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Research Article

Predicting neuropsychological late effects in pediatric brain tumor survivors using the Neurological Predictor Scale and the Pediatric Neuro-Oncology Rating of Treatment Intensity

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Abstract

Objective: The Neurological Predictor Scale (NPS) quantifies cumulative exposure to tumor- and treatment-related neurological risks. The Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI) measures the intensity of different treatment modalities, but research is needed to establish whether it is associated with late effects. This study evaluated the predictive validity of the NPS and PNORTI for neuropsychological outcomes in pediatric brain tumor survivors. **Method:** A retrospective chart review was completed of pediatric brain tumor survivors (PBTS) ($n = 161$, $M_{age} = 13.47$, $SD = 2.80$) who were at least 2 years from the end of tumor-directed treatment. Attention, intellectual functioning, perceptual reasoning, processing speed, verbal reasoning, and working memory were analyzed in relation to the NPS and PNORTI. **Results:** NPS scores ranged from 1 to 11 ($M = 5.57$, $SD = 2.27$) and PNORTI scores ranged from 1 ($n = 101$; 62.7%) to 3 ($n = 18$; 11.2%). When controlling for age, sex, SES factors, and time since treatment, NPS scores significantly predicted intellectual functioning [$F(7,149) = 12.86$, $p < .001$, $R^2 = .38$] and processing speed [$F(7,84) = 5.28$, $p < .001$, $R^2 = .31$]. PNORTI scores did not significantly predict neuropsychological outcomes. **Conclusions:** The findings suggest that the NPS has value in predicting IF and processing speed above-and-beyond demographic variables. The PNORTI was not associated with neuropsychological outcomes. Future research should consider establishing clinical cutoff scores for the NPS to help determine which survivors are most at risk for neuropsychological late effects and warrant additional assessment.

Keywords: cancer; neuropsychological assessment; cognition; attention; intellectual functioning; neurological complications

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Childhood brain and central nervous system (CNS) tumors are the second most common childhood malignancy and account for substantial morbidity and mortality (Armstrong et al., 2009; Miller et al., 2021). Advancements in therapies for pediatric CNS tumors have reduced mortality rates with approximately 80% surviving beyond 5 years (Miller et al., 2021). However, survival is not without cost. The neurological and neurophysiological side effects associated with CNS tumors and their treatments place survivors at risk for adverse neuropsychological outcomes, referred to as neurocognitive "late effects" (Anderson et al., 2001; Turner et al., 2009). These deleterious effects typically emerge within the first few years following treatment and affect over 40% of pediatric brain tumor survivors (PBTS) (Glauser & Packer, 1991). Pediatric brain tumor survivors (PBTS) experience late effects across a core set of cognitive domains, including executive function, processing speed, working memory, and attention (Kiehna et al., 2006; Palmer et al., 2013). Weaknesses in these domains can range from mild difficulties to disrupted functional outcomes that require ongoing need for support into adulthood (Maddrey et al., 2005; Robinson et al., 2010). Moreover, neurocognitive late effects have a significant impact on PBTS' quality of life by impairing academic, psychosocial, and vocational functioning (Ellenberg et al., 2009; Netson et al., 2016).

As survivorship rates increase, there is a growing need to identify risk factors for neurocognitive late effects. Efforts to identify these risk factors have consistently shown that, in addition to tumor location (Patel et al., 2011), each of the three commonly used treatment modalities (e.g., surgical resection, chemotherapy, and cranial/cranio-spinal radiation) affect normal brain development and negatively impact neurocognitive outcomes. For example, surgical resection and its associated perioperative complications (e.g., hydrocephalus) are associated with impaired intellectual and neurocognitive functioning in PBTS (Hardy et al., 2008; Ris & Noll, 1994). Cranial radiation therapy (CRT) is associated with significant declines across multiple domains that persist for years posttreatment, with the incidence and severity of neurocognitive risk being dose- and volume-dependent (Lawrence et al., 2010; Moxon-Emre et al., 2014). Chemotherapy has specific agents that may carry direct risk for cognitive impairment (Verstappen et al., 2003). Moreover, concomitant chemotherapy

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and radiation results in greater neurocognitive deficits and academic difficulties than CRT alone (Bull et al., 2007; Butler et al., 1994). Poorer neurocognitive outcomes are also associated with other neurological risk factors, such as endocrine disruption and seizures (Reimers et al., 2003; Vingerhoets, 2006), and patient/demographic factors, such as age at the time of treatment, time since treatment, socioeconomic status (SES), and sex (Radcliffe et al., 1994; Peterson & King, 2022; Sands et al., 2001; Torres et al., 2021).

Given the complexity of brain tumor treatments, which often involve a multimodal approach combining resection, chemotherapy, and/or radiation therapy, it is challenging to establish a comprehensive endophenotype for classifying neurocognitive outcomes in survivors. Moreover, the appropriate method, timing, and intensity of treatments depend on various tumor-related factors, such as tumor location and histology, and patient demographic factors, including age. Thus, there is a need for refined measures that consider neurological risk and treatment intensity to predict the neurocognitive outcomes of survivors. Despite this, few objective measures quantify the intensity or extent of exposure to tumor-related therapies.

The Neurological Predictor Scale (NPS; Micklewright et al., 2008) is a clinician-generated checklist that quantifies both neurological- and treatment-related risk factors. The NPS measures the receipt of tumor-directed treatments (e.g., radiation, surgical resection, chemotherapy, or combination) and presence of neurological complications (e.g., presence of hydrocephalus, seizures, and hormone deficiencies) in one cumulative score. Prior research has demonstrated the predictive validity of the NPS for IQ and neurocognitive skills (King & Na, 2015; McCurdy et al., 2016; Taiwo et al., 2017).

The Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI; Hocking et al., 2018) was developed by a team of neuro-oncology experts to evaluate the intensity of undergoing certain treatment modalities specific to pediatric brain tumors. The scale classifies treatment variables across varying degrees of radiation and chemotherapy exposures, ranging from low to high intensity. The PNORTI was modeled after the Intensity of Treatment Rating Scale (ITR; Werba et al., 2007), a psychometrically valid measure of the intensity of treatments for childhood malignancies. The validity and utility of the PNORTI in predicting neurocognitive late effects have yet to be established.

The NPS and PNORTI assess treatment-related variables differently. For example, the NPS dichotomizes chemotherapy exposure (i.e., received chemotherapy vs. did not receive chemotherapy), whereas the PNORTI classifies chemotherapy exposure across varying levels of intensity (e.g., low, medium, and high) and incorporates stem cell rescue procedures. Unlike the PNORTI, the NPS measures neurological complications, such as hydrocephalus, seizure medication, and endocrine disruption. When used together, the NPS and the PNORTI may afford clinicians a simple and robust means of capturing both neurological risk factors and the intensity of tumor-directed treatments when evaluating predictors of neurocognitive outcomes in PBTS.

The primary objective of this study is to evaluate the predictive qualities of the NPS and PNORTI. Specifically, this study builds upon previous validation studies with the NPS, utilizing a substantial sample of PBTS, while also evaluating the predictive validity of the PNORTI on neurocognitive outcomes. In accordance with previous findings (Taiwo et al., 2017), we hypothesized that: (1) higher scores on the NPS would be significantly related to poorer posttreatment neuropsychological outcomes while accounting for relevant demographic variables; (2) higher treatment intensity scores on the PNORTI would be significantly related to poorer posttreatment neuropsychological outcomes; and (3) when used in conjunction, both the NPS and PNORTI would provide incremental validity for predicting posttreatment neuropsychological outcomes.

Methods

Participants and procedures

This study was a retrospective chart review, approved by the Institutional Review Board at the pediatric hospital where the research was conducted. All data was obtained in accordance with the ethical standards set forth in the Helsinki Declaration. Potentially eligible participants were identified either through the hospital's tumor registry, through a clinical evaluation, or through participation in the principal investigator's (PI) prior research studies. Participants included in the study from the PI's previous research protocols, as well as those whose neuropsychological testing data were abstracted from clinical evaluation, did not receive any cognitive interventions at our institution as a part of their study enrollment or clinical care based on reviews of their medical records. Participants were included in the current study if they: (1) were between the ages of 5 and 17 years old at the time of neuropsychological evaluation to reflect the hospital's primary patient population, (2) underwent tumor-directed treatments for a brain tumor (e.g., surgical resection, chemotherapy, or focal, cranial, or craniospinal radiation); and (3) had completed initial tumor-directed treatments at least 2 years prior to the time of data collection. Participants were excluded if they (1) had a multisystem genetic disorder that may affect neurocognitive functioning (e.g., Down syndrome, Beckwith-Weidemann syndrome, Wolf Hirschhorn syndrome), and/or neurofibromatosis; (2) had evidence of neurodevelopmental delays or diagnosed with autism spectrum disorder prior to diagnosis of their brain tumor; and (3) underwent tumor biopsy only (i.e., received no additional tumor-directed therapies). Tumor recurrence or progression after treatment was not an exclusion if survivors were at least 2 years removed from the end of therapy for their primary tumor.

Trained study personnel reviewed medical charts for treatment, neurological, sociodemographic, and neuropsychological variables. Study data were collected and managed using REDCap electronic data capture (Harris et al., 2019; Harris et al., 2009). Tumor location (i.e., supratentorial or infratentorial) was based on clinical documentation and MRI reports. Dates extracted included those of diagnosis, completion of primary tumor-directed therapy, and if applicable, date of recurrence and date of completion for recurrent tumor-directed therapy. Neuropsychological and treatment data were extracted from medical records as well as databases from the PI's previous research protocols.

Measures

Neurological Predictor Scale

The Neurological Predictor Scale (NPS; Micklewright et al., 2008) is a clinician-generated checklist that quantifies tumor-related treatments and neurological sequelae with one cumulative score. The NPS is based on treatment factors (i.e., radiation therapy, chemotherapy, and neurosurgery) and the presence or absence of neurological complications (i.e., hormone deficiency, hydrocephalus, and seizure

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medication). The NPS scale ranges from 0 to 11, with higher values reflecting increased neurological risk.

Pediatric Neuro-Oncology Rating of Treatment Intensity

The Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI; Hocking et al., 2018) quantifies the intensity of treatments for pediatric brain tumors. It was developed by neuro-oncology clinicians and consists of three levels that reflect the overall intensity of treatment as an individual goes through it, encompassing factors such as duration, side effects, and recovery time. Level 1 represents patients who received surgical resection, focal radiation, and/or low-intensity chemotherapy. Level 2 characterizes patients who received cranial or cranio-spinal radiation, with or without medium or less intense chemotherapy, or medium intensity chemotherapy alone. Level 3 reflects the most intensive treatment exposure, which includes high-intensity chemotherapy, with or without craniospinal radiation. The intensity of chemotherapy is classified into three levels: (1) low intensity, which includes any outpatient chemotherapy; (2) medium intensity, which comprises any inpatient chemotherapy regimen not included in the high-intensity chemotherapy category; and (3) high intensity, which involves high-dose chemotherapy with a stem cell rescue or cumulative doses of doxorubicin$\geq$300mg/m^2 or methotrexate doses ($\geq$1 g/m^2) requiring leucovorin rescue. Trained study staff generated PNORTI scores based on treatment data extracted as described above.

Sociodemographic variables

Information, such as race, ethnicity, sex, and insurance type (e.g., private or public), was gathered from the medical record. Childhood Opportunity Index (COI; Noelke et al., 2020) scores were calculated based on participant's address at the time of neuropsychological testing. The COI is a validated, census tract-based multidimensional measure of US neighborhood resources and conditions comprised of 29 indicators of social determinants of health across three domains: education, health and environment, and socioeconomic (Acevedo-Garcia et al., 2014). The overall Child Opportunity Score ranges from 0 to 100, with higher scores reflecting more favorable neighborhood opportunities relative to other neighborhoods across the US.

Neuropsychological data

Due to the retrospective nature of the study, a variety of neurocognitive measures were used as a part of routine clinical care. Efforts were made to combine similar measures based on construct area. Intellectual functioning (IF) was assessed with age-appropriate standardized measures, including the Weschler Intelligence Scale for Children-Fourth and Fifth Editions (WISC-IV, WISC-V, 6–16 years old), the Weschler Adult Intelligence Scale-Fourth Edition (WAIS-IV; 16–90 years old), the Weschler Abbreviated Scale of Intelligence-Second Edition (WASI-II; 6–89 years old), or the Differential Abilities Scales-Second Edition (DAS-II; 2–17 years old). Variability in which measure of IF patients were administered (i.e., Weschler vs. DAS-II scales) was due to neuropsychologist's preference for battery construction and the child's age at the time of evaluation. Both the Weschler and DAS scales are founded in the same theoretical model (Cattell-Horn-Carroll Theory of Intelligence) and the literature supports comparable underlying constructs (Alfonso et al., 2005). Further, there is significant evidence supporting strong correlations between the Weschler and DAS scales (Dumont et al., 1996; Dumont et al., 2009; Kuriakose, 2014). Particularly, the Weschler Full-Scale Intelligence Quotient and the DAS-II General Conceptual Ability score are highly correlated.

The Processing Speed Index (PSI) from the age-appropriate Weschler measure assessed Processing Speed (PS) using age-corrected standardized scores, with higher scores indicating greater processing efficiency. Attention was assessed using respective auditory attention subtests from the Wechsler (Digit Span Forward) or DAS-II (Recall of Digits Forward) instruments. Working memory (WM) was assessed using an auditory WM task. Children were administered either the Digit Span Backward subtest from a Weschler measure or Recall of Digits Backward from the DAS-II. Verbal reasoning (VR) and conceptualization abilities were measured using the respective verbal reasoning index and verbal abilities scores from the Weschler or DAS-II scales. Perceptual reasoning (PR) was measured using the respective perceptual reasoning index and nonverbal abilities scores from the Weschler or DAS-II scales.

Sample sizes varied by neuropsychological measures as not all participants completed the same testing battery.

Statistical analyses

Descriptive statistics were computed for relevant demographic, medical, and cognitive variables. Kruskal-Wallis nonparametric tests assessed group differences across PNORTI scores and neuropsychological outcomes. Pearson's correlations assessed associations between neuropsychological outcomes and NPS and COI scores. Independent samples t-tests and ANOVAs assessed the associations among medical and treatment factors, such as tumor location, recurrence, tumor WHO grade, age at diagnosis, time posttreatment, and sex with neuropsychological outcomes. Chi-squared tests examined group statistics between PBTS who were evaluated using Weschler assessments and the DAS-II. Medical, treatment, and demographic factors that were significantly related to neuropsychological outcomes or were significantly related to group differences were controlled for in subsequent analyses. While controlling for covariates, hierarchical linear regressions assessed the predictive validity of the NPS (Hypothesis 1) and PNORTI (Hypothesis 2) for neuropsychological outcomes. To evaluate the predictive utility of the NPS and PNORTI for neuropsychological outcomes in comparison to individual risk factors (Hypothesis 3), hierarchical linear regressions were used. Two-sided p-values < 0.05 were considered significant. Participants were included in the analyses if they had data for at least one outcome variable. Statistical analyses were performed using IBM SPSS Statistics version 28.0.1.1.

Power analysis

A-priori power analyses indicated that samples sizes of 49–103 participants for multiple regression analyses with two predictors (NPS, PNORTI) and upwards of five covariates were needed to detect anticipated effect sizes ranging from .15 to .35, respectively. With a final sample size of 161, the current study is sufficiently powered to detect medium and large effect sizes.

Results

The medical records of 944 patients were initially reviewed. Out of those, 783 patients were excluded from the study for the following reasons: not having completed a neuropsychological assessment ($n = 611$), not being 2 years posttreatment ($n = 115$), or having a preexisting neurodevelopmental delay or an autism spectrum disorder diagnosis prior to brain tumor diagnosis ($n = 12$). In

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addition, there were 45 participants who did not undergo tumor-directed therapy, and this group was excluded from the final analyses because only 3 out of the 45 participants had documented neuropsychological testing data. Of those excluded, 56% of patients were male and patients were approximately 9 years old at the time of diagnosis ($M = 9.50$, $SD = 4.23$). A final sample of 161 PBTS (57.1% male) aged 6–17 years ($M = 13.47$, $SD = 2.80$) was included in the study. Survivors were approximately 7 years post-diagnosis ($M = 6.7$, $SD = 3.68$) and 6 years posttreatment ($M = 6.13$, $SD = 3.39$) at the time of neuropsychological evaluation. Sample demographic information is presented in Table 1. Over half of the sample had private insurance ($n = 96$, 59.6%), and COI levels ranged from very low ($n = 17$, 10.56%), low ($n = 16$, 9.94%), moderate ($n = 22$, 13.66%), high ($n = 42$, 26.09%), and very high ($n = 64$, 39.75%). The majority of participants were diagnosed with low-grade glioma (39.8%), medulloblastoma (19.3%), ependymoma (11.8%), or craniopharyngioma (10.6%). Less than a fourth of the sample ($n = 37$, 23%) had a tumor recurrence. NPS scores ranged from 1 to 11 ($M = 5.57$, $SD = 2.27$) and PNORTI scores ranged from "Level 1" ($n = 101$, 62.7%), "Level 2" ($n = 42$, 26.1%), and "Level 3" ($n = 18$, 11.2%). Inter-rater reliability was evaluated by randomly selecting 30% of the total sample, yielding a 90% agreement rate for the NPS and a 96% agreement rate for the PNORTI between raters. Table 2 displays means, ranges, and standard deviations of the neuropsychological outcome variables.

Preliminary analyses

Among the 124 survivors without a recurrence of their brain tumor, nearly half (approximately 49%) scored below average (1 standard deviation below the mean) on the measure of PS. Moreover, 20–32% demonstrated below-average performance on measures of IF, VR, PR, and attention, exceeding what would be expected in a normal distribution. In the subset of 37 survivors who experienced a recurrence, approximately 42% had below-average scores on PS, with 25–28% with below-average performance on measures of IF, VR, PR, and attention. There were no significant differences in IF scores between survivors with or without a recurrence on a two-tailed Mann-Whitney U test, $U = 2208$, $z = .13$, $p = .90$. Independent-sample t-tests revealed no significant differences in PS, VC, PR, attention, and working memory scores based on recurrence (p's > .05). Chi-square analyses and t-tests revealed no significant differences in sex, age at diagnosis, time since treatment, NPS scores, COI and insurance type based on recurrence (p's > .05).

Tumor location and WHO grade were not related to any cognitive outcomes ($ps > 0.05$; see Supplemental Table 1) and therefore were not included as covariates in subsequent analyses. Age at diagnosis was significantly correlated with IF, ($r = .296$, $p < .001$), PSI ($r = .318$, $p = .002$), and auditory WM, ($r = .419$, $p < .001$). Time from primary treatment was significantly correlated with PS ($r = -.334$, $p < .001$), auditory WM, ($r = -.295$, $p = .005$), and attention ($r = -.270$, $p = .011$). COI scores were significantly correlated with IF ($r = .454$, $p < .001$, $N = 157$), VR ($r = .427$, $p < .001$, $N = 92$), PR ($r = .329$, $p = .007$, $N = 67$), and PSI ($r = .243$, $p = .020$, $N = 92$). Survivors with public insurance had significantly lower IF ($M = 89.70$, $SD = 1.90$, $N = 64$) scores, t (155) = 4.24, $p < .001$, $d = .688$, VR ($M = 88.84$, $SD = 13.19$, $N = 38$) and PSI scores ($M = 82.22$, $SD = 14.63$, $N = 36$) than those with private insurance, t (90) = 4.35, $p < .001$, $d = .917$, and t (90) = 2.28, $p = .013$, $d = .487$, respectively. Males ($M = 100.06$, $SD = 13.58$, $N = 34$) had significantly higher PR scores than females ($M = 88.78$, $SD = 17.60$, $N = 33$), t (65) = −2.95, $p = .004$, $d = -.720$.

Data were normally distributed for participants assessed using the DAS-II and Weschler tests. There were no significant differences in age at diagnosis, age at clinical neuropsychological evaluation, recurrence, tumor location, or sex between those assessed using Weschler instruments and the DAS-II. PBTS administered the DAS-II were a greater number of years posttreatment ($M = 7.24$, $SD = 3.08$) than those assessed using the Weschler tests ($M = 5.76$, $SD = 3.37$), t (148) = −2.36, $p = .020$, $d = -.446$. Therefore, time from primary treatment to neuropsychological evaluation was included as a covariate in subsequent analyses.

Univariate analyses

Pearson bivariate correlations revealed significant correlations between NPS scores and IF ($r = -.181$, $p = .023$) and PS ($r = -.287$, $p = .005$). NPS scores were not correlated with auditory WM ($r = -.060$, $p = .578$), attention ($r = -.125$, $p = .256$), verbal reasoning ($r = -.114$, $p = .278$), or perceptual reasoning ($r = -.034$, $p = .784$). Kruskal-Wallis tests showed no significant differences in any of the neuropsychological outcomes based on PNORTI levels (p's > 0.05; see Supplemental Table 2).

Exploratory analyses

Given the uneven distribution of participants among PNORTI levels, an exploratory analysis evaluated the impact of different treatment modalities. Specifically, PNORTI Level 1 was divided into two groups: (a) patients who underwent surgery only ($n = 54$) and (b) patients who received focal RT/low-intensity chemotherapy ($n = 47$). Two-tailed Mann-Whitney U tests revealed no differences in IF, VR, PR, PS, attention, and auditory working memory scores between the PNORTI Level 1: Surgery Only and PNORTI Level 1: Focal RT/low-intensity chemotherapy groups (p's > .05)

Kruskal-Wallis tests assessed differences across all PNORTI Levels: PNORTI Level 1a: Surgery only, PNORTI Level 1b: Focal RT/Low-intensity chemotherapy, PNORTI Level 2, and PNORTI Level 3. There were no differences in any of the measured neuropsychological outcomes among the groups (p's > .05; see Supplemental Table 3).

Multivariate analyses

A hierarchical multiple linear regression (Table 3) tested the predictive strength of NPS scores on IF. Participant sex, age at diagnosis, time from primary treatment to neuropsychological assessment, insurance type, and COI were entered in the first step, followed by NPS scores in the second step. When sex, age at diagnosis, time from primary treatment, insurance type, and COI were included in the first step, the model explained 31% of the variance. Adding NPS scores significantly improved the model $\Delta R^2 = .04$, $p = .005$, with higher NPS scores predicting lower IF scores, $\beta = -.19$, $p = .007$. The overall model, with NPS scores, included, explained 34% of the variance in IF, $F(6,150) = 14.51$, $p < .001$, and had a large effect (Cohen's $f^2 = .58$).

A second hierarchical multiple linear regression (Table 4) tested the predictive strength of the NPS on PS. Participant sex, age at diagnosis, time from primary treatment to neuropsychological assessment, insurance type, and COI were entered in the first step, followed by NPS scores in the second step. When sex, age at

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Table 1. Participant demographics, diagnoses, and treatment/neurological sequalae

	Without recurrences ($n = 124$)			With recurrences ($n = 37$)			Test statistic	Effect size
	M (*SD*)	Range	*n* (%)	*M* (*SD*)	Range	*n* (%)	*t* or χ^2 (*df*)	*d* or ϕ
Age (years)	13.45 (2.74)	6.92–17.96[a]		13.53 (3.02)	8.02–17.99[a]			
Age at diagnosis	6.83 (3.56)	0.02–14.76		6.28 (4.08)	0.53–14.15		.805 (159)	0.151
Time since treatment (years)	5.99 (3.23)	2.01–16.23		6.60 (3.91)	2.02–15.14		−.958 (159)	−0.179
COI score	66.69 (28.09)	1–100		62.08 (30.36)	2.00–99.00		.860 (159)	0.161
NPS score	5.59 (2.35)	1–11		5.51 (2.04)	1–10		.176 (159)	0.033
Sex							.187 (159)	−0.34
Male			72 (58.1%)			20 (54.1%)		
Female			52 (41.9%)			17 (45.9%)		
Race								
Caucasian/White			94 (75.8%)			28 (75.7%)		
Black			18 (14.5%)			6 (16.2%)		
Asian			1 (0.8%)			2 (5.4%)		
Other/Unknown			11 (8.9%)			1 (2.7%)		
Ethnicity								
Hispanic/Latino			9 (7.3%)			4 (10.8%)		
Not Hispanic/Latino			115 (92.7%)			33 (89.2%)		
Insurance type							.547 (1)	−0.058
Private			72 (58.1%)			24 (64.9%)		
Public			52 (41.9%)			13 (35.1%)		
Tumor histology								
Glioma (low grade)[a]			47 (37.9%)			16 (43.2%)		
Glioma (high grade)[b]			5 (4.0%)			0 (0%)		
Medulloblastoma			29 (23.4%)			2 (5.4%)		
Ependymoma			14 (11.3%)			5 (13.5%)		
Craniopharyngioma			9 (7.3%)			8 (21.6%)		
Meningioma			3 (2.4%)			3 (8.1%)		
PNET			2 (1.6%)			0 (0%)		
DNET			4 (3.2%)			1 (2.7%)		
ATRT			3 (2.4%)			0 (0%)		
Germ cell			3 (2.4%)			0 (0%)		
Germinoma			3 (2.4%)			1 (2.7%)		
Other[c]			3 (2.4%)			1 (2.7%)		
Tumor level								
Supratentorial			56 (45.2%)			24 (64.9%)		
Infratentorial			67 (54.0%)			8 (21.6%)		
Both			1 (0.8%)			5 (13.5%)		
WHO grade								
Grade 1			46 (37.1%)			20 (54.1%)		
Grade 2			29 (23.4%)			12 (32.4%)		
Grade 3			9 (7.3%)			3 (8.1%)		
Grade 4			37 (29.8%)			2 (4.2%)		
Unknown			3 (2.4%)			0 (0%)		
Surgical history								
1 Surgical resection			94(75.8%)			15 (40.5%)		
>1 Surgical resection			19 (15.3%)			20 (50.4%)		
Radiation exposure								
Focal RT			33 (26.6%)			16 (43.2%)		
Cranial/craniospinal RT			30 (24.4%)			6 (16.2%)		
Radiation type								
Proton			47 (37.9%)			19 (51.4%)		
Photon			16 (12.9 %)			4 (10.8%)		
Chemotherapy treatment			59 (47.6%)			17 (45.9%)		
Intrathecal chemotherapy			46 (37.1%)			15 (40.5%)		
Neurological sequelae								
Hormone deficiency			42 (33.9%)			13 (35.1%)		
Seizure medications			44 (35.5%)			14 (37.8%)		
Hydrocephalus			73 (58.9%)			16 (43.2%)		
PNORTI score								
Level 1			74 (59.7%)			27 (73.0%)		
Level 2			34 (27.4%)			8 (21.6%)		
Level 3			16 (12.9%)			2 (5.4%)		

Note. Age at diagnosis and time since treatment are reported in years; PNET = primitive neuro-ectodermal tumor; DNET = dysembryoplastic neuroepithelial tumor; ATRT = Atypical teratoid rhabdoid tumor; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$.

[a]Low-grade gliomas included: pilocytic astrocytoma, fibrillary astrocytoma, optic pathway glioma, tectal glioma, oligodendroglioma, ganglioglioma, pleomorphic xanthoastrocytoma.

[b]High grade gliomas included: anaplstic astrocytyoma, glioblastoma multiforme, diffuse intrinsic pontine glioma.

[c]Other included: pineoblastoma ($n = 1$); ependymoblastoma ($n = 1$), malignant hemangiopericytoma ($n = 1$).

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Table 2. Sample performance across neuropsychological domains

	Without recurrences ($n = 124$)					With recurrences ($n = 37$)					Test statistic	Effect size
Domain/measure	*n*	*M*	*SD*	Range	% Impaired	*n*	*M*	*SD*	Range	% Impaired	*t* or *U* (*df*)	*d* or *r*
Intellectual functioning												
IF Composite (Weschler and DAS-II)[a]	121	95.66	15.06	60–148	26.4%	36	96.97	19.73	67–142	27.8%	2148	−.010
Processing speed												
PSI (Weschler)[a]	68	86.28	16.18	49–149	48.5%	23	98.22	17.51	60–131	41.7%	−.748 (90)	−.178
Attention												
DSF (Weschler and DAS-II)[b]	65	9.12	3.02	4–17	20.0%	23	8.65	2.35	5–13	26.1%	.677 (86)	.164
Working memory												
DSB (Weschler and DAS-II)[b]	65	9.29	2.90	3–15	16.9%	23	9.44	2.98	5–15	13%	−.201 (86)	−.049
Verbal reasoning												
VR Composite (Weschler and DAS-II)[b]	65	94.95	13.30	68–124	24.6%	28	98.04	16.17	73–132	25%	−.969 (91)	−.217
Perceptual reasoning												
PR Composite (Weschler and DAS-II)[b]	44	92.55	15.93	55–125	31.8%	23	98.22	17.51	65–135	26.1%	−1.337 (65)	−.344

Note. IF = Intellectual Functioning, PSI = Processing Speed Index, DSF = Digit Span Forward, DSB = Digit Span Backward, VR = Verbal Reasoning; PR = Perceptual Reasoning; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$.
[a]Standard Score mean = 100, standard deviation = 15.
[b]Scaled score mean = 10, standard deviation = 3.

Table 3. Hierarchical regression analysis predicting IF from tumor and demographic variables, and neurological risk scores

	IF scores		
	ΔR^2	β	*Cohen's* f^2
Step 1	.33**		
Sex		.11	
Age at diagnosis		.30**	
Time from primary treatment		−.02	
Insurance type		−.14	
COI score		.39**	
Step 2	.04**		
Sex		.13	
Age at diagnosis		.31**	
Time from primary treatment		−.02	
Insurance type		−.12	
COI score		.38**	
NPS score		−.19**	
Total adjusted R^2	.34**,[a]		.58

Note. Higher scores on the NPS indicate greater neurological risk; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$.
[a]$F(6,150) = 14.51$, $p < 0.01$.

Table 4. Hierarchical regression analysis predicting PS from tumor and demographic variables, and neurological risk scores

	PSI scores		
	ΔR^2	β	*Cohen's* f^2
Step 1	.24**		
Sex		−.07	
Age at diagnosis		.17	
Time from primary treatment		−.27*	
Insurance Type		−.21	
COI		.18	
Step 2	.07**		
Sex		−.08	
Age at diagnosis		.14	
Time from primary treatment		−.28*	
Insurance Type		−1.76	
COI		.20	
NPS score		−.26**	
Total adjusted R^2	.26**,[a]		.44

Note. Higher scores on the NPS indicate greater neurological risk; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$.
[a]$F(6,85) = 6.23$, $p < .001$.

Table 5. Regression analysis for PNORTI and NPS predicting IF and processing speed

	β	*t*	R^2	*Cohen's* f^2
Outcome: IF			.38*	.61
Sex	.13	2.00*		
Age at diagnosis	.35	4.05**		
Time from primary treatment	.02	.18		
Insurance type	−.11	−1.50		
COI score	.39	5.25**		
NPS score	−.26	−3.19**		
PNORTI score	.12	1.49		
Outcome: PS			.31*	.44
Sex	−.08	−.87		
Age at diagnosis	−.14	1.03		
Time from primary treatment	−.30	−2.05*		
Insurance type	−.18	−1.63		
COI score	.20	1.85		
NPS score	−.26	−2.12*		
PNORTI score	−.01	−.09		

Note. Cohen's f^2 of 0.02, 0.15, and 0.35 considered small, medium, and large, respectively.
$^{*}p \leq 0.05$; $^{**}p \leq 0.01$.

diagnosis, time since primary treatment, insurance type, and COI were included in the first step, the model explained 19.3% of the variance in PS. Adding NPS scores significantly improved the model $\Delta R^2 = .07$, $p = .005$, with higher NPS scores predicting lower PS scores, $\beta = -.26$, $p = .005$. The overall model, with NPS scores, included, explained 25.6% of the variance in PS, $F(6,85) = 6.23$, $p < .001$, and had a large effect (Cohen's $f^2 = .44$).

Combined predictive validity of NPS and PNORTI

Two hierarchical multiple linear regressions evaluated the predictive strength of including both the NPS and PNORTI on IF and PS, respectively (Table 5). The overall models, which included both NPS and PNORTI scores as predictors, significantly predicted IF, $F(7,149) = 12.86$, $p < .001$, $R^2 = .38$, with a large effect (Cohen's $f^2 = .61$), and PS, $F(7,84) = 5.28$, $p < .001$, $R^2 = .31$, with a large effect (Cohen's $f^2 = .44$). Examination of the individual variables indicated that NPS scores significantly predicted IF

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[$t(149) = -3.19$, $p = .002$] and PS [$t(84) = -2.12$, $p = .037$]. PNORTI scores did not significantly predict IF or PS.

Discussion

Survivors experience a multitude of risk factors following diagnosis, making it important to evaluate and validate discrete tools that measure the influence of risk factors on neuropsychological outcomes. The present study is one of the first to examine the predictive validity of the NPS and PNORTI on neuropsychological late effects in a large sample of PBTS with differing diagnoses and treatment regimens. Overall, results indicate that NPS scores significantly predicted IF and PS years after treatment. Conversely, PNORTI scores did not significantly predict neuropsychological functioning. These findings provide further evidence of the NPS' ability to measure the neurological factors that impact later neuropsychological outcomes.

NPS scores predicted IF and PS above-and-beyond time since treatment, demographic, and SES variables. These findings are in accordance with previous studies with PBTS showing NPS scores to predict neurocognitive outcomes (McCurdy et al., 2016; Micklewright et al., 2008; Taiwo et al., 2017). Collectively, this suggests that the NPS is a valid tool that can quickly and efficiently calculate a child's risk for deficits in specific neuropsychological domains. The NPS may also be a particularly useful tool in clinical research to avoid issues of low statistical power in studies with small sample sizes that assess interrelated and overlapping neurological risk factors. To further expand upon the scale's utility, future work should consider establishing clinical cutoff scores for the NPS to help determine which PBTS are most at-risk for neuropsychological late effects and warrant additional assessments and/or intervention.

In the model evaluating the combined predictive validity of the NPS and PNORTI on IF, COI scores accounted for the most variance in the model ($\beta = .386$, $p < .001$). While research on the impact of neighborhood opportunity on cognitive outcomes in PBTS is currently limited, studies have demonstrated the influence of SES factors on cognitive development and academic performance in general (Bradley & Corwyn, 2002; Hackman & Farah, 2009). Furthermore, the impact of neighborhood opportunity on neurocognitive outcomes in PBTS may be influenced by unique factors related to their medical history and treatment. For example, neighborhoods with higher opportunity may offer greater access to quality schools, individualized education plans, and support systems for learning difficulties than neighborhoods with lower opportunity (Acevedo-Garcia et al., 2014). This is particularly relevant for PBTS, who face challenges related to their cognitive function and academic performance in the years following treatment. A study by Torres et al. (2021) demonstrated that SES made a greater relative contribution to IF, academic achievement, and PS in a sample of children with brain tumors treated with photon radiation therapy, compared to other well-established risk factors, such as age at treatment and sex. SES may therefore be a novel predictor of cognitive performance in PBTS, underscoring the need for further research to investigate the impact of neighborhood opportunity, socioeconomic variables, and other social determinants of health on cognitive functioning in this population. Such research is crucial for better understanding potential associations and informing interventions and support strategies to enhance outcomes in PBTS.

Surprisingly, the NPS was not associated with performance on measures of working memory or attention. This contrasts with prior studies establishing the NPS as a predictor of cognitive efficiency and neurocognitive skills in PBTS (Taiwo et al., 2017), and with the well-documented vulnerability of these cognitive domains to tumor-directed treatments during childhood (Conklin et al., 2012; Palmer et al., 2013; Robinson et al., 2010). It is important to note that a majority of the existing studies with the NPS consisted of adulthood survivors of childhood brain tumors who were on average 16 years post-diagnosis (Taiwo et al., 2017; King & Na, 2015). It is possible that contemporary treatments may pose different levels of neurological risks than treatments used over a decade ago, potentially altering the utility of the NPS. For example, in the last decade, proton radiation therapy (PRT) has replaced photon radiation therapy (XRT) as the most common form of radiotherapy for pediatric brain tumors, and research suggests PRT may yield better neurocognitive outcomes compared to XRT (Warren et al., 2022). Moreover, the present study's sample exhibited relatively low rates of impairment in attention and working memory compared to previous literature. These lower impairment rates may have influenced the observed lack of association between the NPS and attention and working memory performance. Given that these domains are typically impaired in this population, future research should evaluate the associations between the NPS using more nuanced measures of attention and working memory, such as the Continuous Performance Task and N-back tasks.

Contrary to hypotheses, the PNORTI did not predict neuropsychological functioning. It is important to note that the PNORTI was designed to be a measure of the intensity of tumor-directed treatments, and not necessarily a rating system of the probability of developing late effects. While treatment intensity may be related to the risk level for late effects, they may not necessarily be directly related. For instance, although craniospinal radiation is a known risk factor for late effects, it was viewed as not having the same level of treatment intensity as high-dose chemotherapy plus stem cell rescue by neuro-oncology experts during the development of the PNORTI. As a result, craniospinal radiation alone would be classified as a PNORTI Level 2, while high-dose chemotherapy and stem cell rescue would be categorized as PNORTI Level 3. Thus, PNORTI ratings may not necessarily confer an individual's risk for developing late effects. The relative distribution of PNORTI scores across the present study's sample should also be considered. PNORTI scores were highly skewed towards Level 1 ($n = 101$) and Level 2 ($n = 42$) compared to Level 3 ($n = 18$). The uneven distribution in scores could have impacted the findings. Moreover, it is also possible that those with higher PNORTI scores might be at greater risk for relapse or death, potentially biasing the present sample towards those with lower risk for adverse outcomes. In fact, 89 patients were excluded from the analyses for not being at least 2 years out from the end of their primary tumor treatment due to recurrence or death.

This study is one of the first to examine the predictive ability of the NPS and PNORTI on neuropsychological late effects in a large sample of PBTS. Despite the strengths of this study, several limitations need to be acknowledged. Given the clinical nature of the sample, measures were selected for administration based on clinical utility, the age of the patient, and clinician preference. As such, not all participants were administered the same measures and the available data for analysis varied by domain. Further, given that most of the sample was referred for neuropsychological evaluation, they may be more likely to demonstrate neurocognitive difficulties, thereby compromising generalization to the broader PBTS population. It is worth noting that the NPS was not initially

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designed to assess individuals who have experienced recurrences. This study adopted an exploratory approach to include this subset of survivors, which is often overlooked in the existing literature. Lastly, it is important to acknowledge that the PSI has a motor component and use of this metric may underestimate processing speed given graphomotor deficits in this population (Duffner et al., 1993). Future studies should consider incorporating assessments of oral processing speed or utilizing the symbol search subtest, which entails fewer motor demands than coding.

The present study demonstrates associations between the NPS, broad global intellectual functioning, and processing speed in survivors of childhood brain tumors, supporting the NPS' ability to predict how cumulative neurological factors impact cognitive outcomes following treatment. Further, the NPS has value in identifying PBTS most at risk for neuropsychological impacts of their tumor and treatments, which has important clinical and research implications. The ability to identify youth at greater risk for neuropsychological late effects can impact monitoring and inform the need for early intervention and long-term care.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617723000589

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