Understanding neurocognitive outcomes in Pediatric Brain Tumour Survivors in context: Examining medical and sociodemographic risk factors

Yustine Alejandra Carruyo Soto¹, Laurianne Buron¹, Clémentine Lopez², Kristopher Lamore², Cécile Flahault², Estelle Favré², Lucille Karsenti³, Serge Sultan¹, Christelle Dufour², Émilie Rondeau¹, and Leandra Desjardins¹

¹Centre de Recherche du Centre Hospitalier Universitaire Sainte-Justine
²Gustave Roussy

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Abstract

Background. Pediatric Brain Tumour Survivors (PBTS) are at risk of neurocognitive impairments. This study assesses both objective and parent-reported cognitive functioning in PBTS and examines how various factors (medical and socio-demographic) may contribute to cognitive outcomes. PBTS (n = 100) were on average 5.77 years old at diagnosis, 12.36 years from diagnosis, and 47% female. Method. Participant IQ was measured using the full-scale IQ of the WISC-IV and WISC-V, and executive function using the BRIEF2 Global Executive Composite. Examined contributors included: age, sex, tumour location, time since diagnosis, radiation type, chemotherapy dose (high versus low), parent's education level and mother's partnered status. Results. Higher IQ was correlated with higher executive function skills. Differential patterns were observed with socio-demographic variables influencing working memory, while radiation influenced processing speed. Higher education level in both mothers and fathers and maternal partnered status were associated with higher child working memory. Proton radiation was associated with higher processing speed scores. However, only time since diagnosis contributed to total IQ and working memory in multiple linear regression analyses. Conclusion. The findings shed light on the sparsely examined domain of the impact of socio-demographic variables on neurocognitive outcomes in PBTS. Time since diagnosis remains a significant predictor of cognitive performance, accentuating the need for early identification and intervention in PBTS.

Affiliations:

1 CHU Sainte-Justine Research Centre, Montreal, Canada
2 Department of Psychology, University of Montreal, Canada
3 Department of Pediatrics, University of Montreal, Canada
4 Gustave Roussy Hospital, Pedopsychiatry, France
5 Gustave Roussy Hospital, Psycho-Oncology Unit, France
6 Laboratory of Psychopathology and Health Process, Paris Cité University, France
Abstract

Background . Pediatric Brain Tumour Survivors (PBTS) are at risk of neurocognitive impairments. This study assesses both objective and parent-reported cognitive functioning in PBTS and examines how various factors (medical and socio-demographic) may contribute to cognitive outcomes. PBTS \( (n = 100) \) were on average 5.77 years old at diagnosis, 12.36 years from diagnosis, and 47% female. Method . Participant IQ was measured using the full-scale IQ of the WISC-IV and WISC-V, and executive function using the BRIEF2 Global Executive Composite. Examined contributors included: age, sex, tumour location, time since diagnosis, radiation type, chemotherapy dose (high versus low), parent’s education level and mother’s partnered status. Results . Higher IQ was correlated with higher executive function skills. Differential patterns were observed with socio-demographic variables influencing working memory, while radiation influenced processing speed. Higher education level in both mothers and fathers and maternal partnered status were associated with higher child working memory. Proton radiation was associated with higher processing speed scores. However, only time since diagnosis contributed to total IQ and working memory in multiple linear regression analyses. Conclusion . The findings shed light on the sparsely examined domain of the impact of socio-demographic variables on neurocognitive outcomes in PBTS. Time since diagnosis remains a significant predictor of cognitive performance, accentuating the need for early identification and intervention in PBTS.
Introduction

Tumours of the central nervous system are the second most common form of pediatric cancer. Advances in diagnostic and treatment techniques have significantly decreased the mortality rate of children diagnosed with brain tumours, leading to a growing number of survivors. With this increasing population, there is a strong need to attend to the quality of their survivorship. Pediatric brain tumour survivors (PBTS) are at risk of several physical and psychosocial late effects. Amongst these late effects experienced by PBTS, cognitive impairments have been highlighted as a significant domain of interest. Attending to cognitive impairments is essential, given their broad impact on other domains of functioning, such as academic achievement, coping, social competence, and overall quality of life.

PBTS are more likely to experience cognitive impairments relative to typically developing peers, as well as children with other forms of pediatric cancer. Most consistently, PBTS have been noted to show impairments in overall IQ, processing speed, working memory, executive functioning, and attention. Cognitive functioning in PBTS has typically been measured based on objective (e.g., Intellectual Quotient [IQ] testing) and/or parent-reported assessments. The Wechsler Intelligence Scale for Children (WISC) and Behavior Rating Inventory of Executive Function (BRIEF) are widely recognized as the gold standard measures for assessing cognitive function in PBTS. The WISC measures a child’s overall intellectual ability, while the BRIEF assesses executive function. On IQ measures, PBTS are generally found to be 12.45 points lower than children without cancer suggesting a significant impact on intellectual abilities of PBTS. For executive function, two studies found between 22% to 31% of PBTS experienced clinically significant scores on the BRIEF Global Executive Composite.

Notably, many PBTS do not experience cognitive impairments throughout their survivorship. Identifying risk factors associated with cognitive impairment in this population is crucial for early identification and intervention, as well as understanding disease and treatment-related morbidity. Previous research has understoodly often examined which medical variables may be associated with greater cognitive impairment in PBTS. Factors associated with neurocognitive impairment in PBTS and other pediatric cancer survivors include: cranial radiation therapy, high dose chemotherapy, younger age at diagnosis, and longer time since diagnosis. Amongst these, young age at diagnosis and cranial radiation have been most consistently associated with a higher likelihood of cognitive impairments. Indeed, young children with a brain tumour, particularly those under the age of five, are more susceptible to poorer cognitive outcomes as their treatment (particularly cranial radiation) may influence neurodevelopment. In addition, longer time since diagnosis has been associated with lower IQ, with patients decreasing an average of 2.21 points yearly. Moreover, neurotoxicity has been associated with high doses of chemotherapeutic agents, particularly when combined with radiation therapy. Finally, more recently, evidence has emerged indicating that focal proton radiotherapy may have a more beneficial impact on cognitive functioning relative to photon radiotherapy, an important finding which may inform treatment approaches and warrants further study.

Although medical variables have been essential targets of investigation of cognitive related morbidity in PBTS, there is also a need to consider the contribution of sociodemographic variables on the neurocognitive outcomes of PBTS. Some evidence suggests that female PBTS are at greater risk of higher neurocognitive impairments, although other studies have found the contrary with males being at higher risk. Moreover, existing literature suggests that pediatric cancer survivors hailing from low socioeconomic backgrounds may face greater risks of experiencing cognitive challenges, whereas those with high socioeconomic status (SES) may be shielded from adverse cognitive problems. Studies of pediatric leukemia survivors have found that parental education and private insurance (as opposed to public) are associated with higher child cognitive functioning. These findings highlight the influence of SES on neurocognitive outcomes. However, few studies have assessed the impact of SES on specific cognitive factors (e.g., processing speed, working memory) and no studies thus far have examined SES-related factors and their impact on both objective and parent-reported cognitive functioning in PBTS. It is essential to investigate both medical and sociodemographic factors impacting PBTS cognitive functioning to fully understand the contextual factors influencing their survivorship.
Here we investigate the role of both medical and SES-related variables on key cognitive outcomes in PBTS. Our primary aim is to report both objective (IQ; total IQ, processing speed, and working memory) and parent-reported (BRIEF; Global Executive Composite) cognitive functioning in a relatively large (n = 100) sample of PBTS. This sample size is notable given the low base rate of pediatric brain tumour diagnoses and inclusion of direct assessment measures. In addition, there has been limited attention to the examination of sociodemographic cognitive risk and protective factors in PBTS. Our secondary aim is therefore to examine the influence of multiple risk factors, including medical (age, sex, time since diagnosis, chemotherapy dose, radiation type) and socio-demographic factors (parent’s education level and mother’s partnered status) on key cognitive outcomes in PBTS. Findings have important implications for informing our understanding of cognitive functioning in this population and identifying points of intervention.

Method

Participants

Participants were recruited from a larger study examining psychosocial functioning in children diagnosed with cancer, taking place at the Gustave Roussy Hospital in Villejuif, France. Youth were eligible to participate in the current study if they had a brain tumour diagnosis, were in remission or without oncological treatment for at least one year, and aged 6 to 16 years old. Parents or legal guardians had to reside in France, be French-speaking and agree that the research team can access the child’s medical record. Exclusion criteria for children and adolescents were: a history of autism spectrum disorder and/or preexisting history of intellectual disability defined as IQ < 70, a relapse at the time of assessment. The exclusion criterion for parents was a diagnosis of a severe psychiatric disorder, psychotic in nature, with the potential to alter their relationship to reality (schizophrenia, schizoaffective disorder, chronic delirium, etc.). All procedures were approved by the institutional review board at Gustave Roussy Cancer Institute. Data collection took place from September 2017 to December 2019. One hundred participants consented to participate in the current study. Participant demographic characteristics are presented in Table 1.

Measures

Cognitive Functioning. Participant IQ was measured using the Full-Scale IQ from the fourth and fifth editions of the Wechsler Intelligence Scale for Children (WISC). The WISC is a series of tests individually administered to evaluate intellectual abilities in school-aged children, specifically those between six and 16 years old. The fourth edition (WISC-IV) consists of ten fundamental subtests that result in four index scores which are then combined to calculate a single Full-Scale Intelligence Quotient (FSIQ) score. The fifth edition (WISC-V) includes 16 subtests, organized into five primary index scores and a FSIQ score. Processing speed was measured using the Coding and Symbol Search subtests from both the WISC-IV & WISC-V. Working memory assessments varied according to the evaluation version: for participants evaluated with the WISC-IV the Digit Span and Letter Number Sequencing subtests were used, whereas those evaluated with the WISC-V completed the Digit Span and Picture Span subtests. Higher scores indicate higher intellectual ability. Raw scores are converted into standardized scores (M=100, SD=15).

Executive function was measured using the second version of the Behavior Rating Inventory of Executive Function (BRIEF2). This is a rating scale designed to evaluate everyday behaviors that reflect executive functions in children and adolescents between the ages of 5 and 18. The parent-report form of the BRIEF2, used in this study, consists of 63 items. The global Executive Composite summary score reflects overall challenges in executive functioning across BRIEF-2 items. Raw scores are converted into T scores (M=50, SD=10).

Medical, Demographic and Socio-demographic Information. Medical data for PBTS was retrieved from their medical charts and the variables examined were: tumour location (supratentorial versus infratentorial), time since diagnosis, type of radiation (photon, proton, photon + proton, no radiation) and chemotherapy dose (low versus high). Age and sex were examined as demographic factors. For SES, the parent’s highest completed education level as well as the mother’s partnered status (single or partnered) were examined.
Statistical Analyses

Descriptive analyses were performed to check for normality and describe participant characteristics. For our primary aim, Pearson correlations were performed to determine associations among objective (WISC-IV, WISC-V) and parent-reported (BRIEF2) measures. For our secondary aim, we examined whether medical or socio-demographic variables were associated with key cognitive variables (total IQ, processing speed, working memory, and executive function) in bivariate analyses. Independent sample t-tests were conducted to examine the difference between sex, chemotherapy dose, tumour location and mother’s partnered status on cognitive variables. One-way ANOVAs were conducted to assess the difference between radiation groups (no radiation, proton, photon, photon + proton) on cognitive variables. Pearson correlation analyses were performed to evaluate the association between age at diagnosis as well as time since diagnosis with cognitive variables. A Spearman rank correlation was conducted to assess the association between parents’ education level and cognitive variables. Baseline medical and socio-demographic characteristics significant at the $P < .10$ level were retained in subsequent multiple regression analyses. For total IQ, regression analyses included parent’s education level, type of radiation and time since diagnosis as predictors. For working memory, the parent’s education level, mothers’ partnered status and time since diagnosis were included as predictors. All p-values were two-sided, and $P < .05$ was considered significant for the results of regression analyses. All analyses were performed using SPSS, version 28.

Results

Preliminary analyses

Descriptive statistics. The mean for total IQ was 88.19 (SD = 17.49), in the below average range, with 16% of scores 2 SD or more below the mean (2% expected). The mean for working memory was 90.12 (SD = 17.76), in the average range, with 16.2% of scores 2 SD or more below the mean (2% expected). For processing speed, the mean was 85.38 (SD = 17.54), in the below-average range, with 18% of scores 2 SD or more below the mean (2% expected). For the BRIEF2 Global Executive Composite, the sample mean was 55.45 (SD = 13.59), in the average range, with 26% obtaining scores 2 SD above the mean (2% expected).

Correlations between objective and parent-reported measures of cognitive functioning

There were significant negative correlations between BRIEF2 Global Executive Composite t-scores and total IQ ($r = -.35, P = <.001$), working memory ($r = -.32, P = .001$), and processing speed ($r = -.36, P = <001$; see Table 2).

Bivariate associations between medical and cognitive variables

There were no significant differences (all $P s > .10$) on all cognitive variables (total IQ, working memory, processing speed, executive function) based on tumor location (supra versus infra) or high dose chemotherapy (yes versus no). A significant effect was found for type of radiation on total IQ [$F(3, 90) = 3.65, P = .015$] and processing speed [$F(3, 96) = 5.74, P = <.001$], where the mean score for the photon group ($M = 84.65, SD = 17.20$) was significantly lower than the mean of the proton group ($M = 97.59, SD = 18.69$) for total IQ. For processing speed, the means of the photon group ($M = 81.38, SD = 16.55$) and the no radiation group ($M = 80.80, SD = 15.76$) were significantly lower than the proton group ($M = 98.11, SD = 18.66$).

There were no significant correlations between age at diagnosis and total IQ, working memory, executive function or processing speed (all $P s > .10$). While there were also no significant correlations between time since diagnosis and processing speed or executive function (both $P s > .10$), time since diagnosis was negatively associated with total IQ ($r = -.24, p = .02$) and with working memory ($r = -.28, P = < .01$).

Bivariate associations between sociodemographic and cognitive variables

There were no significant differences in males versus females for all cognitive variables, $P > .10$. There was a significant difference for mother’s partnered status, $t (96) = -2.00, P = .05$, with PBTS in the single group ($M = 82.84, SD = 18.32$) attaining lower working memory scores compared to the partnered group ($M = 91.86,$
All other cognitive variables were not significantly different ($P > .10$) between the single and partnered groups.

There were significant positive correlations between the mother’s education level on total IQ ($r (91) = .41$, $P = < .001$) and working memory ($r (96) = .40$, $P = < .001$). Father’s education level was also positively associated to total IQ ($r (86) = .36$, $P = < .001$) and working memory ($r (91) = .33$, $P = .001$). There were no significant correlations between parents’ education level and processing speed or executive function ($Ps > .10$) (see Table 3).

**Adjusted multivariate models controlling for total IQ and working memory**

Two exploratory multivariate linear regression analyses were performed for total IQ and working memory, as these were the only variables for which there was more than one significant predictor variable. Based on significant results at the bivariate level ($P < .10$), regression models included mother’s partnered status, parents’ level of education, type of radiation and time since diagnosis for total IQ and working memory only (see Table 4). Results indicated that only time since diagnosis predicted total IQ ($\beta = .22$, $P = .03$) (model $R^2 = .22$). Time since diagnosis was also the only significant predictor of working memory in multivariate analyses ($\beta = -.23$, $P = .02$) (model $R^2 = .27$). Parent’s education level, mother’s partnered status and type of radiation were not significant for either IQ or working memory ($Ps > .05$) (see Table 4).

**Discussion**

Although previous research has largely focused on medical risk factors, and these continue to be important especially as treatment modalities progress, examining sociodemographic variables concurrently remains essential to better understand survivorship in the broader socio-ecological context in which it occurs. In this study differential patterns were observed, with socio-demographic variables influencing working memory and total IQ, while radiation had a significant influence on processing speed and total IQ. Overall, time since diagnosis was found to be a significant predictor of cognitive performance, highlighting the need for early identification and intervention of cognitive functioning in PBTS.

Lower BRIEF2 Global Executive Composite scores were found to be significantly associated with higher WISC Total IQ, Processing Speed and Working Memory. These indicate the potential functional impact (measured by the BRIEF2) that underlying neurocognitive abilities (measured by the WISC) may have. Cognitive screening is a psychosocial standard of care, and the current associations offer support for utilizing the BRIEF2 in this way. However, the moderate effect sizes indicate caution is needed in solely screening with this tool before referral to more comprehensive neuropsychological assessment and intervention. Rather, as broadly suggested in screening, a combined approach involving the BRIEF2, clinical interviewing, and professional judgment is recommended. There is also a need to further explore contributors to functional challenges in PBTS, as there was an absence of significant associations between BRIEF2 scores and medical and sociodemographic variables.

Processing speed had a differential pattern of risk factors compared to working memory. For processing speed, the only significant risk factor was type of radiation. PBTS who received proton radiotherapy had the highest scores on processing speed and total IQ, consistent with previous research. Proton radiotherapy may be more likely to preserve healthy surrounding tissue, but longitudinal studies are needed to determine whether these cognitive preservation effects are sustained over time. Moreover, monitoring disparities in accessing novel care is essential as proton therapy incurs higher costs and limited availability, potentially resulting in unequal access for individuals from lower socioeconomic backgrounds or rural areas.

Lower parental education was associated with lower working memory and total IQ scores. Studies with typically developing children have shown a similar association, and our results suggest it may be similar for PBTS. Interestingly, research indicates that higher education and higher SES are associated with better IQ later in life, but they do not seem to affect processing speed. One possible explanation may be the neurobiological differences associated with SES that specifically influence working memory and IQ but not processing speed. For example, brain regions involved in working memory might be sensitive to chronic...
stress and adversity, often associated with low SES, while regions involved with processing speed are not as sensitive to external factors\textsuperscript{66,67}.

There was also a difference on working memory based on mothers partnered status. It is plausible that partnered status serves as a proxy of socio-economic status, with income potentially impacting the development of working memory\textsuperscript{68}. Indeed, existing research has shown that poverty is linked to lower working memory scores in children in the general population\textsuperscript{69,70}, and households dependent on one source of income are five times more likely to live in poverty than those with two income streams\textsuperscript{71}. The current result of higher working memory in PBTS with partnered mothers emphasizes the need for subsequent investigations delving into the potential moderating roles of parental partnered status and income on cognitive function in PBTS. It also underscores the importance of screening for financial toxicity in parents\textsuperscript{72,73} and providing additional financial and psychosocial support to single parents caring for a child with cancer.

Bivariate and multiple regression results indicated that time since diagnosis was a predictor of lower total IQ and working memory scores, consistent with other studies\textsuperscript{20,51,52}. Some suggest that cognitive abilities in PBTS may not deteriorate over time, but rather that PBTS may have slower skill acquisition compared to their peers\textsuperscript{10}, potentially influenced by the significant absence from school during their treatment\textsuperscript{54,55}. Another possible explanation for this result may be the indirect long-term impact of psychosocial challenges experienced by PBTS (e.g., anxiety, depression, social isolation) on their cognitive functioning\textsuperscript{56-58}. Early identification and cognitive interventions could help reduce the detrimental effects of a longer time since diagnosis. Notably, several cognitive interventions (e.g., psychosocial and school remediation interventions, computerized cognitive training) have been developed\textsuperscript{24,59}. However, there are still inherent challenges to these such as the limited knowledge on their long-term benefits, their costs which are not covered by all insurance providers, as well as the significant time commitment from patients, parents and providers\textsuperscript{59}.

A strength of this study is its sample size, especially considering the low base rate of pediatric brain tumors and the inclusion of time-consuming direct assessment measures. Moreover, the examination of both objective and parent-reported measures in this study offers a comprehensive approach to cognitive functioning, also crucial for making informed choices regarding screening measures. Another strength is the inclusion of sociodemographic variables in addition to medical variables, acknowledging the multifaceted nature of potential risk factors of neurocognitive outcomes within this population.

Limitations of this study present opportunities for further work. First, one study exclusion criterion was of a documented total IQ score below 70, resulting in the exclusion of participants whose cognitive functioning was severely impacted. Second, there was a transition from the WISC-IV to WISC-V version over the course of the study to be consistent with best-recommended clinical practice at the time of assessment. The use of different versions introduced a potential source of variability, although multiple regression findings did not differ with the inclusion of WISC versions in the model. Third, our study was cross-sectional, and it would be important to examine medical and sociodemographic risk factors for changes in neurocognitive functioning longitudinally. For instance, a child with an initial IQ of 120 who experiences a 20-point decline after treatment might still fall within the average IQ range, however; this 20-point reduction is clinically relevant. Finally, our analyses considered only three socio-demographic factors, and future research should consider examining the influence of a multitude of sociodemographic risk factors such as race or ethnicity, language, family dynamics, culture and access to resources\textsuperscript{14}. Although income data was not available in this study, parent’s education level was used as a proxy for assessing longer-term earning potential which is often more stable\textsuperscript{74}.

Overall, each child arrives with a myriad of medical and socio-ecological factors influencing their functioning and developmental trajectory. Social determinants of health are deserving of more attention to better understand additional points of risk and resilience in families. Thus, recognizing and addressing these determinants holds the potential to reshape the trajectory of care and survival for PBTS patients, ultimately translating into improved outcomes and quality of life.

References


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