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RESEARCH ARTICLE

Fatigue mediates the relationship between emotional and cognitive functioning in children post-cancer treatment

Juliette E. M. Greidanus-Jongejan[1] | **Marloes van Gorp**[1] | **Raphaele R. L. van Litsenburg**[1] | **Femke K. Aarsen**[1] | **Merel M. Nap- van der Vlist**[2] | **Sanne Nijhof**[2] | **Martha A. Grootenhuis**[1]

[1]Department of Pediatric Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Juliette Greidanus-Jongejan, Department of Pediatric Oncology, Princess Máxima Center for Pediatric Oncology, 25, 3584 CS Utrecht, The Netherlands.
Email: juliette.jongejan@prinsesmaximacentrum.nl

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Abstract

Background/objectives: Children treated for cancer are at risk to develop cognitive problems. Insight in underlying associations with emotional functioning and fatigue can be used to optimize interventions. We therefore aim to study emotional functioning, fatigue, and cognitive functioning in children postcancer treatment and investigate whether fatigue mediates the relationship between emotional and cognitive functioning.

Design/methods: Emotional functioning, fatigue, and cognitive functioning were assessed in children post-cancer treatment using subscales of the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, Multidimensional Fatigue Scale and Cognitive Functioning Scale. A one sample *t*-test was used to compare outcomes with general population peers and mediation analysis was used to address the effect of fatigue on the relationship between emotional and cognitive functioning.

Results: A total of 137 children (mean age: 13.6, SD ± 3.3 years; mean time since end of treatment: 7.1 months, SD ± 5.9) participated. Lower scores on emotional functioning (Cohen's d [*D*]: 0.4), fatigue (*D*: 0.8) and cognitive functioning (*D*: 0.6) were found ($p < .001$) in children post-cancer treatment than in peers. A medium association was found between emotional and cognitive functioning (standardized regression coefficient [β]: 0.27, $p < .001$), which was mediated by fatigue ($\beta = 0.16$).

Conclusions: Outcomes on emotional and cognitive functioning are decreased and fatigue is increased in children postcancer treatment. Fatigue mediates the relationship between emotional and cognitive functioning. Our results show the importance to focus on fatigue amongst stress as a target for intervention to improve cognitive functioning.

KEYWORDS
children, cognitive, emotional, fatigue, post-cancer

Abbreviations: *B*, regression coefficient; CI, confidence interval; CNS, central nervous system; MFS, multidimensional fatigue scale; *N*, number; PedsQL, Pediatric Quality of Life inventory; SD, standard deviation; β, standardized regression coefficient.

1 | INTRODUCTION

Every year, about 600 children in the Netherlands are newly diagnosed with childhood cancer. Due to improved medical care over the past decades, more children survive and are cured from cancer.[1] It is evident that undergoing childhood cancer is a stressful life-event for the child and family. Some children who receive treatment for cancer show vulnerabilities concerning emotional functioning, fatigue, and cognitive functioning.[2–5] Whereas most research focuses on problems in children during treatment and long-term survivors (≥5 years after treatment), less research is available in children before this transition (post-cancer treatment). However, these children are especially vulnerable due to the discrepancy of finishing treatment but not yet making the transition to survivorship[6] and they experience unmet educational and psychosocial needs.[7]

Although the results are inconclusive,[8] children with cancer generally seem vulnerable to developing emotional problems such as depression and anxiety during different stages of and after treatment,[2,7] especially children treated for a pediatric brain tumor.[5] Furthermore, although fatigue seems to decrease over time,[9] some children treated for cancer still report higher levels of fatigue after treatment compared with peers.[4,10] In addition to emotional functioning and fatigue, there is also an increased focus on cognitive functioning in children treated for childhood cancer. Cognitive problems seem evident in children treated for a brain tumor,[3] and have also been described in other cancer diagnosis groups such as long-term survivors of children treated for a Wilms tumor.[11]

In addition to the extent of problems that children undergoing treatment for cancer experience, the relationship between these problems has also been studied previously.[10,12–15] For example, a review of Marusak et al.[16] described that stress seems to contribute to cognitive problems in children treated for a brain tumor. Significant correlations were also described between stress and fatigue in children during different stages of treatment and in survivors of childhood cancer.[10,14,17] Furthermore, previous research has found an effect of fatigue on cognitive functioning in children treated for cancer.[4,18] Given the amount of reported vulnerabilities regarding emotional functioning, fatigue, and cognitive functioning it is important to study the interplay between these factors to provide more insight into interventions to improve health-related quality of life in children post-cancer treatment. Understanding these underlying mechanisms is especially important because effective interventions to improve cognitive functioning appear to be scarce due to difficulties in generalizing outcomes of cognitive training to daily functioning.[19] It is therefore important to gain insight into the role of other determinants for cognitive interventions such as fatigue on the relationship between emotional and cognitive functioning.

Therefore, we aim (1) to investigate emotional functioning, fatigue, and cognitive functioning in children post-cancer treatment. We hypothesize that functioning in these domains will be significantly lower compared with general population peers; (2) to assess the relationship between emotional and cognitive functioning; and (3) to investigate if this relationship is mediated by fatigue. We hypothesize that the mediation effect can be different for children diagnosed with a central nervous system (CNS) tumor, or relapse of the primary tumor, since these specific groups show relatively more vulnerabilities.[20,21] Finally, we expect that sex, age, tumor type, relapse, and sleep can be confounders because different studies show the influence of these factors on emotional functioning, fatigue, and cognitive functioning.[4,22–25]

2 | METHODS

2.1 | Design

This study is part of the larger PROactive study[26] that investigated fatigue in children with a chronic disease, including children from the Wilhelmina Children's Hospital and the Princess Máxima Center for Pediatric Oncology (from September 2016 to December 2018). In the current study, we focused solely on participants from the Princess Máxima Center for Pediatric Oncology. The institutional review board classified this study as an exemption of the Medical Research Involving Human subjects Act (16-707/C). Participating children >11 years and their parents in those <16 years, provided informed consent for participation and to extract data from their medical record separately.

2.2 | Participants

Eligible participants were children who completed treatment for childhood cancer, referred to as "children post-cancer treatment," and were approached within 1 year after treatment. Children were excluded from the study in the following cases: (1) insufficient understanding of the Dutch language to complete the questionnaires and (2) relapse of the primary diagnosis during the study.

2.3 | Procedure

Three weeks before their regular appointment, patients and their parents were approached via email. They were asked to register at home through a web-based tool, the KLIK PROM portal (www.hetklikt.nu), to complete digital questionnaires. In case of no response, they were reminded once via email and once via telephone. A supportive team was available to answer questions and help with the registration. Children and adolescents aged 8–18 years completed the questionnaires by themselves. Parents could give assistance to children aged 8–11 if needed.

2.4 | Measures

We used subscales of the Dutch self-report version of the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales 4.0 (PedsQL GCS) and PedsQL Multidimensional Fatigue Scale (PedsQL MFS) to asses emotional functioning and fatigue. The subscales emotional functioning (five items, PedsQL GCS) and general fatigue (six items, PedsQL

MFS) were used. The PedsQL cognitive functioning scale (six items, PedsQL CFS) was used to asses cognitive functioning. The PedsQL CFS was used as a stand-alone scale in various pediatric populations and correlates sufficiently with cognitive testing.[27,28] Finally, we used the subscale sleep/rest fatigue (six items, PedsQL MFS) to assess sleep as a confounder. All questionnaires have good psychometric properties.[24,25,29,30] Items were scored with a one-week recall period on a 5-point Likert scale from 1 "never a problem" to 5 "almost always a problem." Subscale items were rescored to a scale from 0 to 100, with higher scores indicating better outcomes (higher emotional functioning and cognitive functioning, or less fatigue). We used the mean scores of the subscales for further analyses. Previous research on outcomes regarding the PedsQL questionnaires in general population peers was available to compare with our sample.[24,25]

2.5 | Sociodemographic and medical information

Diagnosis, type of treatment, relapse, time elapsed between diagnosis and time since end of treatment were extracted from medical records.

2.6 | Data analyses

SPSS, version 26 was used for all analyses, with the PROCESS macro v3. for mediation analyses.[31] To investigate the difference between participants and nonparticipants regarding age, we used a one sample *t*-test. Descriptive statistics were used to study the demographic and clinical variables of the group and the mean emotional functioning, fatigue, and cognitive functioning. To compare the level of emotional functioning, fatigue, and cognitive functioning of children post-cancer treatment with general population peers,[24,25] we used a one sample *t*-test. Mean general population scores and standard deviations were weighted by age and sex to match our sample. Differences were described using the mean difference and Cohen's *d*. We interpreted the effect sizes after Cohen in which 0.2, 0.5, and 0.8 were considered small, medium, and large.[32] The relationship between emotional functioning and cognitive functioning was assessed using linear regression analyses. Next, multiple regression analyses was used to investigate mediation analyses and evaluate if fatigue mediates the relationship between emotional functioning and cognitive functioning. Differences were described using standardized regression coefficients. Beta's of continuous variables of 0.1 were considered small, 0.3 medium, and 0.5 large. Explorative analyses were conducted to check the role of certain moderators (relapse of the primary tumor and the diagnosis of a CNS tumor), which are known factors to correlate with our outcomes.[20,21] We operationalized this analysis by comparing children with a diagnosis of a CNS tumor versus other diagnosis groups (solid tumor, lymphoma, leukemia). Confounding of relevant demographic and clinical variables was evaluated, and the final mediation model was adjusted for sex, age, relapse of the primary tumor, CNS tumor and sleep if a difference >10% in regression coefficients was found.

TABLE 1 Study cohort characteristics of children post-cancer treatment.

Filled out questionnaires (*N*)	137
Gender, *N* (%)	
Male	69 (50.4)
Female	68 (49.6)
Age at follow up, years	
Mean (SD)	13.6 (3.3)
Information of the child's medical record, *N*	130
Primary cancer diagnosis distribution, *N* (%)	
Solid tumor	46 (35.4)
CNS tumor	13 (10.0)
Leukemia	34 (26.2)
Lymphoma	37 (28.5)
Treatment, *N* (%)	
Surgery only	6 (4.6)
Surgery and radiotherapy	1 (0.8)
Surgery and chemotherapy	22 (16.9)
Surgery, radiotherapy, and chemotherapy	23 (17.7)
Chemotherapy only	64 (49.2)
Radiotherapy and chemotherapy	14 (10.8)
Relapse, *N* (%)	
Relapse tumor	12 (9.2)
Time since diagnosis, months	
Missing, *N*	12
Mean (SD)	19.3 (12.6)
Time since end of treatment, months	
Missing, *N*	6
Mean (SD)	7.1 (5.9)

N, number; SD, standard deviation; CNS, central nervous system tumor.

3 | RESULTS

Of 220 eligible children (children post-cancer treatment) a total of 137 (62.4%) provided informed consent and participated by filling out at least one of the questionnaires. There was no significant difference between participants and nonparticipants regarding age. The group with included children had a mean age of 13.6 years (SD ± 3.3) and consisted of 69 (50.4%) males and 68 (49.6%) females. Of these children, 130 (94.9%) additionally consented to extract information from their medical record. The mean time since diagnosis was 19.4 months (SD ± 12.6) and the mean time since end of treatment 7.1 months (SD ± 5.9). Forty six (35.4%) children were diagnosed with a solid tumor, 13 (10.0%) with a CNS tumor, 34 (26.2%) with leukemia and 37 (28.5%) with lymphoma. Table 1 summarizes the demographic and clinical characteristics of the participants. A total of 12 children (9.2%) had a relapse of the primary tumor. Regarding the type of treatment, the largest percentage of the group of children (49.2%) received only chemotherapy and the

TABLE 2 Results questionnaires comparing children post-cancer treatment with general population peers.

	N	Mean (SD)	*N* mean (SD)[b]	Effect size (mean difference)[c]	*p* Value
Self reports[a]					
Emotional functioning	136	72.0 (19.6)	966 79.4 (18.6)	0.4 (7.4)	<.001
Fatigue	132	67.7 (23.4)	298 78.7 (13.8)	0.8 (11.0)	<.001
Cognitive functioning	132	66.1 (25.6)	298 76.6 (16.7)	0.6 (10.0)	<.001

N, number; SD, standard deviation.

[a]Outcomes measured with subscales of the Dutch self-report version of the PedsQL Generic Core Scales 4.0 (PedsQL GCS) and Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS); subscales emotional functioning (PedsQL GCS), general fatigue (PedsQL MFS) and cognitive fatigue (PedsQL MFS).

[b]Peers from normative data on the PedsQL.[25]

[c]Effect sizes (Cohen's *d*).

others were treated with surgery, radiotherapy, and/or a combination of treatments.

3.1 | Outcomes on emotional functioning, fatigue, and cognitive functioning

Descriptive statistics of emotional functioning, fatigue, and cognitive functioning of children post-cancer treatment and general population peers are shown in Table 2. Children post-cancer treatment reported significantly ($p < .001$) lower scores on emotional functioning (Cohen's d [*D*]: 0.4 points), fatigue (*D*: 0.8 points), and cognitive functioning (*D*: 0.6 points) compared with general population peers. The effect sizes of the mean difference between children post-cancer treatment and general population peers on emotional functioning, fatigue, and cognitive functioning were considered medium, large, and medium.

3.2 | Association between emotional functioning and cognitive functioning and mediation by fatigue

Results of the unadjusted and adjusted mediation models are presented in Figure 1. The model was adjusted for sleep, as this was the only relevant confounder. Linear regression showed that there was a significant positive medium association between emotional functioning and cognitive functioning (regression coefficient total effect [95% CI]; 0.36 [0.17–0.55], $\beta = 0.27$, $p < .001$), which means that better emotional functioning is associated with better cognitive functioning. The mediation analysis showed a positive medium association between emotional functioning and fatigue (regression coefficient [95% CI]: 0.36 [0.22–0.49], $\beta = 0.30$, $p < .001$) and positive large association between fatigue and cognitive functioning (regression coefficient [95% CI]: 0.58 [0.36–0.80], $\beta = 0.53$, $p < .001$), this means higher levels of emotional functioning and cognitive functioning were related to less fatigue, which mediated the relationship between emotional functioning and cognitive functioning (indirect effect: regression coefficient [95% CI]: 0.21 [0.09–0.36], $\beta = 0.16$). No significant moderation effects were found between groups regarding relapse (children with relapse of the primary tumor or other) and CNS tumor (children with a CNS tumor or other).

4 | DISCUSSION

We examined emotional functioning, fatigue, and cognitive functioning and the interplay between these constructs in children post-cancer treatment. The results showed that children post-cancer treatment reported more problems on emotional functioning, fatigue, and cognitive functioning compared with general population peers. Emotional functioning and cognitive functioning had a medium association which was mediated by fatigue.

Our findings on emotional functioning and cognitive functioning in children post-cancer treatment are in line with previous research that described more emotional problems and lower cognitive functioning in children treated for cancer compared with the general population.[2,3,7,10,12,20] Because most research concerning cognitive functioning was described in childhood cancer survivors,[20,33] our results underscore the need to focus on cognitive functioning in children sooner after ending their treatment and in other cancer diagnosis groups in addition to children with a brain tumor, where cognitive problems seem more evident.[20] Regarding fatigue in children post-cancer treatment, results of previous research are ambiguous. Whereas some research described no significant differences compared with the general population,[9,34] other studies reported significantly more fatigue in children with cancer during and after treatment compared with the general population.[4] These differences in results between studies could be explained by methodological factors such as measurements at various time-points, differences in sample size and different measures regarding self-report versus proxy-report questionnaires.[35] Considering the literature overall and our results, children post-cancer treatment experience increased fatigue.

Our results showed associations between emotional functioning, fatigue, and cognitive functioning in children post-cancer treatment, which were previously found in subpopulations or different phases of cancer treatment. In the current study, we found a positive association between emotional functioning and cognitive functioning in children post-cancer treatment, which indicates that more emotional stress is related to more cognitive problems, as was previously described in children treated for a pediatric brain tumor.[14,16] Furthermore, the significant positive association between emotional functioning and fatigue found in our study is in line with previous research in

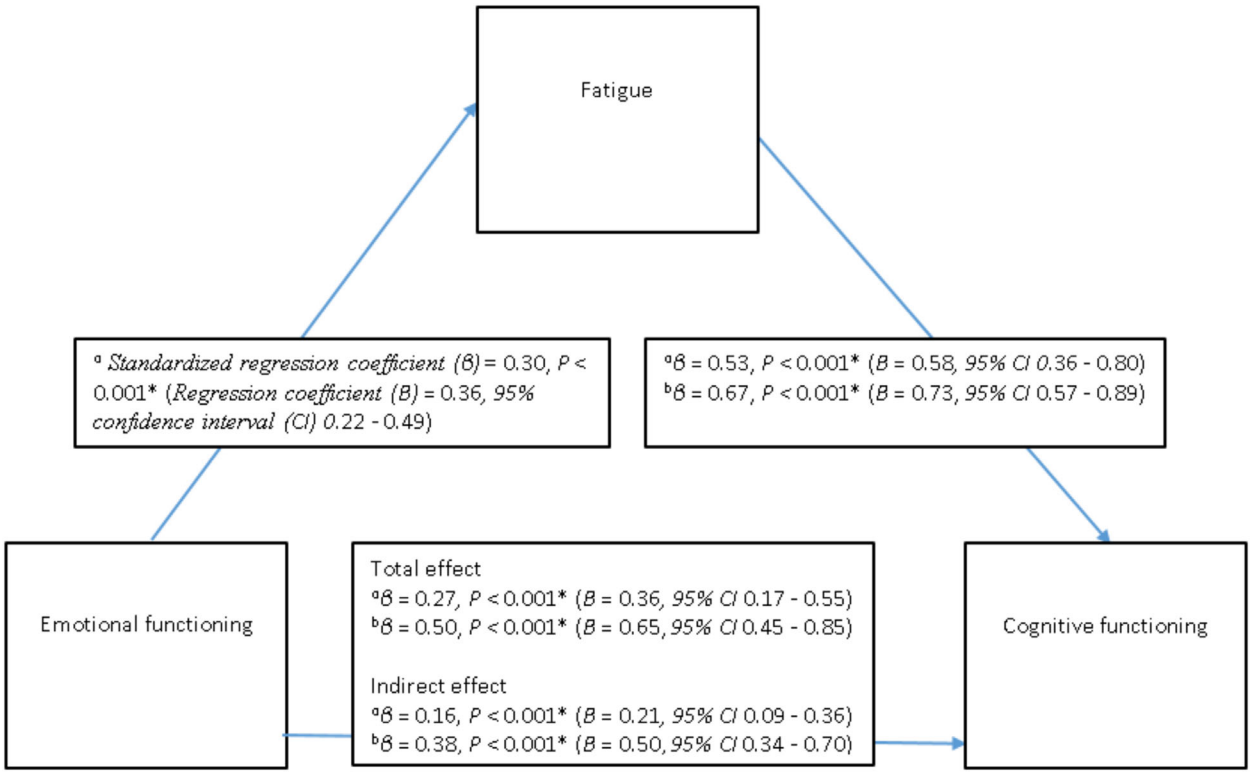

FIGURE 1 Results of the mediation model of emotional functioning, fatigue, and cognitive functioning in children post-cancer treatment. Linear regression showed a significant positive medium association between emotional functioning and cognitive functioning (regression coefficient total effect [95% CI]; 0.36 [0.17–0.55], $\beta = 0.27$, $p < .001$). Mediation analysis showed a positive medium association between emotional functioning and fatigue (regression coefficient [95% CI]: 0.36 [0.22–0.49], $\beta = 0.30$, $p < .001$) and positive large association between fatigue and cognitive functioning (regression coefficient [95% CI]: 0.58 [0.36–0.80], $\beta = 0.53$, $p < .001$), which mediated the relationship between emotional functioning and cognitive functioning (indirect effect: regression coefficient [95% CI]: 0.21 [0.09–0.36], $\beta = 0.16$). [a]Results of the adjusted model when sleep was added as a covariate. [b]Results of the unadjusted model. β, standardized regression coefficient; *B*, regression coefficient; CI, confidence interval.

hospitalized children with cancer[10] and in childhood cancer survivors.[17] The relationship we found between fatigue and cognitive functioning was already evident in childhood cancer survivors and especially in children treated for a brain tumor.[33] An important finding of our study that added to the existing knowledge is that fatigue mediated the relationship between emotional and cognitive functioning. The medium to large associations in our study between emotional functioning, fatigue, and cognitive functioning implicate that the interrelatedness of these factors are of practical significance. The small indirect effect of the mediation model suggests fatigue to be a target for treatment in clinical practice, amongst other factors. The fact that no significant differences were found between groups of moderation factors (relapse of the primary tumor and a diagnosis of a CNS tumor) might be explained by the small sample size of these specific groups in our study.

Based on our findings, we would like to emphasize the need for a broad perspective on cognitive functioning including fatigue in children post-cancer treatment. This is especially important because these children seem to be at risk of developing cognitive problems which can impede their development and effective interventions to improve cognitive functioning seem scarce.[19] Speculations on clinical interventions to improve cognitive functioning could include monitoring and treating fatigue, since we found fatigue to be a mediator on the association between emotional functioning and cognitive functioning. Also, the association between fatigue and cognitive functioning in our study was larger than that of emotional functioning on cognitive functioning which emphasizes this factor as an important determinant for interventions. Monitoring fatigue is in accordance with recent recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization group to implement lifelong screening for fatigue and current standards of care for children during treatment and survivors.[36–38] Concrete elements of interventions to reduce fatigue could be to include cognitive behavioral therapy, relaxation, mindfulness, and physical exercise, as previous research showed some positive effects in children with cancer.[9,38,39] Furthermore, monitoring the role of sleep in relation to fatigue seems to be an important element regarding interventions, since we found sleep to explain part of the associations when comparing our adjusted and unadjusted model. This approach is strengthened by previous research which showed positive associations between sleep and fatigue in childhood cancer survivors[4,18,22] and sleep problems can negatively impact psychosocial and physical health.[40,41] Finally, when taking an individualized approach to interventions in clinical practice, it is important to take all factors into account, but to focus relatively more on fatigue in relation to cognitive functioning.

A strength of this study was the broader understanding it provided in terms of relationships between emotional functioning, fatigue, and cognitive functioning in children post-cancer treatment. This is consistent with previous research that suggested to focus on multiple factors to understand cognitive functioning[14] and was also stressed in adults with a post-COVID 19 condition where correlates were found between neuropsychiatric symptoms, fatigue, and cognitive outcomes.[42] However, our study also contained several limitations that should be mentioned. First, we used self-report questionnaires only which may have given less objective outcomes than if measured with other tests. Although self-report questionnaires seem to give valid outcomes in children with cancer,[24] cognitive functioning especially could be more reliably measured by neuropsychological testing. Therefore, future research should include more (neuro)psychological tests in addition to self-report questionnaires to assess more objective results. Whereas it could be speculated to study emotional functioning by other questionnaires measuring anxiety and stress, we chose the subscale "emotional functioning" of the PedsQL Generic Core Scales to recognize vulnerabilities but not psychopathology as measured with other instruments.[43] Emotional problems in children treated for cancer could therefore be labeled as normal reactions to distressing circumstances such as the diagnosis with childhood cancer. Second, the group of children post-cancer treatment reflected a different ratio in diagnoses than reported in previous research.[44] Because we started the centralization of childhood cancer care in the Princess Máxima Center for children diagnosed with a solid tumor, our sample had relatively more children with a solid tumor. Additionally, the relative smaller number of children in our group with a diagnosis of a brain tumor[44] could be explained because these children could have experienced more difficulties filling out questionnaires due to cognitive problems[45] or due to severe visual and motor problems[46] This might have given an underrepresentation of the outcomes on cognitive functioning because children with a brain tumor experience the highest amount of cognitive problems in the pediatric oncology population.[20] Finally, the assessment of our study was at a single time-point and it is therefore difficult to state confident conclusions of the direction of the associations between emotional functioning, fatigue, and cognitive functioning. To unravel the various pathways between emotional functioning, fatigue, and cognitive functioning more longitudinal research is needed.

Children post-cancer treatment are more vulnerable regarding emotional functioning, fatigue, and cognitive functioning compared with general population peers. Fatigue mediates the relationship between emotional and cognitive functioning. In conclusion, our study emphasizes the need to focus on fatigue as an important determinant for cognitive interventions. Future interventions should therefore consider to systematically monitor and intervene on fatigue to improve cognitive functioning in children postcancer treatment.

AUTHOR CONTRIBUTIONS

All authors contributed to the study in which data collection was performed by Merel Nap-van der Vlist and supervised by Sanne Nijhof and Martha Grootenhuis. Data analysis and interpretation was performed by Juliette Greidanus, Marloes van Gorp and Martha Grootenhuis. The first draft of the manuscript was written by Juliette Greidanus and supervised by Marloes van Gorp and Martha Grootenhuis and all authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or nonfinancial interests to disclose.

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CONSENT TO PARTICIPATE

Informed consent was obtained from all participants included in the study >11 years of age. Informed consent was obtained from legal guardians of participants <16 years of age.

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