Université de Montréal

Inconsistances entre les mesures évaluant les difficultés cognitives chez des survivants de leucémie aigüe lymphoblastique : description et compréhension

par
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Essai doctoral présenté à la Faculté des arts et des sciences
en vue de l'obtention du grade de Doctorat en neuropsychologie clinique (D. Psy.)

Août 2019

Résumé

Introduction – Le taux de survie de la leucémie aigüe lymphoblastique (LAL) dépasse aujourd'hui 90 %. En dépit de traitements moins toxiques, environ 50 % des survivants leucémie aigüe lymphoblastique (LAL) présentent au moins une séquelle cognitive cliniquement significative à long terme. Un problème central quant à l'évaluation cognitive est la présence d'écarts entre les résultats aux tests et les plaintes auto-rapportées. Les hypothèses émises pour expliquer ce phénomène sont nombreuses et mal connues. **Objectifs** – (1) Décrire les écarts entre les difficultés testées et celles auto-rapportées pour les domaines de la mémoire de travail et de l'attention. (2) Évaluer si la détresse émotionnelle, la dépression, l'anxiété, les affects positifs et négatifs et la fatigue permettent d'expliquer ces écarts. **Méthodes** – Nous avons utilisé les données disponibles pour 138 adultes survivants de LAL pédiatrique (cohorte PETALE). La mémoire de travail et l'attention des survivants ont été évaluées avec le WAIS-IV et via des questionnaires auto-rapportés (BRIEF-SR et CAARS-S:L). L'évaluation affective incluait la détresse émotionnelle (BSI-18), les affects (PANAS) et la fatigue (PedsQL-MFS). Nous explorons les écarts à l'aide d'indices diagnostiques, et les expliquons dans des modèles de régression multivariés. **Résultats** – Les déficits en mémoire de travail et en attention sont rapportés par 10 à 11 % des survivants, alors qu'ils sont objectivés chez 15 à 21 % d'entre eux. Les mesures auto-rapportées ne permettent pas d'identifier les déficits objectifs (sensibilité = 0.05-0.16). L'affectivité négative permet d'expliquer partiellement les écarts individuels retrouvés entre ces deux types de mesures au profit des difficultés auto-rapportées. **Conclusions** – L'évaluation cognitive testée et celle auto-rapportée par les survivants doivent être considérées comme des réalités différentes dont les écarts sont probablement influencés par le statut psychologique des répondants.

Mots-clés : survivant, cancer pédiatrique, difficultés cognitives, questionnaire auto-rapporté, test cognitif, attention, mémoire de travail, neuropsychologie clinique

Abstract

Objectives – The frequency of cognitive difficulties in childhood cancer survivors varies according to the measurement strategy. The goal of this research is to (1) describe agreements and differences between measures of working memory and attention (2) identify contributors of differences between measures in the domains of emotional distress, affects, and fatigue. **Methods** – We used data available for 138 adults successfully treated for childhood acute lymphoblastic leukemia (ALL) (PETALE cohort). Working memory and attention were assessed using subtests from the WAIS-IV and self-reported questionnaires (BRIEF-SR and CAARS-S:L). Contributors assessment included emotional distress, anxiety, depression (BSI-18), affects (PANAS), and fatigue (PedsQL-MFS). We explored agreements/differences using diagnostic indices and multivariate regression models. **Results** – The frequencies of working memory and attention deficits were higher when using cognitive tests (15-21%) than with self-reports (10-11%). Self-reported questionnaires showed high specificity (median 0.87) and low sensitivity (median 0.10) suggesting they did not reliably identify positive cases on cognitive tests. We identified negative affectivity as a possible contributor to inconsistencies between self-report and test results. **Conclusions** – When measuring working memory and attention in childhood ALL survivors, cognitive test results and self-reports should not be considered equivalent. At best, self-report may be used for screening (high specificity), but not to assess prevalence in large samples. Self-reported difficulties are also probably influenced by negative mood in this population.

Keywords : attention, cancer, childhood leukemia, cognitive test, oncology, self-report, survivors, working memory

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Liste des abréviations

ALL : Acute Lymphoblastic Leukemia

BRIEF-SR : Behavior Rating Inventory of Executive Function, Self-Report version

BSI-18 : Brief Symptom Inventory-18

CAARS-S:L : Conners' Adult ADHD Rating Scale-Self-Report, Long version

CRT : Cranial Radiotherapy

DSF : Digit Span Forward

ISS : Inattention Symptoms Scale

LAL : Leucémie aigüe lymphoblastique

LNS : Letter-Number Sequencing

PANAS : Positive and Negative Affect Schedule

PedsQL-MFS : Pediatric Quality of Life Multidimensional Fatigue Scale, Standard version, Young adult report

QUHC : Quebec University Health Centre

SJUHC : Sainte-Justine University Health Centre

WAIS-IV : Weschler Adult Intelligence Scale—4th edition—French Canadian version

WMI : Working Memory Index

WMS : Working Memory Scale

Remerciements

En guise d’ouverture de mon essai, je tiens à exprimer ma reconnaissance envers toute l’organisation du projet Pétale duquel découle cette étude. Des participants aux chercheurs, votre temps et vos contributions sont énormément appréciés. De manière plus personnelle,

Je tiens à remercier tout spécialement Étienne Bellavance Martin pour sa présence qui à elle seule m’a apporté force et sérénité lors de ces dernières années. Une pensée pour Stanley, ce petit être merveilleux qui a su rendre mes innombrables journées de travail plus douces et plus légères.

Merci à ma famille d’être présente, chaleureuse et réconfortante.

Merci à mon directeur, Dr Serge Sultan, votre patience et votre dévouement m’ont permis de mener ce projet de recherche à terme avec confiance et plaisir.

Introduction

Dans les prochaines pages, l'article empirique découlant de cette étude sera présenté. Il sera soumis à la Revue *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer* sous forme de Brief Report à l'hiver 2019. Une mise en contexte permettra de mieux comprendre les objectifs de l'étude, puis la méthodologie, les résultats, la discussion et les conclusions seront exposés.

Article

Inconsistencies between measures of cognitive dysfunction in childhood ALL survivors: description and understanding

Short running title: Cognitive dysfunction in childhood leukemia survivors

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Introduction

Therapy advances have led to an increase of the 5-year survival rate of childhood Acute Lymphoblastic Leukemia (ALL) reaching 91%[1-3]. However, about half of the ALL survivors develop at least one clinically significant long-term cognitive sequelae[4]. In addition to the type and intensity of treatment, risk factors known to increase the risk of cognitive difficulties include female sex, early age at diagnosis (≤ 5 years), and some genetic characteristics[5,6].

Various studies have shown that ALL survivors who received chemotherapy, combined or not with cranial radiotherapy (CRT), have a lower overall intellectual potential (6-8 IQ points lower) than a healthy population[7,8]. The most commonly observed cognitive deficits in survivors are a limited attention span, working memory and information processing speed[4,7,9]. These deficits become more obvious 2-7 years after the end of treatment[7,10] and should be routinely evaluated as they affect academic performance and quality of life[5,11]. When quantifying these cognitive difficulties, studies tend to use standardized tests, such as Weschler's intelligence scales[8], and self-reported questionnaires, such as the Conners[12] and the Behavior Rating Inventory of Executive Function (BRIEF) scales[13].

It is common practice in oncology research to consider self-reported questionnaires as reliable tools to assess the frequencies of cognitive late-effects[14]. However, recent studies have reported small associations between tested and self-reported cognitive difficulties[15,16]. Several factors may explain this phenomenon. First, cognitive tests may have limited ecological validity[16]. Considering that cognitive tests are usually taken in environments free of distractions and stressors, we could expect that more cognitive difficulties be self-reported than tested. Second, some studies in adult cancer suggest that lower subjective cognitive function was closely related to self-reported physical and mental health functioning including negative mood[15,16], anxious and depressive symptoms[15,17]and fatigue[17,18], but no such study is yet available in the context of pediatric cancer. Finally, studies have pointed to the tendency to normalize one's own experience that could downplay the self-report of one's own difficulties[19,20].

Few studies have investigated concordance between cognitive measures in the population of pediatric cancer survivors[10,21]. They have estimated the importance of these differences in this population with regards to attention (tested deficits 30% vs. self-reported deficits 10%) and working memory (59% vs. 28%)[10,21]. These two cognitive domains are key in understanding the cascade of cognitive deficits in this population. To our knowledge, no study in pediatric oncology has yet attempted to explain these differences empirically.

The first aim of the current study was to provide a detailed description of agreements and differences in the domains of attention and working memory, as assessed by cognitive tests and self-reports amongst individuals who were successfully treated for childhood ALL. The second aim was to explore the contributing role of emotional status, characterized by emotional distress, depression and anxiety, positive and negative affects, and fatigue.

Methods

Participants

The sample was composed of individuals who had been successfully treated for ALL (PETALE cohort) at the Sainte-Justine University Health Centre (SJUHC) or Quebec University Health Centre (QUHC). A detailed description of the methodology for cohort recruitment and characterization can be found in another article [22]. 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) neither had a relapse nor hematopoietic stem cell transplantation. A total of 374 survivors aged between 13 and 40 were contacted to participate in this study (see online supplemental materials Flow chart Figure S1). The sample of the current study consists of 138 survivors aged 19 and older for whom both the cognitive tests and self-reported questionnaires were available (Table 1). Only the data collected from the adult participants were used to ascertain that status was not reported by a parent. The study protocol was approved by the Research Ethics Board at both sites (SJUHC: #2013-479; QUHC: #MP-20-2015-2176).

Procedure and data collection

The data were collected as part of a study on the biomarkers of the long-term effects of the ALL at the SJUHC and QUHC [22]. 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). Participants' detailed clinical history was collected from their medical records.

Measures

Test-based cognitive measures

The cognitive test battery included subtests from the Weschler Adult Intelligence Scale – 4th edition – French Canadian version (WAIS-IV) [23]. To assess working memory, two scores from the WAIS-IV were used: the Working Memory Index (WMI) and the Letter-Number Sequencing (LNS) subtest (percentiles). To assess attention, the percentile score of the Digit Span Forward (DSF) subtest was used. The DSF subtest assesses attention independently of working memory.

Self-reported cognitive measures

Standardized self-administered cognitive questionnaires were used. To assess working memory difficulties, the adult version of the Behavior Rating Inventory of Executive Function (BRIEF-SR)[24] was administered. The BRIEF-SR is a standardized questionnaire evaluating adults' executive functions and self-regulation in their daily lives over the last six months. In this study, only the Working Memory Scale (WMS) of the BRIEF-SR was used. This scale measures one's ability to retain information when performing a task, coding information, or generating goals or plans in a sequential manner (i.e., "*Forgets what he/she was doing,*" "*When sent to get something, forgets what he/she is supposed to get*"). The scale is composed of 8 items that can be rated from 0 (*never*) to 2 (*often*). Its internal consistency was satisfactory (α=.80). To assess self-reported attention difficulties, the self-administered long version of the Conners Adult ADHD Rating Scale (CAARS-S:L)[12] was used. The CAARS-S:L is a standardized

questionnaire evaluating the presence and intensity of the symptoms associated with attention deficit with or without hyperactivity. In this study, only the Inattention Symptoms Scale (ISS) was used (i.e., "*Inattentive, easily distracted*"). The scale is composed of 9 items rated from 0 (*never*) to 3 (*very often*) (α=.88). For both self-reported questionnaires, the percentile scale scores were reverse coded, with lower percentile scores representing more difficulties.

Affective measures

To assess the presence and intensity of general distress, depressive, and anxious symptoms over the last 7 days, the Brief Symptom Inventory (BSI-18) was used. The BSI-18 is composed of 18 items scored on a scale ranging from 0 (*not at all*) to 4 (*very much*). The scale includes 4 scores, 3 of which were used in this study (we excluded Somatization). The general distress index consists of 18 items and includes depressive, anxious, and somatic symptoms (α=0.89). The depression index consists of 6 items and refers to feelings of loneliness, anxiety, depreciation, and despair (α=0.81). The anxiety index consists of 6 items and refers to feelings of nervousness, tension, agitation, and fear (α=0.80). We used T scores and cut-points from the original manual to determine cases at-risk of distress, anxiety, and depression[25]. To assess participants' overall presentation of affects over the last two weeks, we used the Positive and Negative Affect Schedule (PANAS)[26]. The PANAS includes two scores (ranging from 0 to 50), each consisting of 10 items scored on a scale ranging from 1 (*not at all*) to 5 (*extremely*). The first score indicates the level of negative affect (i.e., to feel "anxious," "angry", α=0.81) whereas the second indicates the level of positive affect (i.e., to feel "interested," "excited", α=0.80). Participants' level of fatigue was determined with the Pediatric Quality of Life Multidimensional Fatigue Scale, Standard version, Young adult report (PedsQL-MFS)[27]. To avoid spurious overlaps with cognitive complaints, only the general fatigue index (ranging from 0 to 100) was used. The scale includes physical fatigue and activity level (i.e., "*I feel too tired to do things that I like to do*"; α=0.91). This index consists of 6 items scored on a scale ranging from 0 (*not at all a problem*) to 4 (*a lot of problem*) that are then recoded to specific percent values (0=100, 1=75, 2=50, 3=25 et 4=0). The final scores were reverse coded, with higher scores indicating a higher level of general fatigue.

Statistical analyses

Preliminary analyses

We sought to optimize the level of agreement between measures on working memory and attention difficulties. We explored sensitivity, specificity, agreement rate using three thresholds commonly used in cognitive functioning measures: -1 SD, -1.2 SD and -1.5 SD. We calculated intercorrelations between cognitive assessments, both self-reported and test-evaluated, and emotional distress and affectivity.

Main analyses

For the first aim of the study, we computed rank differences D based on within sample z-scores for both cognitive tested and self-reported elements using the formula: D=(tested z-score)-(self-reported z-score). This difference was calculated for both cognitive domains of interest in this study, i.e., working memory and attention. For working memory, the WMI and LNS subtest of the WAIS-IV as well as the WMS of the BRIEF-SR were used. As for attention, the DSF subtest of the WAIS-IV as well as the ISS of the CAARS-S:L were used. From here onwards, the differences observed between these measures will be referred to as follows: WMI-WMS, LNS-WMS, and DSF-ISS. For the second aim of the study, we conducted three linear regression models in which each rank difference was in turn the dependent variable. The contributing factors/independent variables were: general distress, depression, anxiety, positive and negative affects, and general fatigue. Models were adjusted for age and gender to account for higher prevalence in older individuals and women.

Results

Cognitive description

In average, our sample did not show greater working memory or attention deficits than normative samples (WMI: M=29.02; SD=26.16, LNS: M=32.69; SD=25.76, DSS: M=30.62; SD=25.33). Yet, when compared to norms, the sample included a higher proportion of participants with clinically significant deficits on working memory (respectively 16% and 15%

vs. 9%) and attention (21% vs. 9%). Participants did not report greater working memory (WMS: M=52.07; SD=27.99) or attention deficits (ISS: M=56.59; SD=31.79) on self-reported questionnaires. With these measures, clinically significant difficulties in working memory (10.4%) and attention (11.6%) were as frequent as in normative samples (9%; Table S1).

Affective description

Compared to the general population, survivors reported similar general distress (M=49.82; SD=9.17), depressive symptoms (M=48.62; SD=8.72), or anxious symptoms (M=48.70; SD=9.46). Participants reported more intense positive (M=33.77; SD=5.17) than negative affect (M=18.15; SD=5.50, $p<0.001$). Participants' perceived general fatigue was also heterogeneous, with a coefficient of variation SD/M of 89% within the sample (PedsQL-MFS, M=23.67; SD=20.98; Table S1).

Preliminary analyses

The most favorable clinical thresholds optimizing agreement rates between tested and self-reported measures were set at -1.5 SD (WMI-WMS, LNS-WMS et DSF-ISS; Figure 1). The specificity/sensitivity imbalance indicated that self-reported measures reliably identified true negatives (median specificity=0.87), but did not identify true positives, i.e. participants presenting actual difficulties on cognitive tests (median sensitivity=0.10). When exploring intercorrelations, we found test-derived measures to be weakly associated with self-reported cognitive functioning on memory (WMI and WMS: r=0.208, p=0.024; LNS and WMS: r=0.175, p=0.040) but not attention (DSF and ISS: r=0.047, p=0.592). We found test-based cognitive measures to be basically uncorrelated with emotional distress and affectivity (median r: WMI: -0.033; LNS: 0.001; DSF: -0.066). In contrast, self-reported cognitive measures were largely associated with these domains (median r: WMS: -0.409; CAARS-S:L: -0.539) (Table S2).

Main analyses

Upon analyzing rank differences between tested and self-reported results for the two domains, all distributions appeared unbiased and centered, suggesting an absence of a systematic pattern in favor of "underestimation" or "overestimation" of difficulties (Figure S2). On average, participants did not differ, with medians of deviation close to 0 (medians: WMI-WMS=0.12, LNS-WMS=-0.50 et DSS-ISS=0.07). However, there was some variability with interquartile ranking differences of 1.68 for WMI-WMS, 1.88 for LNS-WMS, and 1.94 for DSS-ISS.

When analyzing the potential contributors of the differences found between tested and self-reported cognitive abilities, we found that a larger negative affectivity was associated with differences suggesting an imbalance in favor of larger self-reported than tested difficulties. When using a subtest independent of the attention domain (LNS), the differences were significantly associated with increased negative affects (β=0.066; p=0.023). The results were similar for attention, with a contribution of negative affect to the difference (β=0.087; p=0.005). Other associations were unsignificant. Specifically, differences were not associated with age, gender, distress, depression, anxiety, or general fatigue (p>.120) (Table S3).

Discussion

In a cross-sectional study involving 138 childhood ALL adult survivors, we found important inconsistencies between measures on working memory an attention and identified negative affect as a probable contributing factor to the imbalance of self-reported over tested difficulties.

With respect to their cognitive profile, participants' performance on standardized tests assessing working memory and attention appears similar to that found in a recent meta-analysis (M=-0,5 SD)[7]. The rate of significant deficits 15-21% was double that of the general population which reflects long-term cognitive sequelae of ALL treatments. Our data are consistent with the observation that the two cognitive domains of working memory and attention are particularly

affected[7,9]. In comparison, when we applied self-reported questionnaires, the frequency of deficits in working memory and attention was around 10%. This rate is similar to previous studies using self-rated questionnaires[13,14,28]. These findings suggest that studies using exclusively self-reported questionnaires, such as several large-scale studies[13,14], could underestimate neurocognitive late effects. Differences in measurement strategy to test cognitive abilities could also explain the large range of frequencies found in the literature. We also found that, in the context of pediatric oncology, cognitive questionnaires were specific but not sensitive. Consequently, self-reported questionnaires would not be recommended to assess positive cases, but rather would be recommended to discard negative cases. In this population, these cognitive questionnaires should not be considered as a valid approach to assess the neuropsychological status when used alone and should probably not be used to derive prevalence in population-based studies. However, questionnaires designed to screen for cognitive deficits specific to neurological conditions, such dementia[29] and multiple sclerosis[30], are successfully used. Thus, studies should continue developing effective screening questionnaires for pediatric cancer survivors.

One plausible hypothesis to explain apparent inconsistency between methods calls for a general tendency of minimizing one's difficulties (or normalizing) among survivors when self-describing one's functioning[20]. This tendency could reflect a positive adaptation to their situation or growth linked to the stress suffered. In the pediatric population, studies have found that social support including family and peers support[31] and sense of security obtained from teacher[32], was associated with a positive adjustement following cancer. Indeed, we found that their mean self-reported negative affect was about half the size of their self-reported positive affect. The rate of participants with significant affective symptoms was also similar to the general population, with the overall portrait of the group being even more positive than in comparable samples.[20,33,34] Importantly, this predominance of positive affect was observed here in a young adult survivors group, with still few objective sequelae. Previous research have shown that psychological symptoms and negative mood tend to increase with development during adulthood, as responsibilities become more important, social support becomes less present and physical sequelae become more explicit [35].

In our study, we did not identify a systematic pattern toward a clear imbalance between self-reported and cognitive-tested issues. Consequently, there was no tendency to "overestimate" or "underestimate" one's difficulties. In subsequent analyses aiming at explaining differences between measures, we found that only a high level of negative affect, among several other psychological factors (distress, depression, anxiety, and fatigue), could partially explain this phenomenon. Although statistical models only explained a small share of variance in observed differences, this finding highlights the importance of considering negative affect or mood, when interpreting self-report[16]. This observation is consistent with a larger literature about the role of self-reported status in the discrepancy between cognitive tests and questionnaires, across different conditions, in normal controls, and across the lifespan, such as attention disorders, and multiple sclerosis[36]. Conversely, in the case of parent or teacher report, questionnaires have been associated to testing and performance per se[37,38].

We found that participants' self-reported cognitive difficulties were more closely related to their self-reported affect than to their results on standardized tests[39], suggesting methodological variance. Similar findings have been observed in other clinical populations, including in neurology or psychiatry[39-41], suggesting methodological variance is a robust finding and affect pediatric oncology in a similar way as other clinical domains. It is possible that the questionnaires assessed less the cognitive status than the individual perception of cognitive abilities and functioning, i.e. metacognition. The association between negative affect and patients' cognitive self-reports could be explained by a negative feedback loop. Sad, tensed, or angry participants would be more likely to focus on their cognitive failures and to perceive their cognitive "impairment" as more severe than it is. This would in turn increase their feelings of sadness, tension, or anger.[42] Finally, whereas frequencies of cognitive difficulties are systematically higher in girls/women, due to cerebral specificities, we did not find that sex was related with differences between test-based and self-reported cognitive difficulties, consistent with previous analyses performed in the PETALE cohort[43].

Clinical Implications

Our findings suggest that self-reported cognitive questionnaires should not be used to assess the presence of cognitive deficits and derive frequencies in large-scale studies. Corrective

procedures may be elaborated in the future to address this issue. In addition, cognitive tests and self-reports probably do not measure the same type of cognitive activity[16]. As cognitive self-report may be vulnerable to deteriorated mood, it could be useful to control for mood in surveys evaluating cognitive deficits with self-reports.

Study limitations

First, our findings reflect the experience of a relatively small sample of young adult survivors of ALL at a specific time. Thus, these might not be generalized to survivors of other types of cancer and/or at other time points along their trajectory. Second, it should be noted that it is hard to find equivalent domains in both types of measures (test and self-reports). For instance, it was more difficult to clearly distinguish working memory and attention among self-reported questionnaires than among standardized tests, which could represent a bias in the study. In addition, cognitive questionnaires rarely evaluate just one function precisely. For example, the CAARS-S:L questionnaire evaluates, beyond attention, work organization and forgetfulness in daily life which are not considered as such by standardized tests used in our study[12]. Finally, a large proportion of the observed difference between methods still remain unexplained, as the contributors considered here explaining only 14-22% of the inconsistency variance. Future research should include other factors that might influence cognitive assessment in this population, such as coping styles[44].

Conclusions

In conclusion, our study of 138 adult survivors of childhood ALL suggested that deficits in working memory and attention were more frequent when assessed by standardized tests than self-reports. Yet, we found no systematic tendency to overreport or underreport one's difficulties. The study identified negative affect as a factor of imbalance between data acquisition method, favoring higher self-reported cognitive difficulties. Future research should recognize that, in the context of pediatric oncology, tested and self-reported cognitive assessments cannot be considered interchangeably both for frequency assessment or other research and clinical issues. It is likely that the information reported by pediatric cancer survivors depends on a variety of factors, including their emotional status.

Acknowledgements

The team would like to thank all the participants recruited for the study and the clinical research staff.

Funding

This work was supported by the Institute of Cancer Research of the Canadian Institutes of Health Research, in collaboration with C17 Council, Canadian Cancer Society, Cancer Research Society, Garron Family Cancer Centre at the Hospital for Sick Children, Ontario Institute for Cancer Research, Fonds de Recherche du Québec-Santé Cancer Grant, and Pediatric Oncology Group of Ontario grant number TCF 118694.

Conflict of Interest

The authors declare that there is no conflict of interests.

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Table 1.

Sample description of 138 pediatric ALL adult survivors (> 19 years) from two DFCI sites in Quebec, Canada

Participants' characteristics	**Total Sample (N=138) M (SD) or N (%)**	**St-Justine UHC (N=122) M (SD) or N (%)**	**Laval UHC (N=16) M (SD) or N (%)**	**Comparisons[e]**
Sociodemographic characteristics				
Sex				
Male	65 (47.1)	59 (48.4)	6 (37.50)	
Female	73 (52.9)	63 (51.6)	10 (62.50)	*p*=.440
Age at follow up, years	25.91 (4.75)	26.2 (4.90)	25.13 (3.50)	*p*=.601
Marital Status				
Single/Divorced	86 (62.3)	75 (61.5)	11 (68.80)	
Married/Common law	52 (37.6)	47 (38.5)	5 (31.1)	*p*=.785
Ethnicity				
Caucasian	131 (94.9)	115 (94.3)	16 (100.00)	
Other	7 (5,1)	7 (5.7)		n/a
Educational background				
Pre-high school	12 (8,7)	10 (8.20)	2 (12.50)	
High school	22 (15.9)	20 (16.04)	2 (12.50)	
Graduate/PED[a]	30 (21.9)	28 (23.00)	2 (12.50)	
CEGEP[b]	49 (35.5)	41 (33.6)	8 (50.00)	
University (UG/PG)[c]	25 (18)	23 (18.8)	2 (12.5)	n/a
First language				
French	134 (97.1)	118 (96.7)	16 (100.00)	
English	2 (1.4)	2 (1.60)		
Other[d]	2 (1.4)	2 (1.6)		n/a
Clinical characteristics				
Age at diagnosis, years	7.89 (5.01)	7.97 (5.11)	7.31 (4.31)	*p*=.849
Time since diagnosis	18.02 (6.35)	18.05 (6.64)	17.81 (3.50)	*p*=.915
Radiotherapy				
Yes	94 (68.1)	36 (29.5)	8 (50.00)	
No	44 (31.9)	86 (70.5)	8 (50.00)	*p*=.088
ALL risk status				
Standard	51 (37.2)	41 (33.90)	10 (62.50)	
High	86 (62.8)	80 (66.10)	6 (37.50)	*p*=.027*

[a]PED, professional education diploma. [b]CEGEP is the first stage of higher education after high school, exclusively in the province of Quebec, Canada. [c]UG/PG, undergraduate/postgraduate. [d]Other: Vietnamese, Spanish. [e] Due to the small sample at Laval UHC comparaisons were performed with non-parametric Fisher's exact test and Mann-Whitney U test.

*$p < 0.05$

Supplementary Table S1.

Description of working memory and attention difficulties evaluated by cognitive test and self-report measures and affective status in a sample of 138 pediatric ALL adult survivors

Measures	Mean (SD)	Frequency below cutpoint N (%)†
Cognitive measures		
WAIS-IV percentile		
Working Memory Index	30.62 (25.33)	22 (16.1)[a]
Letter-Number Sequencing	32.69 (25.76)	21 (15.3)[a]
Digit Span Forward	29.02 (26.16)	25 (21.1)[a]
BRIEF-SR percentile		
Working Memory Scale	56.59 (31.79)	14 (10.4)[a]
CAARS-S:L percentile		
Inattention Symptoms Scale	47.93 (27.99)	16 (11.6)[a]
Affective measures		
BSI-18 T-score		
General distress	49.82 (9.17)	14 (10.15)[b]
Depression	48.62 (8.72)	13 (9.42)[c]
Anxiety	48.70 (9.46)	12 (8.69)[c]
Somatization	50.95 (8.89)	21 (15.30)[c]
PANAS (raw score)		
Positive affects	33.77 (5.17)	
Negative affects	18.15 (5.50)	
PedsQL-MFS (raw score)		
General fatigue	23.67 (20.98)	

Note. †The frequency in a normative sample is approximately 9% (Normal distribution)

[a] Cut-point = -1.5 SD

[b] Standard algorithm for determining positivity from the BSI-18 manual

[c] Cut-point = 63T score for Depression, Anxiety and Somatization

WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition; BRIEF-SR: Behavior Rating Inventory of Executive Function, Adult version; CAARS-S:L: Conners Adult ADHD Rating Scale, Self-report, Long version; PANAS: Positive and Negative affect Schedule; PedsQL: Pediatric Quality of Life Multidimensional Fatigue Scale, Standard version, Young adult report; BSI-18: Brief Symptom Inventory.

Supplementary Table S2.

Pearson correlations between cognitive test, cognitive self-report measures, and affective status in a sample of 138 pediatric ALL adult survivors

	1	2	3	4	5	6	7	8	9	10	11
1. Working Memory Index (WAIS-IV)	1.00										
2. Letter-Number (WAIS-IV)	0.899***	1.00									
3. DigitSpan Forward (WAIS-IV)	0.737***	0.518***	1.00								
4. Workig Memory Scale (BRIEF-SR)	0.208*	0.175*	0.116	1.00							
5. Inattention Symptom Scale (CAARS:S-L)	0.125	0.044	0.047	0.735***	1.00						
6. General Distress, (BSI-18)	-0.084	-0.064	-0.085	-0.430***	-0.575***	1.00					
7. Anxiety (BSI-18)	-0.027	0.017	-0.043	-0.399***	-0.515***	0.830***	1.00				
8. Depression (BSI-18)	-0.039	-0.015	-0.090	-0.310***	-0.512***	0.779***	0.779***	1.00			
9. Negative Affect (PANAS)	-0.026	-0.045	-0.009	-0.418***	-0.589***	0.672***	0.651***	0.618***	1.00		
10. Positive Affect (PANAS)	-0.005	0.045	-0.046	0.161	0.312***	-0.267**	-0.135	-0.321***	-0.189*	1.00	
11. General fatigue (PedsQL)	-0.101	-0.052	-0.093	-0.470	-0.582***	0.725***	0.624***	0.622***	0.642***	-0.323***	1.00

*p<0.05, **p<0.01, ***p<0.001

Supplementary Table S3.

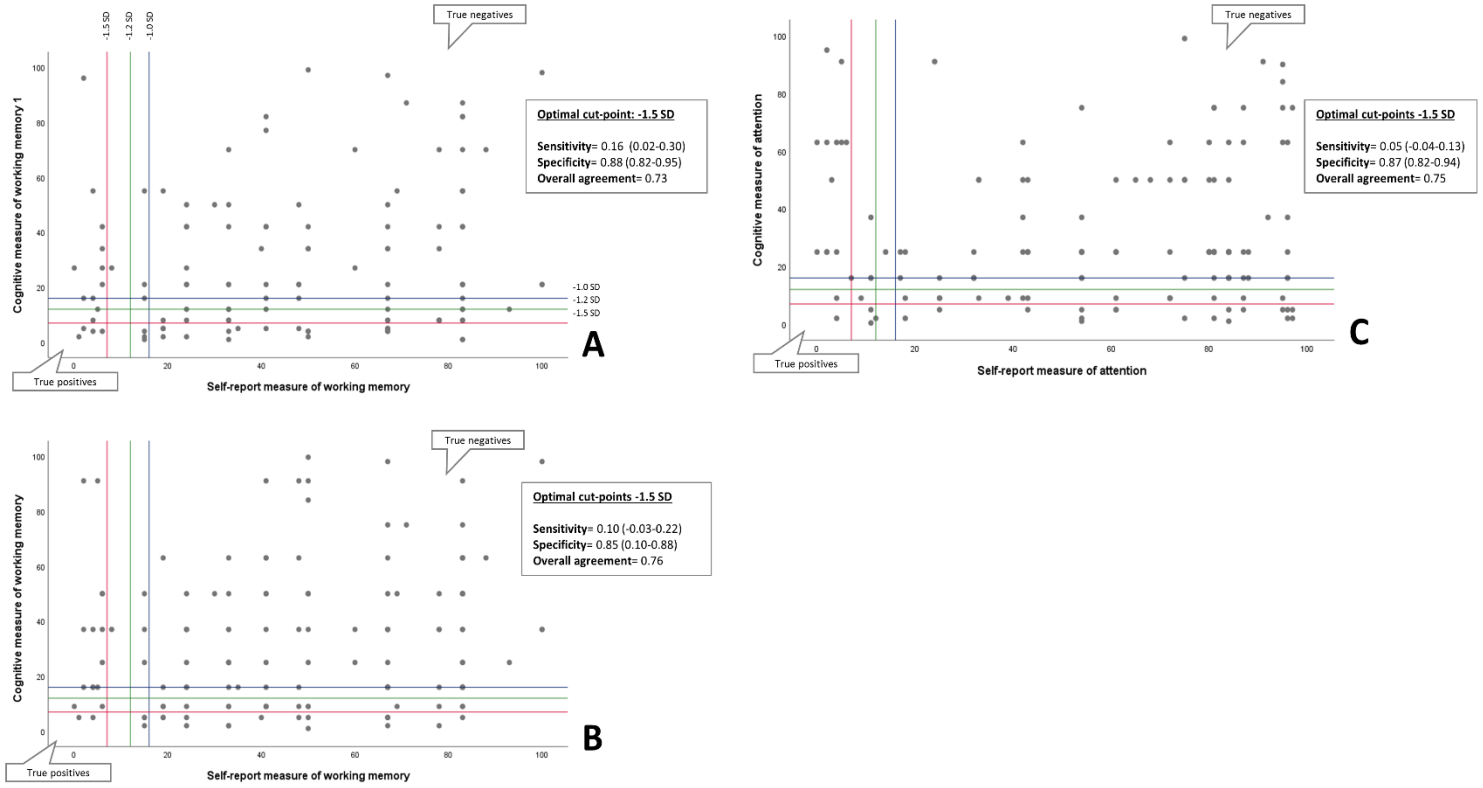
Summary of multiple regression models predicting inconsistency between cognitive measures and self-report measures in domains of working memory and attention difficulties in a sample of 138 pediatric ALL adult survivors

Models	B	Std Error	*B*
A. Inconsistency on working memory			
Block 1			
Age	-.003	.025	-.009
Sex	.232	.242	.091
Block 2			
Positive affect (PANAS)	-.027	.024	-.110
Negative affect (PANAS)	.058	.031	.256
General distress (BSI-18)	-.015	.026	-.022
Depression (BSI-18)	-.003	.033	.156
Anxiety (BSI-18)	.021	.025	-.111
General Fatigue (PedsQL)	.005	.009	.090
B. Inconsistency on working memory			
Block 1			
Age	-.022	.022	-.081
Sex	.368	.223	.145
Block 2			
Positive affect (PANAS)	-.017	.022	-.070
Negative affect (PANAS)	.066	.029	.287*
General distress (BSI-18)	-.018	.023	.007
Depression (BSI-18)	.001	.031	.090
Anxiety (BSI-18)	.012	.022	-.128
General Fatigue (PedsQL)	.010	.008	.169
C. Inconsistency on attention			
Block 1			
Age	-.022	.025	-.074
Sex	.371	.237	.135
Block 2			
Positive affect (PANAS)		.023	-.167
Negative affect (PANAS)	-.044	.031	.352*
General distress (BSI-18)		.024	-.063
Depression (BSI-18)	.087	.033	.051
Anxiety (BSI-18)	.009	.024	.057
General Fatigue (PedsQL)	-.010	.008	.027
	.007		
	.002		

Note. Inconsistencies were measured as a difference between z-scores in tested and self-reported measures, and thus reflect within-sample rank differences. For Model A we used the inconsistency between the WMI (WAIS-IV) and WMS (BRIEF-A). For Model B we used the inconsistency between L-N (WAIS-IV) and WMS (BRIEF-SR). For Model C we used the inconsistency between DSF (WAIS-IV) and ISS (CAARS-S:L).
For model A, contribution ΔR^2 were: Block 1= .002, Block 2= .143. Total model F= 2.278* R^2= .081
For model B, contribution ΔR^2 were: Block 1=.012, Block 2= .164. Total model F= 3.406* R^2= .125
For model C, contribution ΔR^2 were: Block 1= .015, Block 2= .217. Total model F= 4.628** R^2= .181
*p < 0.05
**p < 0.01

Figure 1.

Diagnostic performances of a self-report measures to identify working memory and attention difficulties from cognitive testing in a sample of 138 pediatric ALL adult survivors

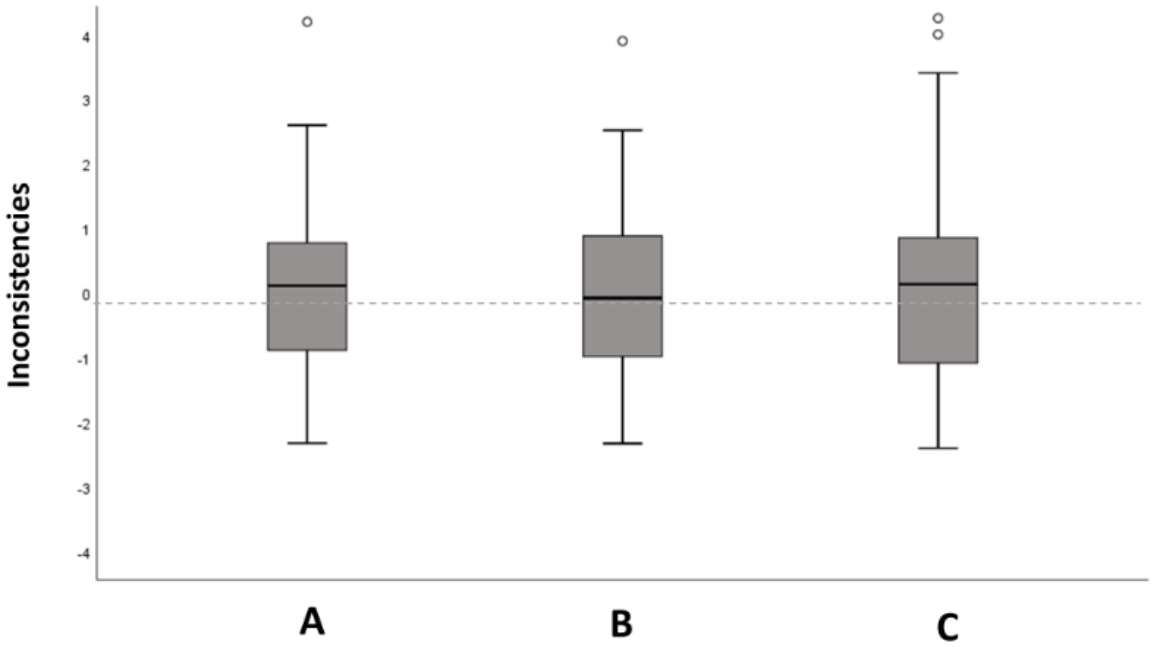


Note. **Panel A** cognitive measure of working memory corresponds to WMI (WAIS-IV) and self-report measure of working memory corresponds to WMS (BRIEF-SR). **Panel B** cognitive measure of working memory corresponds to L-N (WAIS-IV) and self-report measure of working memory corresponds to WMS (BRIEF-SR). **Panel C** cognitive measure of attention corresponds to DSF (WAIS-IV) and self-report measure of attention corresponds to ISS (CAARS-S:L).

Agreement = TP + TN/total, Sensitivity = TP/TP + FN, and Specificity = TN / TN + FP, where TP = true positives, FP = false positives, TN = true negatives and FN = false negatives.

Supplementary Figure S1.

Box plot display of inconsistencies between cognitive measures and self-report measures on working memory and attention difficulties in a sample of 138 pediatric ALL adult survivors



Note. Distribution A describes the differences between Z-scores of WMI (WAIS-IV) and WMS (BRIEF-A). Distribution B between L-N (WAIS-IV) and WMS (BRIEF-A). Distribution C between DSF (WAIS-IV) and ISS (CAARS-S:L). Differences between Z-score are calculated by : cognitive measures – self-report measures.

Supplementary Figure S2.

Study structure and flow Montreal treatment site: Sainte-Justine University Health Center (SJUHC, Montreal, Canada), Quebec treatment site: Quebec University Health Center (QUHC, Quebec, Canada)