CHAPTER 5

Associations between Executive Function Deficits and Quality of Life in Very Long-Term Survivors of Pediatric Lymphoid Malignancies

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Submitted
Abstract

Objective: Quality of Life (QoL) and executive functions (EF) were investigated in a group of long-term survivors of childhood lymphoid malignancies who received central nervous system directed irradiation (CRT) and/or chemotherapy (CT). How QoL and EF relate to each other in this population is not well understood.

Methods: The Amsterdam Neuropsychological Tasks (ANT) program was used to assess EF in 38 CRT-treated survivors (26 years post-diagnosis), 43 CT-treated survivors (21 years post-diagnosis), and 47 controls. Self-reports of physical health (RAND-36), physical and mental fatigue (MFI-20), and cognitive failures (CFQ) were acquired and correlated with ANT measures that discriminated between survivors and controls.

Results: No associations were found between EF deficits measured with the ANT, and cognitive failures reported on the CFQ. However, several significant associations were found with domains of health-related QoL. General associations were found between worse executive visuomotor control and visuospatial sequential working memory, and worse physical functioning, more role limitations due to physical health (especially in CRT-treated and female survivors), and more physical and mental fatigue. Additionally, only in CRT-treated survivors, a significant association between decreased inhibition and worse physical functioning was found. The CT-treated group displayed an association between worse executive visuomotor control and decreased general health.

Conclusion: The outcomes of this study indicate that physicians should not rely solely on self-reports of cognitive failures such as the CFQ, but use objective assessment of EF in long-term follow-up of this population. Especially impaired executive visuomotor control and visuospatial sequential working memory capacity seem to have an impact on QoL, most saliently on role limitations due to physical
health. Physical aspects of QoL and EF deficits might also be affected by a common third, treatment-related, factor.
Introduction

Survival rates of children suffering from pediatric lymphoid malignancies such as acute lymphoblastic leukemia (ALL) have increased substantially over the last decades. As chances of survival approach 90% nowadays, long-term quality of life (QoL) is of imminent importance. However, QoL is compromised by late effects of treatment. Treatment protocols, taking 2-3 years, are intense and toxic overall, and can cause all kinds of long-term chronic health conditions, such as cardiovascular or endocrine dysfunction.\textsuperscript{1,2} Especially the parts of the treatment protocols aimed at eliminating cancer cells hiding in the central nervous system (CNS), consisting of cranial radiation therapy (CRT) and/or intrathecal chemotherapy (CT), are associated with considerable detrimental effects to healthy brain tissue, resulting in neurocognitive sequelae.\textsuperscript{3} Both types of CNS prophylaxis have also been associated with reduced health-related (HR) QoL.\textsuperscript{4} It is, however, unclear whether cognitive deficiencies play a role in this decreased QoL.

Studies of the association between neurocognitive functioning and QoL in adult survivors of pediatric diseases are scarce and the impact of neurocognitive sequelae on QoL is poorly understood. Against expectations, significant associations between subjective and objective neurocognitive function are often not encountered. For example, in a study by Wolters et al. (2015) in adults with acquired brain injury and neuropsychiatric symptoms, performance on traditional executive functioning tests (e.g. the Stroop Colour Word Test and the Trail Making Test), did not correlate with self-report measures of executive functioning (EF) measured by the Life Satisfaction Questionnaire.\textsuperscript{5} They argued that traditional EF tests might not grasp the complexity of EF in daily life, and therefore correlated poorly with self-reported EF difficulties. Several studies in survivors of childhood cancer have reported a similar discrepancy. Krull et al. (2013) reported that direct assessment of EF yielded higher rates of impairment than self-reports from
survivors. They suggested this could indicate some sort of adaptation in very-long-term survivors, or lacking insight into the presence and impact of their cognitive problems. The discrepancy has also been reported in populations with diabetes, chronic sleep restriction, and phenylketonuria (PKU).\textsuperscript{6-8} In a normally aging population, the developers of the Cognitive Failures Questionnaire (CFQ), Ponds et al. (1998), reported absent or modest correlations with compound scores of memory (including some aspects of EF) and cognitive speed.\textsuperscript{9} However, direct associations with EF were not specifically tested. Using compound scores as a strategy to reduce data is often applied by research groups, but in our opinion hinders the differentiation between cognitive deficits that affect QoL and ones that do not. We were not able to find studies of associations between objective and specific measures of EF, and self-reported EF in the population of very-long-term survivors. Potentially, the CFQ could be a useful screening tool, if it would be able to identify those at risk of late cognitive sequelae. Therefore, it is worthwhile to investigate whether it correlates with EF if very specific aspects of EF are assessed. Deprez et al. (2011) demonstrated that the CFQ correlated significantly with measures of white matter integrity in frontal and parietal areas in breast cancer patients, which are also objective and specific.\textsuperscript{10} We wanted to find out whether detailed EF deficits, objectively established by the computerized Amsterdam Neuropsychological Tasks (ANT), would correlate with the CFQ in a population of long-term survivors of pediatric lymphoid malignancies. The current paper is the first to study this association. For comparison, the association will also be studied in controls.

Concurrently, we will study correlations between EF and other (health related) QoL measures. Several findings by other study groups suggest that neuropsychological deficiencies correlate with other aspects of QoL. Harder et al. (2002) reported on neurocognitive effects and QoL in long-term adult survivors of bone marrow transplantation, for which total body irradiation is required, frequently preceded
by treatment with intrathecal CT. They found that a composite score of objectively established cognitive impairment correlated highly with fatigue, and with several functional scales of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, i.e. the physical function, cognitive function, social function and symptom fatigue scales. In a younger population of survivors of ALL (aged 7-17, nine years post-diagnosis), Kunin-Batson et al. (2014) reported on the impact of neurocognitive difficulties on QoL. They found that perceptual reasoning was associated with lower physical QoL (p = .001), and, although not significant, with visual-motor skills (p = .062) and attention variability (p = .062). These studies illustrate that effects of neurocognitive deficits on types of QoL other than subjective cognitive functioning, i.e. physical/health related QoL, might be relevant and these associations need to be better understood.

The cohort currently under study was assessed with the ANT (see Schuitema et al. (2015) regarding the outcomes in CRT-treated survivors (Chapter 2) and Schuitema et al. (2016a) regarding CT-treated survivors (Chapter 3)), and was asked to fill out four questionnaires on health related QoL, i.e. the RAND-36, POMS, MFI-20, and CFQ (see Schuitema et al., 2016b (Chapter 4)). CRT-treated survivors were shown to perform worse than controls on baseline motor speed, (visuospatial and sequential) working memory, sustained attention, executive visuomotor control, inhibition, and cognitive flexibility. Nonetheless, they did not report more cognitive failures in daily life than controls. CRT-treated survivors reported worse physical functioning and general health, more role limitations due to physical health, and more (physical and mental) fatigue. The CT-treated survivors performed worse than controls only on executive visuomotor control. Like CRT-treated survivors, they did not report more cognitive failures than controls. However, they also reported more mental fatigue than controls. The current paper will focus on the associations between the neuropsychological deficiencies and domains of QoL mentioned above.
Additionally, a marked difference between male and female survivors, both on the neuropsychological performance and on the QoL measures, was encountered in this cohort. Female survivors demonstrated a deficit in executive visuomotor control more frequently than controls and male survivors.\textsuperscript{14,15} They also reported relatively more role limitations due to physical health, worse physical functioning, and worse general health.\textsuperscript{16} Therefore, associations between these QoL scales and diminished executive control are also studied specifically amongst female survivors.

Several treatment and patient factors have been reported to influence late effects. Dose effects of CT and CRT have been described, just as increasing impairment with time passed since treatment and younger age at diagnosis (AaD).\textsuperscript{17-19} As mentioned before, female gender is also of influence.\textsuperscript{20} Therefore, these factors will be controlled for in the correlation analyses.

Summarized, we seek to 1) study the convergent validity of the CFQ by associating subjective cognitive complaints reported on the CFQ with objective EF deficits measured by the ANT in very long-term survivors of childhood lymphoid malignancies, and 2) to identify associations between EF dysfunctions measured by the ANT and health related QoL in the domains of physical health and fatigue. For comparison, these associations are studied in controls as well.

**Methods**

**Participants**

QoL questionnaire data and neuropsychological assessments were analyzed of 43 CT-treated survivors, 38 CRT-treated survivors and 47 controls. The cohort was identified from records of the VU University Medical Center, the Academic Medical Center Amsterdam (The Netherlands) and the University Hospitals Leuven.
(Belgium). Participating survivors were asked to bring along a sibling, spouse or close friend as a control. The ethical principles of the Helsinki Declaration were followed and approval was obtained from the ethical committees of all participating centers. Survivors were considered eligible if they were diagnosed after 1978 and at least 18 years post-diagnosis. Survivors and controls were not included if they reported use of psychotropic medication, neurological or psychiatric diagnoses, pregnancy, or color-blindness. They also needed to master the Dutch language.

The analyzed sample is the same as the one analyzed in Schuitema et al., 2016b.\textsuperscript{16} Details about the treatment protocols can be found there. In short, 27 standard-risk CT-treated patients were included. They were treated according to the Dutch Childhood Leukemia Study Group (DCLSG) protocol ALL-6. Furthermore, 16 high-risk CT-treated patients were included in this study. They were treated with customized protocols based on either EORTC Trial 58832, the BACOP protocol, or ALL-6, all without CRT.\textsuperscript{21}

Furthermore, 22 standard-risk CRT-treated survivors, five high-risk CRT-treated survivors, and 11 survivors treated for relapse were included. These survivors were treated according to Berlin-Frankfurt-Münster (BFM)-based protocols.\textsuperscript{22} Standard-risk patients were treated according to DCLSG protocol ALL-5 or the Riehm protocol.\textsuperscript{22} High-risk patients were treated with additional customized intravenous (IV) high-dose methotrexate (MTX). As IV and intrathecal (IT) MTX doses varied greatly in the high-risk groups, dose was analyzed as a continuous variable (covariate) instead of two risk categories.

**Neuropsychological Assessment**

The Amsterdam Neuropsychological Tasks (ANT) program was used to assess EF.\textsuperscript{23} The program manipulates task load to examine whether increased demands on complexity of information processing, working memory, executive visuomotor
control, inhibition, and cognitive flexibility differentiate survivors from controls in terms of speed and accuracy.

The procedure of administration and details about the subtasks are provided in Schuitema et al., 2016a.\textsuperscript{15} The subtasks used here are the subtasks that discriminated between survivors and controls, i.e. Baseline Speed (measuring simple response speed, alertness), Memory Search Objects 2D (measuring working memory speed and accuracy), Sustained Attention Dots (measuring work pace and attentional fluctuations), Set Shifting Visual (measuring inhibition and cognitive flexibility), Tracking & Pursuit (measuring executive visuomotor control), and Visuospatial Sequencing (measuring visuospatial sequential working memory).

**Measurements of Health Related QoL**

Only questionnaires that discriminated between survivors and controls were deployed (described below). More elaborate descriptions of these instruments can be found in Schuitema et al., 2016b.\textsuperscript{16}

The RAND 36-Item Health Survey is a self-report measure tapping on eight health scales (n items) with reference to the past four weeks: physical functioning (10), bodily pain (2), role limitations due to physical problems (4), role limitations due to personal or emotional problems (3), emotional well-being (5), social functioning (2), energy/fatigue (4), and general health perceptions (5)\textsuperscript{24,25}. A high score represents a more favorable health evaluation.

The Multidimensional Fatigue Inventory (MFI-20) is a 20-item self-report instrument designed to measure fatigue in cancer patients. It consists of five subscales (4 items each): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. On a 7-point scale, respondents indicate to what extent a particular statement applied to them at that moment. Higher scores represent higher levels of fatigue.
The *Cognitive Failure Questionnaire* (CFQ) assesses the frequency of experienced failures in perception, memory, and motor function in everyday life.\(^{26}\) We used the Dutch translation of the CFQ\(^ {27,28}\). The CFQ consists of 25 items, of which 17 create the following four subscales (n items): Distractibility (7), Distractibility in Social Situations (4), Names and Words (3) and Orientation (3). Respondents indicated how often a particular ‘failure’ has happened to them in the past 6 months on a scale from very often (4) to never (0). Higher scores indicate more frequent failures.

*Statistical analyses*

Measures of cognition that survivors performed significantly worse on than controls, (i.e. baseline speed, working memory errors, work pace during sustained attention, attentional fluctuations, executive visuomotor control, inhibition, cognitive flexibility, and visuospatial sequential working memory (see Schuitema et al., 2015\(^ {14}\) and Schuitema et al., 2016a\(^ {15}\))), were correlated with QoL domains that discriminated between survivors and controls, i.e. physical functioning, role limitations due to physical health, energy/fatigue, general health, physical fatigue, and mental fatigue (see Schuitema et al., 2016b\(^ {16}\)), and additionally with the subscales of the CFQ.

SPSS (version 23; SPSS Inc., Chicago, IL) was used for statistical analyses. Because of differences in mean age, age at assessment (AaA) was controlled for where possible. Two-sided \(p\)-values < .05 were regarded as significant.

Non-parametric tests should be used because of the ordinal nature of the QoL variables. As SPSS does not readily provide a method for calculating partial non-parametric correlations, we first used Pearson’s correlations to explore all correlation coefficients between QoL and ANT variables simultaneously, controlling for AaA and gender. We first did this for the overall sample, then separately within controls, CRT-treated survivors, and CT-treated survivors.
Subsequently, we used syntax to recalculate individual significant Pearson’s correlation coefficients ($p \leq .05$) using Spearman’s partial rank correlations, controlling for AaA and gender, and where applicable for AaD, MTX IT, MTX IV, and dose of CRT. The /MATRIX OUT subcommand in the NONPAR CORR procedure was used to save a matrix of Spearman’s rho correlations as the current data set. The PARTIAL CORR procedure can read this matrix as the input data by using the /MATRIX IN subcommand.\textsuperscript{29} Spearman’s partial rank correlation coefficients with a $p$-value $\leq .05$ were regarded as significant.

**Results**

Descriptives of the groups are reported in Table 1. The groups differed significantly from each other in AaA ($F(2,125) = 11.7, p < .001$, see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the participating groups</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>QoL data available (%)</td>
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<tr>
<td>Males, $N$ (%)</td>
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<tr>
<td>Age at Assessment, years, $M$ (SD)</td>
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<td>Age at Diagnosis, years, $M$ (SD)</td>
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<td>Time since Diagnosis, years, $M$ (SD)</td>
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<td>Cumulative dose CRT, Gy, $M$ (SD)</td>
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<td>Cumulative dose MTX IV, mg/m$^2$, $M$ (SD)</td>
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<td>Cumulative dose MTX IT, mg, $M$ (SD)</td>
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<tr>
<td>Estimated IQ, $M$ (SD)</td>
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<td>Employed, $N$ (%)</td>
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*Note. $N =$ number; $M =$ mean; $SD =$ standard deviation; MTX $=$ methotrexate; IV $=$ intravenous; IT $=$ intrathecal; ($m$)$g =$ (milli)gram; $m^2 =$ square meter (of body surface); N/A $=$ not applicable*
Looking at each group separately following the same steps, we found a significant correlation amongst controls, controlling for AaA and gender, between Visuospatial Sequential Working Memory and Mental Fatigue (rho = -0.333, p = .025). In the CT-treated group, controlling for AaA, AaD, gender, dose of MTX IT and dose of MTX IV, there were significant associations between Executive Visuomotor Control and Energy/Fatigue (rho = -0.346, p = .027), Physical Fatigue (rho = 0.386, p = .013), and General Health (rho = -0.311, p = .048). In the CRT-treated group, controlling for AaA, AaD, gender, dose of CRT, and dose of MTX IT, we found significant associations between Executive Visuomotor Control and Physical Functioning (rho = -0.479, p = .003), Executive Visuomotor Control and Role Limitations due to Physical Health (rho = -0.417, p = .011), and between Inhibition and Physical Functioning (rho = -0.342, p = .041).

As Executive Visuomotor Control and Physical Functioning, Role Limitations due to Physical Health, and General Health discriminated significantly between male and

<table>
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<tr>
<th>Physical Functioning†, rho (p)</th>
<th>-0.239 (.007)</th>
<th>0.220 (.014)</th>
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<tbody>
<tr>
<td>Role Limitations due to Physical Health†, rho (p)</td>
<td>-0.267 (.003)</td>
<td>0.168 (.061)</td>
</tr>
<tr>
<td>Energy/Fatigue†, rho (p)</td>
<td>-0.264 (.003)</td>
<td></td>
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<tr>
<td>Physical Fatigue‡, rho (p)</td>
<td>0.234 (.008)</td>
<td></td>
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<tr>
<td>Mental Fatigue‡, rho (p)</td>
<td>0.213 (.016)</td>
<td>-0.238 (.007)</td>
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</tbody>
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† = a higher score represents a more favorable evaluation; ‡ = a higher score represents a less favorable outcome; **bold** = significant at p ≤ .05
female survivors, these outcomes were correlated in all female survivors (CT-treated and CRT-treated), controlling for AaA, AaD, and dose of MTX IT. The partial Spearman correlation between Executive Visuomotor Control and Physical Functioning was not significant (rho = -.308, p = .098). The partial correlation between Executive Visuomotor Control and Role Limitations due to Physical Health was highly significant (rho = -.597, p < .0001). The partial correlation between Executive Visuomotor Control and General Health was not significant (rho = -.283, p = .129). We did not find any significant correlations between CFQ scales and ANT variables within any of the (partial or total) participant groups.

**Discussion**

In this cohort of survivors of childhood lymphoid malignancies, treated with either CT alone, or a combination of CT and CRT, and a group of healthy controls, no associations were found between aspects of EF that discriminated between survivors and controls, objectively established with the ANT, and cognitive failures reported on the CFQ. However, several significant associations were found between domains of health-related QoL and EF measured by the ANT. Amongst the entire group of participants, significant associations were found between worse executive visuomotor control and worse physical functioning, more role limitations due to physical health (attributable to the group of CRT-treated survivors), less energy, more physical fatigue (attributable to the CT-treated survivors), and more mental fatigue. Furthermore, smaller visuospatial sequential working memory capacity was associated with worse physical functioning and more mental fatigue (mostly attributable to controls). Additionally, only in the CRT-treated group, a significant association between decreased inhibition and worse physical functioning was found. The CT-treated group displayed an association between worse executive visuomotor control and decreased general health. In the subgroup
of female survivors, both CT-treated and CRT-treated, we discovered that worse executive visuomotor control was associated with more role limitations due to physical health.

We could not find a relation between subjective cognitive complaints measured by the CFQ and objectively established cognitive deficiencies measured by the ANT. These outcomes are in line with a study by Liemburg et al. (2015) on the usefulness of the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) in identifying EF deficits in adults with phenylketonuria identified by the ANT. No correlations between the BRIEF and the ANT were found either. A possible explanation might be that adults with EF deficits have difficulty monitoring their own performance in general. In survivors of childhood cancer, the most common explanation is that they have no record of their level of premorbid cognitive functioning to compare their current functioning with, resulting in a lack of insight, and that they are accustomed to their limitations. Although this might be plausible for other types of psychosocial distress, the current study shows that there is no significant association between subjective and objective EF measures in the control group either. This suggests that the CFQ is not a sensitive instrument for cognitive deficiencies which can be objectively detected with computerized neuropsychological batteries like the ANT program. Ponds et al. reported absent or modest correlations between the CFQ and memory scores and cognitive speed. Notably, instead, they found large correlations with subjective health, distress, and worry about dementia. Kenzik et al. (2015) describe it as neurocognitive distress. Toplak et al. (2015) theorize that objective assessments and self-ratings measure two different constructs. Hypothetically, the objective tests assess the processing efficiency of EF, while self-ratings assess the extent to which goals are achieved, hence efficacy. The word ‘failures’ in the name of the CFQ already implies occurrence of not reaching a goal. New measures targeted at subjective experience of decreased cognitive efficiency are therefore desired.
Looking at CT-treated and CRT-treated female survivors together, our study showed an association between executive visuomotor control and role limitations due to physical health. This association was also significant within the overall sample. A similar association has been observed in multiple sclerosis patients with mild levels of disability including mild (covert) balance impairment.\textsuperscript{34} Postural control demands compensating cognitive strategies (attentional resources) in this population.\textsuperscript{35} Experiments have demonstrated that cognitive-motor interference is higher than in controls when a cognitive task needs to be performed during postural control, in magnitude expressed as dual-task cost.\textsuperscript{36,37} Castelli et al. (2016) hypothesized that dual-task cost would have an impact on QoL.\textsuperscript{34} They asked patients to perform both quiet standing and dual task balance trials, where they needed to perform the Stroop color-word test while undergoing a static posturography on a grade force platform. They were instructed to prioritize the Stroop task. It was demonstrated that balance deteriorated when concurrently the task was performed, and that higher dual-task cost was significantly associated with more role limitations due to physical health. Just like our measure of executive visuomotor control, the dual-task required continuous and intense monitoring (executive control) in the visuomotor domain\textsuperscript{35}, which supports the association we observed. Leone et al. (2015) stated that tasks that require both motor and cognitive resources reflect real-life performance better than tasks assessing these aspects individually.\textsuperscript{38} Think e.g. of walking while attending to a conversation. Zooming in on the questions concerning role limitations due to physical problems, we see that survivors were asked about limitations in time or accomplishment in both general daily activity and work, and whether these activities took extra effort. It is plausible that reduced executive visuomotor control reduces efficiency in daily activities, because switch cost is higher, resulting in an increase of the time and effort needed to accomplish the task. This could also explain the significant association between executive visuomotor control and
mental fatigue observed in the entire sample, a notion supported by Lorist et al. (2005). It seems like these QoL domains pinpoint how reduced efficiency of EF is experienced in daily life.

Visuospatial sequential working memory capacity was also significantly associated with mental fatigue in the overall sample. Mental fatigue is a complaint from both CRT-treated and CT-treated survivors. The concept of mental fatigue is intended to represent fatigue in the cognitive domain. In our sample, this construct was associated with executive visuomotor control and visuospatial sequential working memory. It is conceivable that these deficits create the need to put in more mental effort, and therefore cause mental fatigue. Additionally, a dopaminergic route involving the anterior cingulate cortex has been identified supporting these associations. However, it is questionable whether subjectively perceived mental fatigue can be adequately assessed with just four questions, which is why the results of the current study should be regarded as a suggestion for further, more differentiated research into the relationship between mental fatigue and neuropsychological deficiencies.

In CRT-treated survivors, reduced inhibition was associated with worse physical functioning. In both survivor groups, worse executive visuomotor control was also associated with worse physical functioning and related domains such as physical fatigue, energy/fatigue, and general/physical health. Theoretically, there might be a third factor as a common denominator: treatment factors that caused more physical damage, leading to less energy, more physical fatigue, and reduced physical functioning, could also have caused worse function in executive control and inhibition. As we could not incorporate information on the actual physical status of our participants, no conclusions can be drawn here.
Methodological considerations

A strength of this study was the use of an adequate control group, including siblings, spouses, and friends of the survivors. Presumably, this strategy helped to control for potential differences in socio-economic status. Another strength was that isolated aspects of EF were studied here, instead of composite cognitive scores covering various domains. Furthermore, it must be kept in mind that this was a cross-sectional study, and correlations do not prove causal relations. Therefore, the results need to be interpreted with some caution.

Conclusion

The outcomes of this study indicate that physicians should not rely solely on self-reports of cognitive failures such as the CFQ, but use objective assessment of EF that gives insight into EF efficiency, in long-term follow-up of survivors of pediatric lymphoid malignancies. EF deficits measured by the ANT were associated with role limitations due to physical health, especially in CRT-treated and female survivors. Hypothetically, this domain is a more reliable indicator of EF efficiency in daily life. Especially impaired executive visuomotor control and visuospatial sequential working memory capacity seem to have an impact on QoL.
References


