Université de Montréal

How does Fatigue Contribute to Cognitive Dysfunction in Childhood Acute Lymphoblastic Leukemia Survivors

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Résumé

Introduction : Les survivants traités pour une leucémie lymphoblastique aigüe (LLA) dans l'enfance souffrent à la fois de difficultés neurocognitives et de fatigue en raison des traitements et du cancer. Si des arguments plaident pour une exacerbation de certains déficits neurocognitifs par la fatigue, les associations entre les deux domaines ne sont pas bien comprises. **Objectifs** : La présente étude vise à (1) décrire les difficultés neurocognitives et la fatigue dans une cohorte bien caractérisée de survivants à long terme de la LLA et (2) explorer la contribution de la fatigue auto-rapportée aux difficultés neurocognitives objectives typiquement étudiées dans cette population. **Méthode** : Les survivants de la LLA pédiatrique (N = 285) de la cohorte PETALE PSY-ALL ont complété la batterie de tests cognitifs DIVERGT, le Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) et le Distress Thermometer (DT). Nous avons mené des analyses fréquentielles et de comparaisons pour les facteurs d'intérêt, puis réalisé des modèles de régression multiple pour évaluer le poids relatif de la fatigue dans l'explication des différents déficits cognitifs au-delà des facteurs de risque connus (âge, sexe, statut de risque de la LLA et détresse émotionnelle). **Résultats** : Les difficultés cognitives (une échelle de DIVERGT < 1,5 SD) sont survenues chez 66% des participants. Les fonctions les plus affectées étaient la fluence verbale, la mémoire de travail et la motricité fine. Les participants avaient des niveaux normaux de fatigue sauf pour la sous-échelle Sleep/rest fatigue montrant une fatigue de 7% plus élevée chez ceux de moins de 18 ans que dans un échantillon de comparaison pour la même tranche d'âge. Cette sous-échelle était associée à la mémoire de travail (Digit Span total, $r = 0{,}117$; $p = 0{,}049$). La fatigue n'a pas permis d'expliquer le dysfonctionnement neurocognitif au-delà des facteurs de risque connus en lien avec l'histoire clinique. **Conclusions** : Les survivants de la LLA pédiatrique présentent de nombreuses difficultés cognitives, sans compter qu'ils éprouvent une fatigue importante due à des problèmes de sommeil et/ou de repos. La contribution de la fatigue au dysfonctionnement neurocognitif est plus faible que prévu, ce qui peut être dû aux spécificités des dysfonctionnements cognitifs dans cette population, à l'impact des processus de normalisation sur la mesure de la fatigue ou à la faible sensibilité de nos mesures de la fatigue.

Mots-clés : cancer, fatigue, leucémie lymphoblastique aigüe pédiatrique, neurocognitif, oncologie, survivants.

Abstract

Objectives: The present study aims to (1) describe neurocognitive difficulties and fatigue in a well-characterized cohort of long-term acute lymphoblastic leukemia (ALL) survivors and (2) explore the contribution of self-reported fatigue to objective neurocognitive difficulties typically studied in this population. **Method**: Pediatric ALL survivors (N = 285) from the PETALE PSY-ALL cohort completed the DIVERGT battery of cognitive tests, the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) and the Distress Thermometer (DT). We conducted frequency and comparison analyses for factors of interest. We performed multiple regression models to assess the contribution of fatigue in explaining cognitive deficits beyond known risk factors (age, age at diagnosis, sex, ALL risk status, emotional distress). **Results**: At least one cognitive difficulty (one DIVERGT scale <1.5 SD) occurred in 66% of participants. Domains primarily affected were verbal fluency, working memory and fine motor skills. Participants had normal levels of fatigue except for the subscale Sleep/rest fatigue showing 7% higher fatigue in those <18 years than in comparison samples across ages. Sleep/rest fatigue was associated with working memory (Digit Span Total score, $r = 0.117$; $p = 0.049$). Fatigue did not explain neurocognitive dysfunction beyond known risk factors from the clinical history. **Conclusions**: Pediatric ALL survivors have many cognitive difficulties and experience fatigue due to sleep/rest issues. The contribution of fatigue to cognitive dysfunction is lower than expected, which may be due to specificities of cognitive dysfunctions, the impact of normalization processes on the measure of fatigue or the lack of sensibility of our fatigue measure.

Keywords: cancer, fatigue, neurocognitive, oncology, pediatric acute lymphoblastic leukemia, survivors.

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ALL: Acute Lymphoblastic Leukemia

DFCI: Dana Farber Cancer Institute

DS: Digit Span

DT: Distress Thermometer

D-KEFS: Delis-Kaplan Executive Function System

GP: Klove-Matthew-Grooved Pegboard

- GPd: Grooved Pegboard dominant hand

- GPnd: Grooved Pegboard non dominant hand

IQ: Intelligence quotient

MCH: McMaster Children's Hospital

PedsQL MFS: Pediatric Quality of Life Inventory Multidimensional Fatigue Scale

QUHC: Quebec University Health Centre

SJUHC: Sainte-Justine University Health Centre

TMT: Trail Making Test

- TMT1: Trail Making Test condition 1

- TMT2: Trail Making Test condition 2

- TMT3: Trail Making Test condition 3

- TMT4: Trail Making Test condition 4

VF: Verbal Fluency

- VF1: Verbal Fluency condition 1

- VF2: Verbal Fluency condition 2

- VF3: Verbal Fluency condition 3

WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition

WISC-IV: Wechsler Intelligence Scale for Children – Fourth Edition

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Introduction

L'article empirique découlant de cette étude est présenté dans les prochaines pages du présent document. Il sera soumis à la Revue *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer* sous forme de Original Paper à l'hiver 2022. Il comprend une mise en contexte, permettant de mieux comprendre les objectifs de la recherche, qui est suivie par la méthodologie, les résultats, la discussion et les conclusions.

Article

How does Fatigue Contribute to Cognitive Dysfunction in Childhood Acute Lymphoblastic Leukemia Survivors

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Background

Scientific advances in the treatment of childhood acute lymphoblastic leukemia (ALL) have helped achieve a five-year survival rate of more than 90%[1, 2]. Current treatments based on a better scaling of treatments according to the ALL risk status which depends on biological aspects of the disease, use of chemotherapy-focused treatment protocols, and optimized supportive care[3, 4]. However, treatments for ALL remain neurotoxic, and they are associated with a wide array of multiple long-term effects interfering with brain development of children[5].

Neuroanatomical brain alterations have primarily been described especially on white matter, but also on gray matter. In 80% of survivors, chronic deep white matter lesions have been observed and identified as signs of leukoencephalopathy[6]. Exposure to chemotherapy agents, such as methotrexate, has been associated with markers of demyelination and neuronal and axonal damage[7]. Studies have found that the volume of white matter was reduced by 6% and that of gray matter by 5% in ALL survivors, compared to healthy controls[8, 9]. This observation was even clearer in the long-term.

These alterations result in various cognitive deficits, even in those who have received recent treatment protocol deemed to be less toxic: approximately 50% of young people in remission from ALL have clinically significant deficits[10, 11]. The cognitive domains that appear most impacted have been executive function, working memory, attention and information processing speed[6, 12, 13]. Some studies also reported impairment of fine motor skills as well as memory[14-16]. Ultimately, these impairments seem to translate into the intelligence level, ALL long-term survivors having an intelligence quotient (IQ) 6 to 8 points below healthy controls[16].

ALL has also been associated with significant and persistent fatigue. It is a central issue for patients, with vitality and fatigue problems being systematically associated with a lower quality of life[17, 18]. This fatigue is thought to be caused by dysregulation of the immune system and neurotransmission, impairment of nerve conduction and depletion of energy resources[19]. However, studies do not agree on the frequency and importance of the phenomenon in ALL survivors compared to the normative population, with rates varying 22-30% compared to 8-45% in normative groups[20-22].

Both cognitive deficits and fatigue have been related with several pre-existing factors including a female sex, younger age at diagnosis, and higher intensity treatments[12, 23, 24]. Yet, these factors have only explained a small to moderate variability of cognitive functioning[12]. Given the high frequency of cognitive deficits, it is essential to identify other explanatory factors, in view of identifying new targets for intervention with survivors.

There are several ways to consider fatigue as a possible contributing factor to cognitive functioning. First, fatigue could be caused by biological mechanisms intricated with those of cognitive functioning[25]. Second, as was shown in normal populations, fatigue is likely to intensify how cognitive difficulties present themselves[26]. This general observation is consistent with studies in pediatric cancer survivors indicating that individuals reporting higher levels of fatigue also show more deficits in executive functions, attention, and information processing speed[21, 25, 27]. Yet, this link appears to be moderated by sex, with sensitivity of cognitive performance to fatigue levels being higher in male or female survivors depending on the cognitive function[25].

Considering the increased survival rate of pediatric ALL and the large proportion of survivors with cognitive long-term effects, it is important to identify new contributing factors of these effects especially if they are amenable to change, as is fatigue[28]. This is especially true in the context of childhood cancer as the young individuals suffer from these effects differently and for much longer than the adult cancer population[29, 30]. Their developing brain is more vulnerable due to its greater metabolic activity and lower stability of newly synthesized myelin[3].

The first objective of the present study is therefore to describe the neurocognitive difficulties objectively measured and the fatigue reported subjectively by survivors of childhood ALL. The second objective is to assess the contribution of fatigue to each of the domains of neurocognitive difficulties. If this contribution is significant, we wish to compare it across cognitive domains, and identify whether fatigue could explain the variability of cognitive functioning beyond known risk factors (sex, age, age at diagnosis, ALL risk status (standard or high)). A control for psychological distress is also add because of its correlation with fatigue[31].

Methods

Participants

The sample was composed of individuals who had been successfully treated for ALL at the Sainte-Justine University Health Centre (SJUHC), Quebec University Health Centre (QUHC), and Hamilton's McMaster Children's Hospital (MCH). A detailed description of the methodology for cohort recruitment and characterization is available in another report[32]. The inclusion criteria were: 1) diagnosis of ALL prior 19 years, 2) treatment per Dana Farber Cancer Institute (DFCI) protocol, 3) more than 5 years post diagnosis and 4) no relapse or transplantation. Participants also needed to speak either French or English[17, 32].

A total of 545 survivors were contacted to participate in this study (Figure 1). The final sample of the current study consists of 285 ALL survivors (146 or 51% female sex, age 21 ± 7 years, 90% Caucasian), for whom both cognitive tests and self-reported questionnaires were available. Of these survivors, 223 were treated at the SJUHC, 45 at the QUHC and 17 at the MCH (Table 1). When comparing the group with full available data (N = 285) and those with incomplete data (N = 70), we found the study group to include more French-speaking participants ($p < 0.001$), which reflected that missing values came predominantly (41%) from one English-speaking site (MCH Ontario).

Procedure

The data were collected as part of a research project describing the long-term effects of the ALL on survivors and their families. The study protocol was approved by the Research Ethics Board at all sites (SJUHC: #2013-479; QUHC: #MP-20-2015-2176; MCH: #0304). Patients were contacted by phone by a research nurse who told them about the study. They subsequently gave their informed written consent by reading and signing a consent form they received by mail. On site, participants took part in a short neuropsychological assessment (cognitive tests: 30 minutes) followed by self-reported cognitive and affective questionnaires (45 minutes). Tests and self-reports were selected based on previous use in similar populations[29, 32]. A detailed clinical history of participants was collected from their medical records.

Measures

Cognitive measures. We administered the DIVERGT neuropsychological battery to survivors. This is recognized to be a quick and valid measure of the general cognitive functioning and has been used in the same population[29]. This screening battery includes four tasks: (1) The Digit Span (DS) subtest of the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)[33] or the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)[34] is used to assess working memory. We used the total score. (2) The Verbal Fluency (VF) test of the Delis-Kaplan Executive Function System (D-KEFS) measures verbal fluency. It has three conditions; condition 1 - Letter Fluency (VF1) assesses phonological fluency, condition 2 - Category Fluency (VF2), assesses categorical fluency and condition 3 - Category Switching (VF3), grasps cognitive flexibility[35]. (3) The Grooved Pegboard (GP) gives an index of visual-motor coordination, fine dexterity and motor speed. It is used as an index of fine motor functioning for the dominant hand (GPd) and the non-dominant hand (GPnd)[36]. (4) The D-KEFS Trail Making Test (TMT) includes four conditions; condition 1 - Visual Scanning (TMT1) is a visual search task that offers an index of selective attention, condition 2 - Number Sequencing (TMT2) and condition 3 - Letter Sequencing (TMT3) offers an index of the information processing speed, while condition 4 - Number-Letter Swtiching (TMT4) offers an index of cognitive flexibility[35].

Raw cognitive test scores were converted to standardized scores based on population means (M = 10, SD = 3) and adjusted for patient age. GP were inverted so that low scores will reflect poor performance. Following previous reports using the DIVERGT, we computed two scores: DIVERGT-10 averaging all standardized scores, and DIVERGT-4 averaging TMT1, VF1, DP, GPd[29, 37]. We defined scores below 1.5 SD or below 2.0 SD, respectively as a sign of difficulty or deficit[38]. For comparison purposes, we defined poor performance on DIVERGT-4 as the presence of at least 1 deficit or 2 difficulties[29].

Fatigue measures. We used the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) questionnaire to collect fatigue levels. It consists of a total of 18 statements to which respondents indicate frequencies on a five-point scale (0 = never, 4 = almost always). These statements focus on the signs and symptoms of fatigue that have been present in the past month[39]. The tool reliably assesses three domains of fatigue, namely General Fatigue (in our sample α = 0.894), fatigue related to Sleep/Rest (α = 0.732) and Cognitive Fatigue

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(α = 0.924). A total fatigue score, which is the average of the scores for the three previous domains, was computed (α = 0.917).

Although we describe all fatigue scores, we decided to only use the scales General Fatigue and Sleep/Rest Fatigue in association analyses to avoid spurious associations due to conceptual overlap with Cognitive Fatigue. In fact, when examining the content of items, we realized that the Cognitive Fatigue scale was in fact composed of self-reported cognitive symptoms. Sample items from the adult report are: "It is hard for me to keep my attention on things" and "It is hard for me to think quickly". Scores were transformed to a 0-100 scale following the PedsQL framework and higher scores reflects better level of functioning (high vitality, lower fatigue)[39].

Affective measures. We used the Distress Thermometer (DT) visual digital scale to assess emotional distress. Participant were invited to report their level of emotional distress from the previous week on a scale from 0 (no distress) to 10 (extreme distress). Multiple studies show convergent validity with a variety of measures of distress in survivors. We considered a cut-point of 4+ to identify significant distress[40, 41].

Statistical analyses

Preliminary analyses. We did not impute missing values because most of them were from one site (MCH): 63.0% of Hamilton participants had missed at least one whole section, and in 86% of cases, the whole cognitive battery was missing. This was due to an acute shortage in specialized staff. We compared socio-demographic and clinical characteristics across sites using Chi-square, Kruskal-Wallis, and Mann-Whitney, and their parametric counterparts if appropriate.

Main analyses. For the first objective, we described the cognitive difficulties, fatigue and emotional distress using frequencies, means and standard deviations of the scores. In the absence of norms, we compared the levels obtained in our sample with those obtained in cancer and healthy samples using Cohen's d[42]. For the second objective, we computed Pearson correlations between fatigue and each cognitive domain. After examining basic assumptions (extreme scores, collinearity, sample size), we carried out a series of hierarchical linear regressions to evaluate, in three blocks introduced subsequently, the relative contribution of sociodemographic variables including the ALL risk status (block 1), fatigue (block 2) and emotional distress (block 3) to

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cognitive functioning as assessed by DIVERGT. Since emotional distress is a potential confounding factor of fatigue, it was add in the third block to see if the associations would change. The same model was computed for each cognitive score from the DIVERGT battery and the summary indices (DIVERGT-4 and 10).

Results

Preliminary results

We observed differences across treatment sites. Participants from Quebec UHC were younger than in the two other sites, and those from Hamilton MCH were older. Those from Quebec UHC also had a more frequent standard risk status of ALL, and logically had been less exposed to radiotherapy (Table 1). We also found specificities in the Hamilton MCH subsample, with higher global performance on the DIVERGT-10 index and higher psychological distress than in the other sites (Table 2). These results bring additional arguments to control for age, ALL risk status, and psychological distress in subsequent analyses.

Neurocognitive functioning

Across tasks, participants obtained average standard scores from 8.21 ± 2.89 to 11.02 ± 2.05 (Table S1). They also obtained standard scores of 8.72 ± 2.17 on DIVERGT-4 and 9.66 ± 1.87 on DIVERGT-10, which is close to the norm of 10 (Table 2). However, this hides an important heterogeneity within the group. When looking into frequencies according to cutpoints, we found consistent higher frequencies of difficulties and deficits with a median frequency of difficulties (< 1.5 SD) of 12.45%, as compared to the expected norm of 6.7%. VF1 (30.18%), DS (28.42%) and GPd (21.75%) were the tasks with highest frequency. We observed a similar pattern for deficits (< 2 SD) with a median of 5.61% across tasks compared to a 2.3% in a normative sample. Deficits were present in all tasks but were most frequent on VF1 (8.77%), DS (10.18%) and GPd (9.12%) (Figure 2 and Table S2). Overall, 187 participants (65.61%) had at least one difficulty score and 89 participants (31.23%) had at least one deficit. Ninety-two participants (32.2%) also were classified as having a poor performance on DIVERGT-4.

Fatigue

The mean total fatigue score of the participants was 75.26 (100 = no fatigue) in children and adolescents (N = 106), and 70.48 in adults (N = 179). Comparison of fatigue levels with external pediatric and adult samples using the same instrument showed that levels reported by children in our sample were similar to those in healthy children (median $d = 0.10$) and lower than fatigue reported by children with cancer (median $d = 0.23$). This was true for all fatigue scores except for the Sleep/rest fatigue scale. Children and adolescents in our sample tended to report more issues than healthy children and adolescents ($d = 0.35$). Interestingly, this observation was reversed for adults, as our adult sample reported less fatigue than the comparison normative samples ($d = 0.38$) (Table S3).

Association between cognitive functioning and fatigue

When examining Pearson's correlations between the two spheres, we observed a very low association level with median $r = 0.04$, ns (Table S4). Yet, the median r was higher with Cognitive fatigue (median $r = 0.12$, $P<0.05$, N=14 associations). We found that 8 of the 14 cognitive measures (indices and scores) were associated with Cognitive fatigue in the expected direction (DIVERGT-4, DIVERGT-10, number of difficulties, TMT3, VF1, VF2, VF3, DS). (Table S4) This is not surprising given that this fatigue subscore reflects subjective cognitive complaints and potentially overlaps with actual neurocognitive issues. When looking into the other fatigue scores, we found that DS was significantly associated with Total fatigue ($r = 0.158$, $P<0.01$) and Sleep/rest fatigue ($r = 0.117$, $P < 0.05$). No other correlation was found significant with other tasks or indices. When testing the difference between the sleep/rest fatigue correlation and the median correlation, we found no significant difference (z = 0.92; $P = 0.179$).

When running the multivariate models, we found no significant contribution of fatigue (other than cognitive) beyond the effect of known risk factors to the variability of cognitive indices (DIVERGT-4 and -10), and individual task scores (Tables S5 to S18).

When looking at traditional risk factors in these multivariate models, DIVERGT-4 and DIVERGT-10 showed the same associative patterns (Tables S5-S18). Overall lower neurocognitive performance was associated with male sex ($\beta = -0.137$; $P = 0.018$ and $\beta = -0.124$; $P = 0.031$), ALL high-risk status ($\beta = -0.243$; $P <0.001$ and $\beta = -0.233$; $P <0.001$) and younger

age at diagnosis ($\beta = 0.292$; *P* <0.001 and $\beta = 0.298$; *P* <0.001). We counted significant associations found for each risk factor across models explaining the 10 tasks of the DIVERGT battery. Contributors to pervasive lower performance were younger age at diagnosis (7/10 associations, median $\beta = 0.190$; *P* <0.011) and ALL high-risk status for ALL (5/10 associations, median $\beta = -0.165$; *P* = 0.013). They were followed by male sex (3/10 associations, median $\beta = -0.177$; *P* = 0.003) and a younger age at the time of testing (2/10 associations, median $\beta = 0.178$; *P* = 0.022).

Discussion

The present study, carried out on a sample of 285 childhood ALL survivors, aimed to describe their neurocognitive difficulties and fatigue, and explore the potential contribution of fatigue on cognitive functions. We found that survivors had cognitive difficulties (< 1.5 SD) and deficits (< 2.0 SD) approximately twice as frequently as in normative samples. This was particularly the case in the areas of verbal fluency, working memory and fine motor skills, and to a lesser extent, mental flexibility, information processing speed and visual selective attention. The reported fatigue levels were comparable to those in healthy individuals, except for fatigue related to sleep and rest. The youth in our sample showed significant higher levels of issues on sleep and rest than age-matched comparison samples (small-medium effect size) whereas the adults had lower fatigue than age-matched comparison samples (small-medium effect size). Sleep and rest issues were associated with lower scores on working memory (DS). Interestingly, for all the cognitive domains considered, fatigue did not explain the variability of neurocognitive functioning beyond known risk factors, i.e. sex, age, age at diagnosis, ALL risk status and level of psychological distress. Pervasive contributors to lower cognitive functioning were younger age at diagnosis and high ALL risk status.

On the neurocognitive level, the difficulties we found are consistent with recent studies in the same population. The frequency of difficulties found in our sample (66%) is comparable with studies reporting 48%[10] and 59%[11]. As for cognitive domains affected, the pattern found was also much consistent with the literature[16], although issues on attention, processing speed, and executive

function did not appear clearly in our analyses[6, 12]. This is probably due to the limitations of the DIVERGT battery that we used here.

Regarding fatigue, the portrait was overall more favorable, with levels close to the norm in almost all dimensions. This is good news and is consistent with recent data. Indeed, a study also using the PedsQL MFS did not find any difference between rates reported by childhood ALL survivors between 22 and 62 months after the end of treatments, and healthy comparison samples[18]. Given the important physical sequelae of this population, this result may seem surprising. It could be explained different ways. First, it could reflect the great resilience of pediatric cancer survivors, leading them to report normative levels on a wide array of quality of life dimensions[43]. It is also possible that neurocognitive dysfunctions are so severe in this specific population that they are expressed regardless of the individual's fatigue level. One alternative hypothesis deals with the lack of consensus on the definition of fatigue and its dimensions[19, 44]. One dimension of fatigue stood out in the younger subsample, i.e. the one related to sleep and rest issues. Although differences with healthy sample are modest (small-large effect size), it suggests that the field of sleep is an important aspect to consider in future research, particularly when developing new supportive care modalities as is the case in adult oncology and other types of cancer[45].

When examining associations between neurocognitive functioning and fatigue, we found few significant associations. Among the 28 associations explored, only 1 showed that lower working memory as measured with the Digit Span task was associated with higher sleep and rest fatigue. While this finding can be attributed to a Type 1 error due to lack of power, it may also suggest the deleterious effects of difficulty sleeping and resting on working memory and attention. This type of fatigue has been shown to be particularly associated with cognitive functioning in healthy individuals[46]. Contrasting with our findings, recent studies have shown much larger associations with fatigue. For instance, survivors' self-reported and performance scores on executive, attentional, and information processing speed have been associated with self-reported fatigue[25, 27]. In the study by Cheung and al. (2017), the authors used a wider panel of cognitive tasks to increase the sensitivity of their analyses and interpreted the Cognitive fatigue scale as true fatigue, while the items clearly overlap with objective cognitive functioning[25]. These

differences across studies underscore the need to better operationalize fatigue in the future, as well as to use standard batteries to assess neurocognitive functioning.

In subsequent multivariate models, we found no indication that fatigue would contribute to neurocognitive difficulties beyond the role of known risk factors and the same result was obtain when excluding Hamilton participants. This applies to the only significant bivariate association found between working memory (DS) and sleep and rest issues. As the association disappeared when clinical history risk factors were controlled for, it suggests that both domains are in fact impacted by clinical history such as age of exposure and intensity of treatment. This was confirmed by supplementary analyses where we regressed fatigue scales on those factors. We found that higher general fatigue was associated with male sex ($\beta = 0.198$; $P = 0.001$), younger age at diagnosis ($\beta = 0.160$; $P = 0.034$) and older age at the time of testing ($\beta = -0.199$; $P = 0.006$), while lower sleep/rest fatigue was only associated with male sex ($\beta = 0,166$; $P = 0.005$) (Table S19 et S20).

Clinical implications

Neurocognitive difficulties appear to be predominant in pediatric ALL survivors. It appears key to prevent them by a continuous refinement of treatment scaling and minimizing neurotoxicity. Developing remediation and support interventions could be beneficial when issues are present. Some programs have already been shown effective in pediatric cancer survivors like education programs and pharmacologic treatment (e.g. methylphenidate). Education programs may include behavioral or cognitive remediation components, compensatory strategies, computerized training or school-based interventions[47, 48]. Sleep and rest issues should not be overlooked, however, given their high frequency within the younger sample and their possible impact of important functions such as working memory. Strategies already applied in cancer survivors could be used with ALL survivors to promote a better sleep-wake cycle. Those strategies may include exercise, cognitive behavioral therapy, behavioral therapy and psychoeducational interventions[49]. Yet given that fatigue did not share a substantial part of variance with neurocognitive outcomes, it is still unclear is such fatigue targeted programs would contribute to improving neurocognitive functioning over time.

Study limitations

We must recognize certain limitations to this study. First, multiple analyses entailed non-negligible risks of type 1 error. This means that certain associations identified could be the result of chance. Second, since the design is cross-sectional, it is not possible to interpret the associations as a causal contribution of fatigue on cognitive functioning. Third, the DIVERGT battery that we used is a limited tool that does not describe in detail memory functions, nor all executive and attentional functions, while these have been identified as an important point of neurocognitive sequelae in this population[5, 6, 12]. It also only offers global scores for some cognitive function while fatigue may influence just a few scores within those global scores. Finally, the different measurement sources must be considered as a hypothesis to explain the quasi absence of association between the two spheres considered, one being self-reported, the perception of fatigue, and the other being a performance assessment, neurocognitive functioning[50]. To address this limitation, one strategy could be using more objective biophysiological measures of fatigue such as cytokine levels[51].

Conclusions

In a cross-sectional study of 285 long-term survivors of childhood ALL treated with a DFCI protocol at three sites in Canada, we found that 66% of participants had at least one cognitive difficulty (<1.5 SD) and 31% had at least one deficit (<2.0 SD). The most common difficulties and deficits derived from the DIVERGT battery related to verbal fluency, working memory and fine motor skills. Fatigue levels were close to normal except for sleep and rest fatigue which was 7% higher in the young people in our sample than those in a comparison sample. When excluding for the measure of fatigue overlapping with cognitive complaints, we found that the perception of fatigue did not appear to contribute significantly to overall cognitive functioning. It was, however, associated with working memory, measured in the Digit Span task. Fatigue and working memory issues may be both due to clinical history. We also found a pervasive association age at diagnosis and ALL risk status on neurocognitive outcomes. If these results are replicated in independent samples, it would be beneficial to operationalize fatigue more clearly and use standard batteries for neurocognitive functioning assessment.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Table 1

Sample description of 285 childhood ALL survivors from three DFCI sites in Canada

Participants' characteristics	Total sample (N = 285) M (SD) or N (%)	St-Justine UHC (N = 223) M (SD) or N (%)	Quebec UHC (N = 45) M (SD) or N (%)	Hamilton MCH (N = 17) M (SD) or N (%)	Comparisons P value[a]
Sociodemographic characteristics					
Sex					
Male	139 (48.8)	109 (48.9)	20 (44.4)	10 (58.8)	
Female	146 (51.2)	114 (51.1)	25 (55.6)	7 (41.2)	0.599
Age at follow-up (years)	21.21 (6.72)	21.66 (6.43)	17.82 (6.66)	24.24 (7.86)	0.001**
8-12	19 (6.7)	6 (2.7)	13 (28.9)	-	
13-18	102 (35.8)	84 (37.7)	13 (28.9)	5 (29.4)	
19+	164 (57.5)	133 (59.6)	19 (42.2)	12 (70.6)	
Marital status (for those over 18 years old) (N = 179)					
Single/Divorced	123 (68.7)	96	16	11	
Married/Common law	56 (31.3)	48	6	2	0.338
Ethnicity					
Caucasian	258 (90.5)	215 (96.4)	43 (95.6)	-	
Other	10 (3.5)	8 (3.6)	2 (4.4)	-	
Missing	17 (6.0)	-	-	17 (100)	n/a
Educational background					
Pre-high school	102 (35.8)	88 (39.5)	11 (24.4)	3 (17.6)	
High school	50 (17.5)	34 (15.2)	8 (17.8)	8 (47.1)	
College	57 (20.0)	48 (21.5)	7 (15.6)	2 (11.8)	
University	29 (10.2)	23 (10.3)	2 (4.4)	4 (24.5)	
Other	47 (16.5)	30 (13.5)	17 (37.8)	-	n/a
First Language					
French	257 (90.2)	214 (96.0)	43 (95.6)	-	
English	21 (7.4)	4 (1.8)	-	17 (100)	
Other	7 (2.5)	5 (2.2)	2 (4.4)	-	n/a
Clinical characteristics					
Age at diagnosis, years	6.00 (4.47)	6.15 (4.60)	5.27 (3.33)	6.00 (5.27)	0.893
Time since diagnosis, years	14.73 (5.45)	15.00 (5.34)	12.16 (5.01)	17.88 (5.74)	0.001**
Radiotherapy					
Yes	159 (55.8)	136 (61.0)	11 (24.4)	12 (70.6)	
No	126 (44.2)	87 (39.0)	34 (75.6)	5 (29.4)	<0.001***
ALL risk status					
Standard	142 (49.8)	99 (44.4)	35 (77.8)	8 (47.1)	
High	143 (50.2)	124 (55.6)	10 (22.2)	9 (52.9)	0.001**
Treatment protocol					
DFCI 87-01	21 (7.4)	18 (8.1)	-	3 (17.6)	
DFCI 91-01	49 (17.2)	41 (18.4)	6 (13.3)	2 (11.8)	
DFCI 95-01	78 (27.4)	63 (28.3)	11 (24.4)	4 (24.5)	
DFCI 2000-01	84 (29.5)	71 (31.8)	7 (15.6)	6 (35.3)	
DFCI 2005-01	48 (16.8)	25 (11.2)	21 (46.7)	2 (11.8)	
Other	5 (1.8)	5 (2.2)	-	-	n/a

[a]Comparisons were performed with non-parametric Kruskal-Wallis test for continuous variables and chi-squared test for categorical variables followed by Mann-Whitney test when necessary due to the small sample size of MHC.
** $P < 0.01$.
*** $P < 0.001$.

Table 2

Description of DIVERGT indices, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) and the Distress Thermometer (DT) scores in 285 childhood ALL survivors

	Total sample (N = 285) M (SD) or N (%)	Sainte-Justine UHC (N = 223) M (SD) or N (%)	Quebec UHC (N = 45) M (SD) or N (%)	Hamilton MCH (N = 17) M (SD) or N (%)	Comparison *P* value[d]
DIVERGT					
DIVERGT-4	8.72 (2.17)	8.64 (2.27)	8.67 (1.73)	9.86 (1.58)	0.074
Low[a]	92 (32.28)	73 (32.74)	15 (33.33)	4 (23.53)	
High	193 (67.72)	150 (67.27)	30 (66.67)	13 (76.47)	
DIVERGT-10	9.66 (1.87)	9.50 (1.92)	10.01 (1.63)	10.78 (1.35)	0.006**
PedsQL MFS[b]					
Total fatigue	72.25 (16.60)	72.27 (16.72)	74.35 (14.80)	66.50 (19.06)	0.397
General fatigue	77.57 (19.34)	77.15 (19.55)	82.04 (16.87)	71.32 (21.39)	0.138
Sleep/rest fatigue	67.53 (17.40)	67.41 (17.51)	69.35 (16.76)	64.22 (18.05)	0.669
Cognitive fatigue	71.65 (22.76)	72.23 (22.22)	71.67 (23.55)	63.97 (27.44)	0.571
DT[c]					
Total	2.11 (2.27)	2.06 (2.18)	1.53 (2.09)	4.35 (2.69)	<0.001***
DT > 3	69 (24.21)	51 (22.87)	8 (17.78)	10 (58.82)	

Note. Raw scores on DIVERGT were converted to age-adjusted scaled scores based on the normative population mean and are centred around a mean of 10 and an SD of 3.

[a]DIVERGT-4 Low includes participants with a standardized score of 4 or less, or two of 6 or less.

[b]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.

[c]DT, Distress Thermometer.

[d]Comparisons were performed with non-parametric Kruskal-Wallis test and Mann-Whitney test due to the small sample size of MHC.

** $P < 0.01$.

*** $P < 0.001$.

Supplementary table S1

Description of scaled scores of the DIVERGT battery in participants from three treatment sites

Tasks	Total sample (N = 285) M (SD)	SJUCH[a] (N = 223) M (SD)	QUHC[b] (N = 45) M (SD)	MHC[c] (N = 17) M (SD)	Comparisons P values[d]
Trail Making Test (TMT)					
Condition 1 – Visual Scanning					
Condition 2 – Number Sequencing	11.02 (2.05)	11.09 (1.86)	10.76 (2.70)	10.76 (2.54)	0.920
Condition 3 – Letter Sequencing	10.16 (2.84)	9.87 (2.94)	11.18 (2.32)	11.18 (1.98)	0.008**
Condition 4 – Number-Letter	10.39 (2.98)	10.17 (3.03)	11.09 (2.93)	11.41 (1.94)	0.024*
Switching	9.59 (2.95)	9.47 (3.00)	9.98 (2.86)	10.18 (2.56)	0.434
Verbal Fluency					
Condition 1 – Letter Fluency	8.21 (2.89)	7.94 (2.86)	8.38 (2.23)	11.41 (3.08)	<0.001***
Condition 2 – Category Fluency	10.12 (3.39)	9.75 (3.40)	11.02 (2.71)	12.52 (3.66)	0.001**
Condition 3 – Category Switching	10.41 (3.40)	9.90 (3.31)	12.53 (2.82)	11.47 (3.02)	<0.001***
Digit Span	8.21 (3.00)	8.11 (2.97)	8.84 (2.82)	7.88 (3.79)	0.217
Grooved Pegboard					
Dominant Hand	8.87 (3.90)	9.07 (3.97)	7.50 (3.62)	9.96 (2.86)	0.006**
Non-dominant Hand	9.60 (3.02)	9.64 (2.83)	8.85 (3.95)	11.05 (1.93)	0.056

Note. Raw scores were converted to age-adjusted scaled scores based on the normative population mean and are centred around a mean of 10 and an SD of 3. The differences between the treatment sites are probably the product of the differences in sociodemographic and clinical characteristics that were found in Table 1.

[a]SJUCH, Sainte-Justine University Health Centre in Montreal, Canada.

[b]QUHC, Quebec University Health Centre in Quebec, Canada.

[c]MCH, Hamilton's McMaster Children's Hospital in Ontario, Canada.

[d]Comparison were performed with non-parametric Kruskal-Wallis test and Mann-Whitney test due to the small sample size at MHC.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Supplementary table S2

Frequencies of neurocognitive difficulties (scores < 1.5 SD) and deficits (scores < 2.0 SD) in the total sample as measured by the DIVERGT battery (N = 285)

Tasks	Difficulties Scores < 1.5 SD N (%)	Deficits Scores < 2.0 SD N (%)
Trail Making Test		
Condition 1 – Visual Scanning	8 (2.81)	2 (0.70)
Condition 2 – Number Sequencing	30 (10.53)	13 (4.56)
Condition 3 – Letter Sequencing	28 (9.82)	17 (5.96)
Condition 4 – Number-Letter Switching	40 (14.04)	16 (5.61)
Verbal Fluency		
Condition 1 – Letter Fluency	86 (30.18)	25 (8.77)
Condition 2 – Category Fluency	35 (12.28)	11 (3.86)
Condition 3 – Category Switching	36 (12.62)	12 (4.21)
Digit Span	81 (28.42)	29 (10.18)
Grooved Pegboard		
Dominant Hand	62 (21.75)	26 (9.12)
Non-dominant Hand	27 (9.47)	16 (5.61)

Note. In a normal distribution only 6.7% would have scores under the mean below 1.5 SD which represent a difficulty, and 2.3% below 2 SD which represent a deficit.

Supplementary table S3

Comparison of fatigue scores on the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) in survivors of pediatric ALL, pediatric cancer patients (ages 5-18), healthy non clinical children (ages 5-18) and healthy non clinical young adults (ages 18-25)

| | ALL survivors in our sample (n = 285) | | Comparative samples | | | | | |
	Children (n = 106) M (SD)	Adults (n = 179) M (SD)	Cancer children (n = 220) M (SD)	Healthy children (n = 366) M (SD)	Healthy young adults (n = 391) M (SD)	ALL children vs. Cancer children Cohen's d[a]	ALL children vs. healthy children Cohen's d	ALL adults vs. healthy young adults Cohen's d
Total fatigue	75.26 (14.14)	70.48 (17.70)	70.98 (18.20)	76.84 (12.67)	67.18 (13.92)	0.26	0.12	0.21
General fatigue	81.53 (16.41)	75.23 (20.58)	74.99 (19.59)	80.29 (14.39)	70.92 (16.94)	0.36	0.08	0.23
Sleep/rest fatigue	69.10 (15.45)	66.60 (18.43)	67.03 (23.08)	74.49 (15.60)	59.76 (17.10)	0.11	0.35	0.38
Cognitive fatigue	75.08 (20.87)	69.62 (23.63)	70.92 (22.35)	75.69 (18.18)	70.88 (18.15)	0.19	0.03	0.06

Note. Comparison samples are from the following reports. Cancer children: Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL™ in pediatric cancer: Reliability and validity of the pediatric quality of life inventory™ generic core scales, multidimensional fatigue scale, and cancer module. Cancer. 2002;94(7):2090-106. Healthy children: Gordijn MS, van Litsenburg RR, Gemke RJ, Huisman J, Bierings MB, Hoogerbrugge PM, et al. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. Pediatric Blood & Cancer. 2013;60(3):479-85. Healthy young adults: Varni JW, Limbers CA. The PedsQL™ Multidimensional Fatigue Scale in young adults: Feasibility, reliability and validity in a University student population. Quality of Life Research. 2008;17(1):105-14.

[a]Effect sizes: Small effect: $d = 0.2$; medium effect: $d = 0.5$; large effect: $d = 0.8$.

Supplementary table S4

Correlation table of fatigue and distress scores with neurocognitive functioning on the DIVERGT in a sample of 285 childhood ALL survivors

					Trail Making Test				Verbal Fluency				Grooved Pegboard	
	DIVERGT-4	DIVERGT-10	Number of difficulties	Number of deficits	Condition 1 – Visual Scanning	Condition 2 – Number Sequencing	Condition 3 – Letter Sequencing	Condition 4 – Number-Letter Switching	Condition 1 – Letter Fluency	Condition 2 – Category Fluency	Condition 3 – Category Switching	Digit span	Dominant hand	Non-dominant Hand
Total fatigue	0.065	0.075	-0.045	-0.007	0.027	-0.040	0.063	-0.001	0.106	0.087	0.111	0.158**	-0.055	0.010
General fatigue	-0.002	0.016	0.015	0.043	0.013	-0.077	0.027	-0.051	0.052	0.069	0.067	0.104	-0.084	-0.011
Sleep/rest fatigue	0.004	-0.006	0.016	0.055	-0.036	-0.044	-0.001	-0.045	0.065	0.017	0.062	0.117*	-0.096	-0.070
Cognitive fatigue	0.140*	0.154**	-0.125*	-0.095	0.075	0.010	0.117*	0.075	0.137*	0.119*	0.138*	0.167**	0.025	0.085
Distress Thermometer	-0.002	-0.007	0.023	-0.001	-0.028	0.040	-0.045	-0.011	-0.028	-0.023	-0.005	-0.101	0.073	0.061
Distress Thermometer>3	0.016	0.009	-0.034	-0.027	0.015	0.055	-0.033	0.036	-0.008	-0.034	-0.037	-0.070	0.068	0.063

* $P < 0.05$.

** $P < 0.01$.

Supplementary table S5

Summary of hierarchical regression analysis predicting DIVERGT 4 with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.593	0.249	-0.137	0.018*
Age	0.042	0.023	0.131	0.067
Age at diagnosis	0.142	0.036	0.292	<0.001***
AAA risk status[b]	-0.055	0.278	-0.243	<0.001***
Block 2				
PedsQL MFS[c] general fatigue	0.001	0.009	0.007	0.930
PedsQL MFS sleep/rest fatigue	0.040	0.009	0.030	0.676
Block 3				
DT[d]	0.004	0.061	0.004	0.949

Note. Block 1 $\Delta R^2 = 0.135$, $P < 0.001$; Block 2 $\Delta R^2 = 0.001$, $P = 0.844$; Block 3 $\Delta R^2 < 0.001$, $P = 0.949$. Total $R^2 = 0.136$, $P < 0.001$. Total adjusted $R^2 = 0,114$, P < 0.001.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.
*** $P < 0.001$.

Supplementary table S6

Summary of hierarchical regression analysis predicting DIVERGT 10 with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.465	0.214	-0.124	0.031*
Age	0.037	0.020	0.134	0.060
Age at diagnosis	0.125	0.031	0.298	<0.001***
ALL risk status[b]	-0.870	0.239	-0.233	<0.001***
Block 2				
PedsQL MFS[c] general fatigue	0.005	0.007	0.056	0.472
PedsQL MFS sleep/rest fatigue	-0.001	0.008	-0.006	0.929
Block 3				
DT[d]	0.023	0.052	0.027	0.666

Note. Block 1 $\Delta R^2 = 0.134$, $P < 0.001$; Block 2 $\Delta R^2 = 0.002$, $P = 0.784$; Block 3 $\Delta R^2 = 0.001$, $P = 0.666$. Total $R^2 = 0.136$, $P < 0.001$. Total adjusted $R^2 = 0.114$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.
*** $P < 0.001$.

Supplementary table S7

Summary of hierarchical regression analysis predicting the number of difficulties with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	0.225	0.117	0.113	0.056
Age	-0.001	0.011	-0.007	0.920
Age at diagnosis	-0.062	0.017	-0.280	<0.001***
ALL risk status[b]	0.511	0.131	0.257	<0.001***
Block 2				
PedsQL MFS[c] general fatigue	0.002	0.004	0.034	0.673
PedsQL MFS sleep/rest fatigue	-0.001	0.004	-0.022	0.770
Block 3				
DT[d]	0.011	0.029	0.024	0.712

Note. Block 1 $\Delta R^2 = 0.093$, $P < 0.001$; Block 2 $\Delta R^2 < 0.001$, $P = 0.942$; Block 3 $\Delta R^2 < 0.001$, $P = 0.712$. Total $R^2 = 0.093$, $P < 0.001$. Total adjusted $R^2 = 0.071$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
*** $P < 0.001$.

Supplementary table S8

Summary of hierarchical regression analysis predicting the number of deficits with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	0.226	0.079	0.167	0.005**
Age	-0.011	0.007	-0.107	0.142
Age at diagnosis	-0.033	0.011	-0.218	0.004**
ALL risk status[b]	0.282	0.088	0.209	0.002**
Block 2				
PedsQL MFS[c] general fatigue	<0.001	0.003	0.006	0.944
PedsQL MFS sleep/rest fatigue	0.001	0.003	0.020	0.789
Block 3				
DT[d]	0.004	0.019	0.013	0.836

Note. Block 1 $\Delta R^2 = 0.101$, $P < 0.001$; Block 2 $\Delta R^2 < 0.001$, $P = 0.946$; Block 3 $\Delta R^2 < 0.001$, $P = 0.836$. Total $R^2 = 0.102$, $P < 0.001$. Total adjusted $R^2 = 0.079$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
** $P < 0.01$.

Supplementary table S9

Summary of hierarchical regression analysis predicting Trail Making Test Condition 1 – Visual Scanning with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex	-0.206	0.251	-0.050	0.413
Age	0.022	0.023	0.072	0.344
Age at diagnosis	0.027	0.036	0.059	0.455
ALL risk status	-0.316	0.280	-0.077	0.260
Block 2				
PedsQL MFS[a] general fatigue	0.006	0.009	0.054	0.512
PedsQL MFS sleep/rest fatigue	-0.007	0.009	-0.063	0.412
Block 3				
DT[b]	-0.023	0.061	-0.025	0.710

Note. Block 1 $\Delta R^2 = 0.014$, $P = 0.411$; Block 2 $\Delta R^2 = 0.003$, $P = 0.654$; Block 3 $\Delta R^2 < 0.001$, $P = 0.710$. Total $R^2 = 0.017$, $P = 0.026$. Total adjusted $R^2 = -0.007$, $P = 0.157$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.

Supplementary table S10

Summary of hierarchical regression analysis predicting Trail Making Test Condition 2 – Number Sequencing with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.147	0.343	-0.026	0.667
Age	0.022	0.032	0.051	0.496
Age at diagnosis	0.119	0.049	0.186	0.017*
ALL risk status[b]	-0.645	0.382	-0.114	0.093
Block 2				
PedsQL MFS[c] general fatigue	-0.010	0.012	-0.068	0.403
PedsQL MFS sleep/rest fatigue	0.002	0.012	0.009	0.902
Block 3				
DT[d]	0.035	0.084	0.028	0.674

Note. Block 1 $\Delta R^2 = 0.038$, $P = 0.027$; Block 2 $\Delta R^2 = 0.005$, $P = 0.469$; Block 3 $\Delta R^2 = 0.001$, $P = 0.674$. Total $R^2 = 0.044$, $P < 0.001$. Total adjusted $R^2 = 0.020$, $P = 0.017$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.

Supplementary table S11

Summary of hierarchical regression analysis predicting Trail Making Test Condition 3 – Letter Sequencing with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.041	0.355	-0.007	0.909
Age	0.060	0.033	0.136	0.068
Age at diagnosis	0.120	0.051	0.179	0.020*
ALL risk status[b]	-0.683	0.397	-0.115	0.087
Block 2				
PedsQL MFS[c] general fatigue	0.008	0.012	0.049	0.544
PedsQL MFS sleep/rest fatigue	-0.006	0.013	-0.034	0.653
Block 3				
DT[d]	-0.018	0.087	-0.014	0.834

Note. Block 1 $\Delta R^2 = 0.062$, $P = 0.001$; Block 2 $\Delta R^2 = 0.002$, $P = 0.769$; Block 3 $\Delta R^2 < 0.001$, $P = 0.834$. Total $R^2 = 0.064$, $P < 0.001$. Total adjusted $R^2 = 0.041$, $P = 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.

Supplementary table S12

Summary of hierarchical regression analysis predicting Trail Making Test Condition 4 – Number-Letter Switching with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.260	0.344	-0.044	0.450
Age	0.069	0.032	0.157	0.031*
Age at diagnosis	0.160	0.050	0.242	0.001**
ALL risk status[b]	-0.767	0.384	-0.130	0.047*
Block 2				
PedsQL MFS[c] general fatigue	-0.003	0.012	-0.023	0.773
PedsQL MFS sleep/rest fatigue	-0.005	0.012	-0.028	0.707
Block 3				
DT[d]	-0.011	0.084	-0.009	0.892

Note. Block 1 $\Delta R^2 = 0.104$, $P < 0.001$; Block 2 $\Delta R^2 = 0.002$, $P = 0.775$; Block 3 $\Delta R^2 < 0.001$, $P = 0.892$. Total $R^2 = 0.106$, $P < 0.001$. Total adjusted $R^2 = 0.083$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.
** $P < 0.01$.

Supplementary table S13

Summary of hierarchical regression analysis predicting Verbal Fluency Condition 1 – Letter Fluency with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.065	0.352	-0.011	0.853
Age	0.033	0.033	0.077	0.308
Age at diagnosis	0.071	0.051	0.109	0.166
ALL risk status[b]	-0.604	0.393	-0.104	0.125
Block 2				
PedsQL MFS[c] general fatigue	0.003	0.012	0.023	0.778
PedsQL MFS sleep/rest fatigue	0.010	0.013	0.060	0.432
Block 3				
DT[d]	0.012	0.086	0.009	0.890

Note. Block 1 $\Delta R^2 = 0.022$, $P = 0.189$; Block 2 $\Delta R^2 = 0.005$, $P = 0.486$; Block 3 $\Delta R^2 < 0.001$, $P = 0.890$. Total $R^2 = 0.027$, $P = 0.006$. Total adjusted $R^2 = 0.002$, $P = 0.449$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.

Supplementary table S14

Summary of hierarchical regression analysis predicting Verbal Fluency Condition 2 – Category Fluency with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	0.219	0.409	0.032	0.593
Age	0.025	0.038	0.049	0.510
Age at diagnosis	0.128	0.059	0.169	0.031*
ALL risk status[b]	-0.986	0.457	-0.146	0.032*
Block 2				
PedsQL MFS[c] general fatigue	0.016	0.014	0.091	0.266
PedsQL MFS sleep/rest fatigue	-0.006	0.015	-0.032	0.677
Block 3				
DT[d]	0.046	0.100	0.031	0.646

Note. Block 1 $\Delta R^2 = 0.036$, $P = 0.035$; Block 2 $\Delta R^2 = 0.004$, $P = 0.579$; Block 3 $\Delta R^2 = 0.001$, $P = 0.646$. Total $R^2 = 0.041$, $P = 0.001$. Total adjusted $R^2 = 0.016$, $P = 0.033$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.

Supplementary table S15

Summary of hierarchical regression analysis predicting Verbal Fluency Condition 3 – Category Switching with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-1.206	0.400	-0.177	0.003**
Age	-0.013	0.037	-0.025	0.730
Age at diagnosis	0.208	0.058	0.273	<0.001***
ALL risk status[b]	-1.121	0.446	-0.165	0.013*
Block 2				
PedsQL MFS[c] general fatigue	0.012	0.014	0.068	0.390
PedsQL MFS sleep/rest fatigue	0.012	0.014	0.059	0.424
Block 3				
DT[d]	0.066	0.098	0.044	0.499

Note. Block 1 $\Delta R^2 = 0.082$, $P < 0.001$; Block 2 $\Delta R^2 = 0.009$, $P = 0.261$; Block 3 $\Delta R^2 = 0.002$, $P = 0.499$. Total $R^2 = 0.092$, $P < 0.001$. Total adjusted $R^2 = 0.069$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Supplementary table S16

Summary of hierarchical regression analysis predicting Digit Span with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.210	0.354	-0.035	0.554
Age	-0.001	0.033	-0.003	0.971
Age at diagnosis	0.172	0.051	0.256	0.001**
ALL risk status[b]	-1.346	0.396	-0.225	0.001**
Block 2				
PedsQL MFS[c] general fatigue	0.001	0.012	0.008	0.916
PedsQL MFS sleep/rest fatigue	0.018	0.013	0.107	0.150
Block 3				
DT[d]	-0.061	0.086	-0.046	0.483

Note. Block 1 $\Delta R^2 = 0.066$, $P = 0.001$; Block 2 $\Delta R^2 = 0.015$, $P = 0.103$; Block 3 $\Delta R^2 = 0.002$, $P = 0.483$. Total $R^2 = 0.083$, $P < 0.001$. Total adjusted $R^2 = 0.060$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
** $P < 0.01$.

Supplementary table S17

Summary of hierarchical regression analysis predicting Grooved Pegboard Dominant Hand with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-1.838	0.449	-0.236	<0.001***
Age	0.068	0.041	0.117	0.102
Age at diagnosis	0.166	0.065	0.190	0.011*
ALL risk status[b]	-1.503	0.501	-0.193	0.003**
Block 2				
PedsQL MFS[c] general fatigue	0.002	0.016	0.009	0.911
PedsQL MFS sleep/rest fatigue	-0.009	0.016	-0.039	0.590
Block 3				
DT[d]	0.076	0.110	0.044	0.489

Note. Block 1 $\Delta R^2 = 0.024$, $P < 0.001$; Block 2 $\Delta R^2 = 0.002$, $P = 0.722$; Block 3 $\Delta R^2 = 0.002$, $P = 0.489$. Total $R^2 = 0.127$, $P < 0.001$. Total adjusted $R^2 = 0.105$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Supplementary table S18

Summary of hierarchical regression analysis predicting Grooved Pegboard Non-Dominant Hand with descriptive and clinical variables (Block 1), fatigue (Block 2), and emotional distress (Block 3)

	B	SE	β	*P*
Block 1				
Sex[a]	-0.989	0.354	-0.149	0.012*
Age	0.089	0.033	0.199	0.007**
Age at diagnosis	0.079	0.051	0.118	0.121
ALL risk status[b]	-0.726	0.395	-0.121	0.067
Block 2				
PedsQL MFS[c] general fatigue	0.020	0.012	0.126	0.114
PedsQL MFS sleep/rest fatigue	-0.016	0.013	-0.090	0.221
Block 3				
DT[d]	0.104	0.086	0.079	0.227

Note. Block 1 $\Delta R^2 = 0.083$, $P < 0.001$; Block 2 $\Delta R^2 = 0.006$, $P = 0.380$; Block 3 $\Delta R^2 = 0.005$, $P = 0.227$. Total $R^2 = 0.095$, $P < 0.001$. Total adjusted $R^2 = 0.072$, $P < 0.001$.
[a]Sex: 0 = female; 1 = male.
[b]ALL risk status: 1 = standard risk; 2 = high risk.
[c]PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.
[d]DT, Distress Thermometer.
* $P < 0.05$.

** $P < 0.01$.

Supplementary table S19

Regression analysis predicting General fatigue from the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) with descriptive and clinical variables

	B	SE	β	P
Sex	7.642	2.230	0.198	0.001**
Age	-0.573	0.209	-0.199	0.006**
Age at diagnosis	0.692	0.326	0.160	0.034*
ALL risk status	-1.522	2.527	-0.039	0.547

Note. $R^2 = 0.069$, $P < 0.001$. Adjusted $R^2 = 0.056$, $P < 0.001$.
* $P < 0.05$.
** $P < 0.01$.

Supplementary table S20

Regression analysis predicting Sleep/rest fatigue from the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) with descriptive and clinical variables

	B	SE	β	P
Sex	5.759	2.026	0.166	0.005**
Age	-0.316	0.189	-0.122	0.096
Age at diagnosis	0.392	0.296	0.101	0.186
ALL risk status	3.497	2.296	0.101	0.129

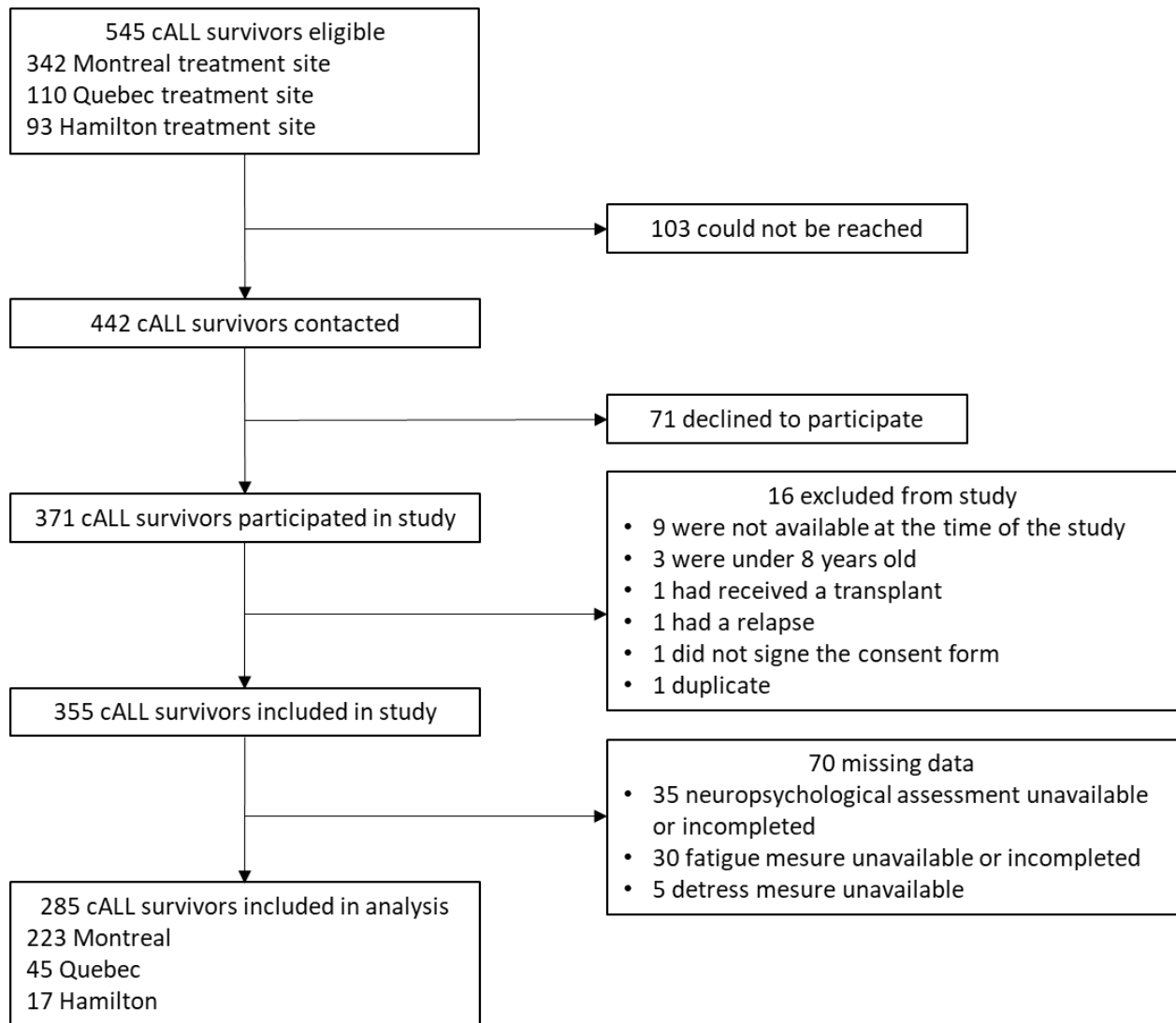*Note*. $R^2 = 0.050$, $P < 0.001$. Adjusted $R^2 = 0.037$, $P = 0.001$.
** $P < 0.01$.

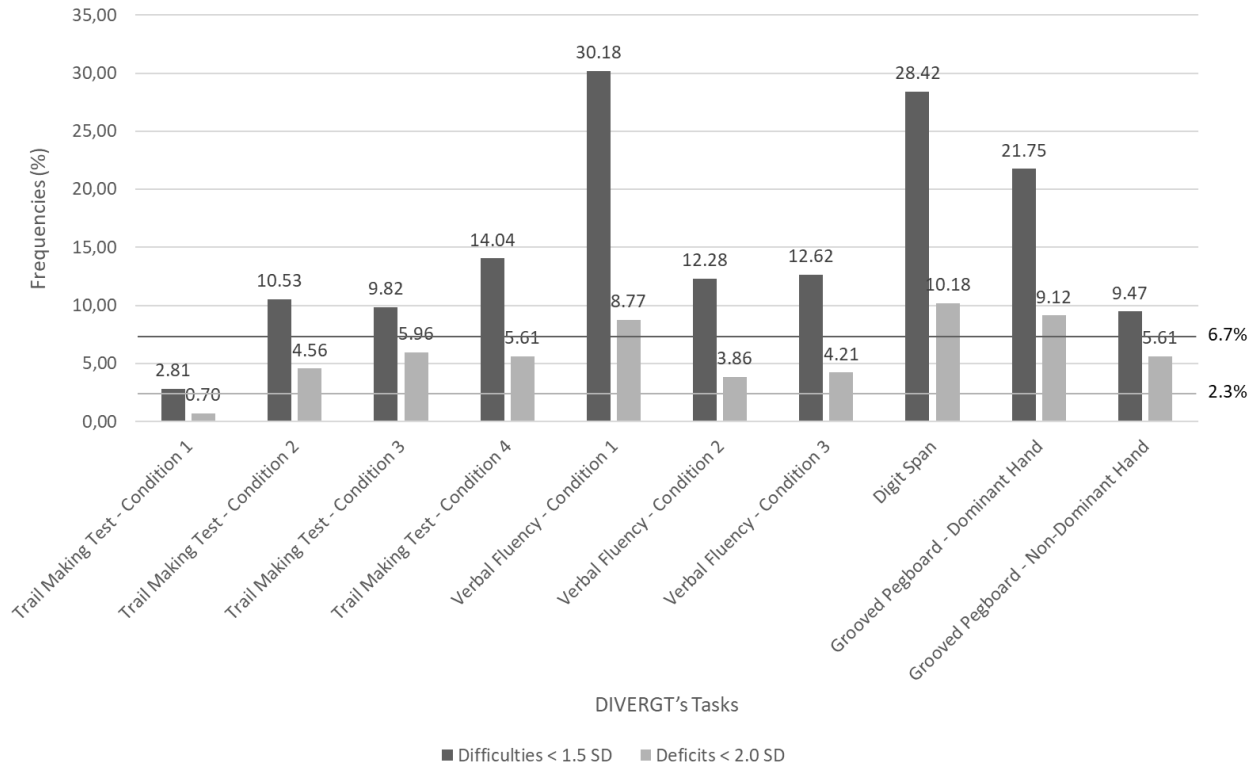*Figure 1.* Participant flow chart.

Figure 2. Frequency of neurocognitive difficulties and deficits from the DIVERGT battery in a group of 285 childhood ALL survivors. The frequency of scores considered to represent a difficulty (< 1.5 SD) is 6.7% in the norm and that of scores considered in deficit (< 2.0 SD) is 2.3%.