found a distinct clinical profile, where all survivors with impaired processing speed also experience cognitive fatigue. Moreover, survivors with the largest decrease in processing speed between baseline and follow-up also expressed the highest levels of cognitive fatigue.

Cognitive processing speed was associated with cognitive fatigue, which is commonly reported in adults following traumatic brain injuries (Ashman et al., 2008; Johansson et al., 2009, 2015, 2018). While studies on adult survivors of childhood cancers reported associations between cognitive fatigue and impairments in attention, memory, and executive functions (Cheung et al., 2017; Clanton et al., 2011; Puhr et al., 2019), we observed no such associations in children and adolescents. The lack of associations between executive functions and fatigue could be caused by a non-representative sample in this aspect, while the associations found between processing speed and fatigue are more likely to be generalisable. We did not find the relationship between general fatigue and cognition that we

hypothesised based on research on adult survivors of childhood leukaemia. Small study samples in combination with different aetiologies and the use of different measurements inflates the risk of type II errors. Hence, this hypothesis needs to be further investigated in future studies.

The association between cognitive fatigue and cognitive processing speed presented in the current study was previously demonstrated in adults after stroke or traumatic brain injury (Johansson et al., 2009, 2015, 2018). A study on acquired brain injuries in children and adolescents showed that participants reported more cognitive fatigue after non-traumatic brain injuries (including brain tumours) compared to traumatic brain injuries (van Markus-Doornbosch et al., 2016). This could be caused by the additional impact of chemotherapy, radiotherapy, and/or brain surgery. A recent study on cognitive fatigue in adult survivors of paediatric brain tumours showed that surgery in combination with chemotherapy and radiotherapy increased the risk for severe fatigue (Puhr et al., 2019), while another study on fatigue in childhood cancer survivors reported that radiotherapy – but not chemotherapy – increased the risk for fatigue (Mulrooney et al., 2008). While the effect of different treatments on fatigue in survivors of childhood cancer remains to be elucidated, previous research has shown that survivors of paediatric brain tumours suffer more fatigue than survivors of acute lymphoblastic leukaemia (Irestorm et al., 2020; Meeske et al., 2004; Mulrooney et al., 2008). One possible explanation for this is the impact of brain surgery in combination with higher radiation dosages. Thus, it is evident that survivors of paediatric brain tumours are at risk for experiencing fatigue and they should therefore be clinically monitored. While cranial radiotherapy has been shown to have a negative impact on cognitive processing speed (Kahalley et al., 2013; Palmer et al., 2013; Scantlebury et al., 2016; Tonning Olsson et al., 2014), in a large study from the Childhood Cancer Survivor Study, Clanton et al. (2011)

reported that the impact of fatigue on neurocognitive outcomes in adult survivors of childhood cancer was independent of the effects of both cranial radiotherapy and chemotherapy. Hence, cognition in long-term survivors of childhood cancers seems to be vulnerable to the effects of fatigue, which makes fatigue an important target for both further research and clinical management. In adults, fatigue has been associated with disabilities in personal life, altered ability to gain and maintain employment, and socio-economic effects (Engberg, Segerstedt, Waller, Wennberg, & Eliasson, 2017; Huang et al., 2019; Johansson & Ronnback, 2014).

Cognitive fatigue was the only fatigue subscale to be associated with cognition and was furthermore the subscale where the survivors scored the lowest results. The average result for the study sample was approximately 2 *SD* below that of healthy children and adolescents (Gordijn et al., 2011; Irestorm et al., 2020). While the scales are not standardised, this is still an apparent difference compared to the other two subscales, where the mean scores were approximately 1 *SD* below the mean of healthy children and adolescents. If fatigue had been measured with a unidimensional instrument, this difference would most likely have been masked and the high prevalence of cognitive fatigue might not have been detected. Multidimensional instruments are recommended in order to facilitate discrimination between depression and fatigue (Berger, Mitchell, et al., 2015; Berger, Mooney, et al., 2015), and for evaluating the impact of interventions (Cramp & Byron-Daniel, 2012). Additionally, multidimensional scales are reported to have better accuracy (Brand, Chordas, Liptak, Manley, & Recklitis, 2016). Our results further support that fatigue is a multidimensional concept, which should be measured accordingly.

In the explorative analysis, all survivors with impaired processing speed also experienced cognitive fatigue. At the same time, those experiencing the least cognitive fatigue had the fastest processing speed. The results indicate that there are three clinically disparate groups of survivors that experience different constellations of symptoms. While impaired processing speed and cognitive fatigue seem to co-exist in many survivors, the relationship between the two is unclear. There could be a causal relationship, but the impairments can also be co-existing, or there is an overlap either in symptoms or in assessment tools. While the fact that all survivors with impaired processing speed also experienced cognitive fatigue supports overlapping, the existence of survivors experiencing cognitive fatigue without impaired processing speed, as revealed by the explorative analysis, supports the opposite. Future research efforts should be directed towards elucidation of possible explanations for the latter group's subjective deficits.

As demonstrated in the explorative analysis, not all PSI scores declined although survivors with the largest decrease in processing speed experienced more cognitive fatigue. The participants in the current study scored below the normative mean at baseline and the mean score had further decreased at follow-up. This is in line with previous research showing that processing speed can be reduced already at baseline (Irestorm, Perrin, & Tonning Olsson, 2018). Hence, a reduction in processing speed is associated with cognitive fatigue.

Even though the mean results were statistically lower than normative means both at baseline and follow-up, the magnitude of this difference is within 1 *SD* and it is therefore not indicative of impairment in the group as total. However, these results are in line with previous research demonstrating that cognitive deficits after paediatric brain tumours are typically progressive (De Ruiter, Van Mourik, Schouten-van Meeteren, Grootenhuis, & Oosterlaan, 2013; Merchant et al., 2009; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). In summary, the overlap between impaired processing speed scores and cognitive fatigue implies that reduced processing speed could either be considered a symptom of cognitive fatigue or viewed as a possible explanation thereof.

As fatigue can be one of the most distressing and disabling symptoms in childhood cancer survivors (Kanellopoulos et al., 2013; Meeske et al., 2007; Spathis et al., 2015), the current results have clinical implications for neuropsychologists working within a paediatric setting. While there was an association between cognitive fatigue and impairments in processing speed, the explorative analysis also revealed the presence of survivors that experience cognitive fatigue without exhibiting impaired cognition. The results indicate discrepancies between self-report measures and neuropsychological test scores of this patient cohort. Neuropsychological testing alone might not fully reveal the extent of cognitive fatigue, and the survivors' subjective view of the symptoms should also be considered. Self-rating measurements of fatigue would improve assessments and should therefore be included in follow-up protocols. Aetiology and type of cancer treatment should also be considered when conducting the assessments, as treatment might affect both the type and severity of fatigue.

The diagnosis distribution of brain tumours in the study cohort was in accordance with national data (Lannering et al., 2009), while the number of participants treated with radiotherapy was lower compared to studies with non-population-based samples (Brinkman et al., 2016). Since radiotherapy is a known risk factor for decreased processing speed (Kahalley et al., 2013; Palmer et al., 2013; Scantlebury et al., 2016), this must be taken into account when interpreting the results. Both PSI and working memory at follow-up was in line with previous research (Brinkman et al., 2016; Scantlebury et al., 2016), while the sample had a poorer performance for mean hit reaction time than previously reported (De Ruiter et al., 2013), and better scores for executive measures than described in other studies (Brinkman et al., 2016; Scantlebury et al., 2016). Regarding fatigue, both cognitive fatigue and general fatigue were prevalent in a large number of survivors. This is in line with previous reports demonstrating that survivors experience cancer-related fatigue as one of the most prevalent and distressing symptoms after treatment for childhood cancer (Kanellopoulos et al., 2013; Meeske et al., 2007; Spathis et al., 2015). All in all, this supports that the results are generalisable to other population-based samples of survivors of paediatric brain tumours.

The relatively small study cohort of survivors also leads to low statistical power which may limit the identification of the associations between cognitive fatigue and the cognitive domains reported for adults. Since the association between

cognitive fatigue and cognitive processing speed has not been previously described in children and adolescents, the results require verification in another cohort. As the results are based on a cross-sectional observation longitudinal studies are required and in order to reach causal conclusions on fatigue and to examine the impact of different treatment modalities as well as to investigate potential changes in fatigue over time.

In conclusion, there is an association between cognitive fatigue and cognitive processing speed, and survivors who are most impaired in processing speed also express the most severe cognitive fatigue. The study supports that fatigue is a multidimensional concept, and that appropriate measurements of fatigue should be included in follow-up protocols for survivors of paediatric brain tumours.

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ETHICS STATEMENT

Participation in the screening was voluntary and the study was conducted in accordance with the Helsinki declaration. All data were anonymised and approval for the study was received from the Lund regional ethics committee (Nr 500/2007).

CONFLICTS OF INTERESTS

H.L. has co-founded and is part-time employed by a start-up company (Concidera Health) that develops decision support tools for childhood cancer survivorship. The company has no specific interest in the tests used in this study. The remaining authors report no conflicts of interest.

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