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CLINICAL STUDY

Associations among treatment-related neurological risk factors and neuropsychological functioning in survivors of childhood brain tumor

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Abstract Adverse neurological side effects associated with childhood brain tumors and their treatments contribute to long-term neurocognitive morbidity. Measures designed to quantify tumor-related risk factors are lacking. The neurological predictor scale (NPS) is designed to assess treatment-related neurological risks. Preliminary validation established associations between the NPS and global cognitive functioning in this population, though its associations with specific neurobehavioral domains has yet to be addressed. Participants referred for outpatient neuropsychological assessment completed performance-based measures of intellectual, attentional, working memory, motor speed, and executive abilities. Caregivers completed ratings of adaptive functioning. Neuropsychological and adaptive data were available for 100 brain tumor survivors (51 % female), ages 6 to 22 years ($M = 12.83$, $SD = 4.37$). Total NPS scores were generated via retrospective medical record review. Total NPS scores were significantly associated with several neurocognitive composite scores including verbal reasoning and working memory, after controlling for years post-diagnosis ($ps < .05$). NPS scores also were significantly associated with performance-based measures of attention, executive functioning, and cognitive efficiency ($ps < .05$). No significant relationship was demonstrated between NPS scores and caregiver-reported adaptive behavior skills ($ps > .05$). Results indicate that the NPS is associated with performance-based neurocognitive functioning and executive skills but not with functioning in specific caregiver-reported adaptive behavior domains. The NPS offers some value as a resource for understanding associations between treatment-related neurological risks and select aspects of neurocognitive morbidity. Future studies should examine whether the NPS can aid in planning appropriate therapeutic intervention as survivors progress into early adulthood.

Keywords Reasoning · Attention · Processing speed · Children · Functioning

Introduction

With recent advances in detection and treatment, a growing number of individuals diagnosed with childhood brain tumors will become long-term survivors [1]. Unfortunately, neurological side effects associated with brain tumors and associated treatments place survivors at risk for protracted adverse cognitive and behavioral outcomes [2]. These neurocognitive 'late effects' may contribute to reduced quality of life and disrupted functional outcomes as survivors transition into adulthood [3, 4]. Despite efforts to adjust treatment modalities to minimize neurocognitive morbidity, current treatment options for pediatric brain tumors still confer substantial risks to the developing nervous system.

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Surgical resection alone may contribute to diminished white matter integrity [5], reduced intellectual ability [6], and deficits in attention, processing speed, and memory [7]. Cranial radiation-related decreases in white matter volume have been associated with reduced cognitive abilities across domains, including global intelligence [8], attention and working memory [9, 10], and executive dysfunction [11]. Survivors also demonstrate higher rates of educational and social difficulties following cranial radiation [11]. Intrathecal chemotherapy has been associated with reduced academic achievement, deficits in attention and working memory, and slowed processing speed [12], perhaps due to disruption of white matter circuitry in the developing brain [13, 14].

Secondary neurological comorbidities such as seizures, endocrine disruption, and hydrocephalus may result from tumor-directed treatments, tumor associated mass effect, or a combination thereof [15]. The presence of tumor- and treatment-related neurological comorbidities have been associated with reductions in global intellectual functioning, information processing speed, psychomotor speed, executive and attentional control [16–21].

While the associations between specific treatment modalities and neurocognitive late-effects is well-recognized, few studies have examined the cumulative contribution of these risk factors on neuropsychological functioning in survivors of pediatric brain tumor. Only two published measures exist that quantify neurological risk in this population and consider both treatment exposure and secondary neurological complications. The neurological severity score (NSS), a measure of cumulative neurological symptoms and adverse medical events [22], has demonstrated significant negative correlations with post-surgical cognitive functioning (i.e., performance IQ, memory, visual-spatial abilities, and attention; $ps = -0.29$ to -0.38 [22]. However, the calculations required for the NSS are time prohibitive for medical personnel as they require a thorough review of medical records across multiple timepoints and also involve querying for various treatment and procedure exposures, ultimately resulting in limited clinical feasibility.

The neurological predictor scale (NPS [23]), represents an appealing alternative in busy medical practices as this scale was designed to significantly reduce the effort needed to quantify risk variables via a brief clinician-generated checklist indexing tumor- and treatment-related risk factors. For the NPS, only a brief review of the medical record is necessary to quantify complications associated with four major brain tumor-related treatment domains: surgical resection, radiotherapy, chemotherapy, and comorbid neurological conditions (Online Appendix). Preliminary validation studies have established utility of the NPS in predicting neurocognitive outcomes (i.e., global intelligence) [23, 24] and proxy-reported adaptive functioning [24, 25]. However, these validation studies were limited by small sample sizes and lack of inclusion of domain-specific skills known to be impacted by treatment factors, such as attention, working memory, executive function, and psychomotor speed.

The primary aim of the present study was to replicate the findings of Micklewright and colleagues [23, 25] through hypothesis testing of the NPS with a larger clinically referred sample of survivors of pediatric brain tumor. Cancer survivorship is defined as "the process of living with, through, and beyond cancer and begins at diagnosis" (National Coalition of Cancer Survivorship 1986) as such, the sample includes both individuals who were undergoing treatment at the time of evaluation and those who had completed treatment. This study also sought to extend previous results by investigating the scale's associations with more domain-specific neurocognitive skills and caregiver reports of adaptive behavior skills. Consistent with Micklewright et al. [23], we hypothesized that higher NPS scores would be associated with poorer global cognitive functioning. We also hypothesized that scores on the NPS would be associated with diminished executive, processing speed, and motor speed performance in survivors, and lower caregiver-reported adaptive skills.

Methods

Procedure

Data were collected from youth referred for clinical neuropsychological assessment at a Neuro-oncology Specialty Clinic in a large, outpatient hospital-based Neuropsychology Department. After obtaining Institutional Review Board approval, de-identified patient records were retrieved from the department clinical database along with medical and demographic variables. Participants were included in the study if they met the following criteria: 1) history of brain tumor as confirmed by medical record review; 2) $\geq$6 years of age at the time of assessment (in order to allow for the evaluation of higher-order cognitive domains and provide consistency of measures among younger and older participants); and, 3) complete data from at least one cognitive measure and/or adaptive rating scale. Because participants varied in age and these data were collected as part of a clinical neuropsychological assessment process, not all study participants were required to complete the same standardized battery. All study participants were administered age-appropriate measures designed to address the referral concerns.

Measures

Neurological Predictor Scale (NPS [23])

The NPS is a clinician-generated checklist designed to quantify the severity and extent of neurological and medical complications associated with a child's brain tumor and/or related treatment (Online Appendix). Items were selected based upon existing research [22, 26], and include relevant treatment factors and neurological complications such as extent of neurosurgical intervention, radiotherapy, chemotherapy, and other comorbid neurological concerns. Rated on an ordinal scale from 0 to 11, higher values reflect more extensive tumor-related burden and overall trauma to neural tissue [23, 26].

Wechsler Intelligence Scale for Children, Fourth & Fifth Editions (WISC—IV/V [27, 28]); Wechsler Adult Intelligence Scale, Third & Fourth Editions (WAIS—III/IV [29, 30, 31])

The Wechsler intelligence scales are psychometrically-sound, commonly administered measures of cognitive abilities for children (WISC-IV/V) and older adolescents/adults (WAIS-III/IV). Measures yield index scores measuring verbal comprehension (VCI), working memory (WMI), and processing speed (PSI). All WISC-IV/V and WAIS-III/IV subscale composites demonstrate good internal consistency (r_{α}s > 0.88) and test-retest reliability coefficients (rs > 0.86) [27, 29]. Wechsler WMI measures include an auditory attention-span task that requires the participant to repeat a series of numbers read aloud by the examiner [Digit span forward (DSF)], and an auditory attention and working memory task in which participants must repeat digits in reverse order [Digit span backward (DSB)]. Test-retest reliability coefficients for the DSF and DSB tasks on the WISC-IV (DSF $r = 0.76$; DSB $r = 0.74$), WISC-V (DSF $r = 0.82$; DSB $r = 0.76$), WAIS-III ($r = 0.83$), and WAIS-IV (DSF $r = 0.74$; DSB $r = 0.71$) are acceptable [27–31].

Test of Everyday Attention for Children (TEA-Ch; [32]) Creature Counting & Score!

The TEA-Ch is a widely-used measure of attention and executive functioning, normed for children ages 6 through 15 years. The Creature Counting subtest assesses flexibility of thinking, working memory, and attentional shifting. Raw scores are converted to age-normed scores for the speed of accurate completion, which evidences an acceptable test-retest coefficient ($r = 0.73$) [33]. The Score! subtest is a measure of sustained attention, and yields good test-retest reliability ($r = 0.76$) [33].

Delis–Kaplan Executive Function System (D-KEFS [34]) Category Switching Accuracy & Number–Letter Switching

Designed for individuals from ages 8 to 89 years, the D-KEFS Category Switching is a verbal fluency task that assesses lexical retrieval, flexibility of thinking, working memory, and attentional shifting. Number–letter switching is a measure of cognitive flexibility. For both subtests, total correct is converted to an age-normed score. Internal consistency estimates are acceptable for Category Switching (r_{α}s $= 0.53$ to 0.76) and number–letter switching (r_{α}s $= 0.57$ to 0.79), though with lower test-retest coefficients (category switching, $r = 0.52$; number–letter switching, $r = 0.38$) [34].

Delis–Kaplan Executive Function System (D-KEFS [34]) Motor Speed

An individually-administered paper-pencil measure of motor speed, this task requires the participant to trace a line connecting circles as quickly as possible with their preferred hand. Total completion time is converted to an age-normed score. The Motor Speed subtest demonstrates good test-retest reliability (rs $= 0.73$ to 0.82) [34].

Purdue Pegboard & Grooved Pegboard ([35] [36])

Pegboard tasks provide a measure of hand-eye coordination and motor speed; these tasks consist of a board with a matrix of 25 keyholes (grooved pegboard) or two parallel columns of 25 holes each (Purdue Pegboard), in which the participant must insert pegs as quickly as possible. Completion time is converted to an age- and sex-normed score for both dominant and non-dominant hands. Test-retest reliability estimates for one-trial administration of the Purdue Pegboard suggest good reliability in neurological populations ($r = 0.85$–0.90) [43]. Grooved Pegboard has good test-retest reliability for dominant ($r = 0.91$) and non-dominant hands ($r = 0.85$), and is moderately correlated with the Purdue Pegboard (rs > 0.73 [37]).

Adaptive Behavior Assessment System, Second Edition (ABAS-II [38])

The ABAS-II is a caregiver rating measure designed to assess daily adaptive behaviors and skills of daily living. Items yield a norm-referenced general adaptive composite (GAC) standard score, with higher scores indicating better adaptive functioning relative to same-age peers. Internal consistency and test-retest reliabilities for the GAC exceed 0.90 [38].

Data analysis

NPS scores were generated via retrospective medical record review. Because data were collected as part of clinical assessments, participants were administered age-appropriate subtests from a variety of commonly used intelligence, attention/executive, and motor speed measures. Each participant was administered subtests from an age-appropriate Wechsler measure, and analogous subscale and index scores were aggregated into a single composite variable. That is, composite variables were created to reflect age-normed scores across analogous verbal, working memory, processing speed, and digit span subscales/indices for participants with available Wechsler data. For example, if participant A was administered digit span forward from the WAIS-IV, and participant B was administered digit span forward from the WISC-IV, both participant's age-normed scaled scores were included in the digit span forward composite variable.

Mean sample performance for each of the neurocognitive outcome variables was compared to normative means via one-sample t-tests. Next, a series of linear regressions were conducted to examine the relationship between NPS scores and global and specific neuropsychological and adaptive outcome measures. Assumptions of linear regression were assessed and moderate skew was noted for several outcome variables, including the verbal comprehension composite ($p < .01$), non-dominant Grooved Pegboard ($p = .03$), and D-KEFS motor speed ($p < .01$) and category switching ($p = .01$). Box–Cox transformations were performed on all skewed variables, which significantly corrected skew for all ($ps > .05$). Transformed variables were used in subsequent regression analysis. No other violations of assumptions of linear regression were found for remaining variables.

Results

Participants

The sample consisted of 100 youth (51 % female) between the ages of 6 and 22 years ($M = 12.83$, $SD = 4.37$) at the time of neuropsychological assessment. Approximately half of the sample was Caucasian (56 %) with the remainder identifying as Black/African-American (18%) or other/unknown (22 %). Age at brain tumor diagnosis ranged from <1 year to 20.58 years ($M = 9.70$, $SD = 4.97$). Years post-diagnosis ranged from 0 years to 19.58 years ($M = 3.22$, $SD = 3.84$). Sixty-three percent of participants had a tumor in the supratentorial region, with the remainder located infratentorially. Twelve participants were assessed prior to undergoing tumor-directed treatment and an additional 23 were currently receiving treatment (i.e., prescribed seizure medication, chemotherapy) at the time of their neuropsychological assessment. The remaining 65 participants underwent neuropsychological testing between 1 month and 14 years post-treatment ($M = 2.51$ years, $SD = 3.10$). Medical and neurological risk data are presented in Table 1. NPS scores in the present sample ranged from 0 to 10 ($M = 4.70$, $SD = 2.56$).

Neuropsychological functioning

Mean performance on composites and each of the neuropsychological and adaptive measures are presented in Table 2. Compared to normative means, the sample evidenced significantly worse performance on several tasks of executive functioning, motor speed, and processing speed. In addition, caregiver ratings of adaptive behavior revealed significantly more problems relative to same-age peers.

Neurological predictor scale (NPS) & neuropsychological functioning

NPS scores were not significantly associated with participants' current age ($r = .02$, $p = .86$), age at diagnosis ($r = -.15$, $p = 0.14$), or years post-treatment ($r = .05$, $p = .64$), but were positively correlated with years post-diagnosis ($r = .21$, $p = .04$). Because of the association between years post-diagnosis and neurocognitive functioning, years post-diagnosis was included as a covariate in all regression analyses. Results are presented in Table 3.

Intellectual functioning

NPS scores were significantly associated with overall verbal reasoning ability. Higher NPS scores corresponded to lower verbal comprehension index scores, and accounted for an additional 8 % of variability above and beyond years post-diagnosis.

Attention, working memory/executive function

NPS scores were significantly associated with working memory, as measured by performance on the Wechsler working memory index. Total NPS scores were also significantly related to brief auditory attention on the Wechsler digit span forward tasks, accounting for 18 % of the variability in performance after considering years post-diagnosis. However, NPS scores were not associated with sustained attention performance on the TEA-Ch Score! subtest.

NPS scores were associated with efficiency of performance on several more complex tasks of attention, working memory, and cognitive efficiency. Specifically, NPS scores

Table 1 Medical, neurological, and treatment risk factor frequencies

Risk factor (N = 100)	n
Medical/neurological	
Hormone dysfunction	21
Seizure medication	27
Hydrocephalus	44
Treatment	
Biopsy*	10
1 Surgical resection	58
>1 Surgical resection	15
Focal RT	17
Cranial or craniospinal RT	7
Cranial RT + focal boost	18
Chemotherapy	52

* Patients underwent tumor biopsy without subsequent resection

were related to speed of completion on the TEA-Ch Creature Counting task and accuracy on a timed verbal cognitive flexibility task (D-KEFS Verbal Fluency Test: Category Switching). Furthermore, NPS scores were significantly associated with digit span backward performance, accounting for 22 % of the variability in scores overall. However, NPS scores were not associated with D-KEFS number–letter switching performance.

Motor and processing speed

NPS scores were not associated with simple speeded graphomotor performance or speeded fine motor dexterity for dominant and non-dominant hands. NPS scores were correlated with the Wechsler processing speed index ($r = -0.29$, $p = .01$), though this association only neared significance after controlling for years post-diagnosis ($p = .06$), accounting for 24 % of the variance in scores. When performance on Wechsler Processing Speed subtests was examined separately, NPS scores did not show a significant association with performance on Coding ($\beta = -.18$, $\Delta R^2 = .03$, $p = .11$), but were associated with Symbol Search performance after controlling for years post-diagnosis ($\beta = -.22$, $\Delta R^2 = .05$, $p = .05$).

Adaptive functioning

Total NPS scores were not associated with caregiver-reported adaptive behaviors as measured by the global adaptive composite on the ABAS-II.

Discussion

Findings from the current study indicate that the total NPS score, a quantified measure of neurologic and treatment-related risk factors, is associated with global intellectual abilities as measured by verbal reasoning composites of age-appropriate cognitive batteries. These results are consistent with those of Micklewright and colleagues [23], who also found NPS scores to be predictive of global cognitive functioning in a smaller sample of survivors of pediatric brain tumor. The current findings are also

Table 2 Sample performance across neuropsychological domains

Domain/measure	n	M	SD	t	*p*
Intellectual functioning					
Verbal comprehension (VCI)	86	99.20	17.99	−0.41	.68
Attention and executive function					
Working memory (WMI)	73	96.01	13.44	−2.54	.01**
Digit span forward	51	9.08	2.82	−2.33	.02*
Digit span backward	48	9.71	2.57	−0.79	.44
TEA-Ch creature counting timing	22	6.00	2.65	−7.07	<.01**
TEA-Ch score!	52	8.15	3.89	−3.42	<.01**
D-KEFS category switching accuracy	57	9.53	3.84	−0.93	.36
D-KEFS number-letter switching	66	7.89	3.90	−4.38	<.01**
Motor & processing speed					
Processing speed (PSI)	75	85.80	14.25	−8.63	<.01**
D-KEFS motor speed	67	9.28	3.34	−1.75	.08
Grooved pegboard dominant hand	60	−1.58	1.79	−6.83	<.01**
Grooved pegboard non-dominant hand	60	−1.47	1.80	−6.36	<.01**
Adaptive functioning					
ABAS-II GAC	63	86.57	20.04	−5.32	<.01**

p values represent one-sample t-tests comparing sample mean performance to norm-referenced mean values
* $p \leq 0.05$; ** $p \leq 0.01$

Table 3 Hierarchical multiple regression analyses; associations with NPS

Domain	Predictor	β	Total model R^2	ΔR^2 (block)	p
Intellectual functioning					
Verbal reasoning (VCI)[a]	Years post-diagnosis			.02	.17
	NPS score	−.29	.10	.08	.01**
Attention and executive functioning					
Working memory (WMI)	Years post-diagnosis			.02	.31
	NPS score	−.24	.07	.06	.05*
Digit span forward	Years post-diagnosis			<.01	.91
	NPS score	−.44	.18	.18	<.01**
Digit span backward	Years post-diagnosis			<.01	.91
	NPS score	−.48	.22	.22	<.01**
TEA-Ch creature counting timing	Years post-diagnosis			<.01	.81
	NPS score	−.48	.22	.22	.04*
TEA-Ch score!	Years post-diagnosis			.03	.27
	NPS score	−.01	.03	.01	.94
D-KEFS category switching accuracy[a]	Years post-diagnosis			.13	.01**
	NPS Score	−.34	.24	.11	.01**
D-KEFS number–letter switching	Years post-diagnosis			.01	.35
	NPS score	−.03	.02	<.01	.80
Motor and processing speed					
Processing speed (PSI)	Years post-diagnosis			.20	<.01**
	NPS score	−.21	.24	.04	.06
Coding	Years post-diagnosis			.13	<.01**
	NPS score	−.18	.16	.03	.11
Symbol search	Years post-diagnosis			.15	<.01**
	NPS Score	−.22	.20	.05	.05*
D-KEFS motor speed[a]	Years post-diagnosis			.11	.01**
	NPS score	−.12	.12	.01	.34
Pegboard dominant hand	Years post-diagnosis			.03	.22
	NPS score	−.01	.03	<.01	.98
Pegboard non-dominant hand[a]	Years post-diagnosis			.01	.61
	NPS score	−.18	.04	.03	.24
Adaptive functioning					
ABAS-II GAC	Years post-diagnosis			.05	.09
	NPS score	−.18	.08	.03	.16

In each regression, years post-diagnosis was entered on the first block, and NPS scores in the second block

[a] Regression performed with Box–Cox transformed variable

* $p \leq .05$, ** $p \leq .01$

consistent with the larger body of evidence regarding neurocognitive functioning which suggests that, although mean scores are not substantially below average for this population, intellectual and executive functioning scores generally fall below those of same age-peers [39] and the severity of medical and treatment-related risk factors is correlated with overall cognitive functioning [2, 17, 20].

NPS scores were associated with measures of simple auditory attention and working memory in the present study, which have been found to be negatively impacted by cancer treatments in some [40, 41], but not all [10] studies . In the current study, NPS scores were associated with performance on several tasks of complex working memory, set-shifting, and cognitive flexibility, particularly when such tasks required rapid and efficient completion. These results suggest that cognitive efficiency appears to be impacted by treatment-related neurological risk factors such that reductions in efficiency of task completion, and

presumably of information processing more broadly, likely play a role in the decline in academic performance observed in survivors of childhood brain tumors [42]. As children move through school, basic rote learning is replaced by demands for greater integration and application of knowledge in an efficient manner, thereby placing children with such weaknesses at heightened disadvantage over time. Our finding of reduced cognitive efficiency also is consistent with studies that report decreased white matter integrity in children treated with radiation and/or systemic chemotherapies [8, 42]. Taken together, white matter injury and the associated reductions in rapid processing may represent one factor involved in emergence of neurocognitive "late effects" of treatment.

Consistent with prior work suggesting reduced fine motor speed in this population [39], our sample demonstrated lower performance relative to the normative sample on measures of fine motor dexterity and graphomotor speed. However, NPS scores were not significantly associated with performance on measures of graphomotor speed in the present study. Furthermore, although NPS scores were not related to overall psychomotor performance, associations were found with a measure of visual scanning with reduced motor demands (symbol search). This finding likely indicates that in pediatric brain tumor survivors, speed of information processing may be more affected by treatment-related risk factors than pure motor speed.

NPS scores were not related to caregiver-reported adaptive behaviors. These findings contribute to the mixed results seen in previous studies examining the NPS and adaptive behaviors. In one study by Papazoglou et al., [43] the NPS did not predict adaptive functioning on the total composite score on the Vineland Adaptive Behavior Scale (VABS). However, findings from a follow-up study indicated that the NPS was related to the Communication and Daily Living subscales of the VABS [25]. The current findings may be due in part to the relatively acute assessment period of participants, with findings likely to be more pronounced as children advance into young adulthood. Other potential explanations for this discrepancy include the presence of external supports in daily routines or that caregivers of survivors of childhood brain tumor may be less likely to report severe adaptive dysfunction in their children, secondary to reduced expectations during treatment or empathy for their child's situation. Additional research is needed to examine the association between treatment variables and caregiver observations of their child's adaptive behavior in this population.

Despite the strengths of this study, several important limitations need to be acknowledged. Findings of the present study are limited by the large age range, lack of available data pertaining to socioeconomic status, and diversity of measures used for analysis. Given the clinical nature of the sample, measures were selected for administration based upon clinical utility, as well as age of the patient. As such, not all participants were administered the same measures and the available data for analysis varied by domain. Therefore, some analyses may be underpowered, though the current study represents an improvement in sample size over the initial NPS validation study [23]. Furthermore, given the referred nature of the sample, these participants may be more likely to be impacted by their tumor and/or treatment, as assessments were not completed as a routine part of oncologic care, thereby compromising generalization to the broader population of survivors of brain tumor. As NPS scores were positively correlated with time post-diagnosis, the sample may be biased towards participants with greater long-term cognitive morbidity who are therefore more likely to seek neuropsychological evaluation. Alternatively, this pattern may be reflective of that seen in a mixed sample of BT survivors, in which children seen pre- or peri-operatively may not yet have had time to complete additional therapies (e.g., chemotherapy, radiation) or exhibit additional complications.

Overall, findings support associations between the NPS and broad intellectual functioning and cognitive efficiency in survivors of childhood brain tumor, but the results are mixed for associations with more specific graphomotor and adaptive domains. This suggests that use of the NPS may be valuable for identifying those patients most at risk for global neurocognitive impacts of their tumor or treatments, but holds limited value for identifying specific caregiver-reported functional difficulties. Given the idiosyncratic presentation of youth post-brain tumor treatment, these findings highlight the importance of comprehensive neuropsychological assessments that can better evaluate specific neurobehavioral domains.

Compliance with ethical standard

Conflict of Interest The authors (Mr. Mark D. McCurdy, Dr. Shruti Rane, Dr. Brian P. Daly, and Dr. Lisa A. Jacobson) declare that they have no conflict of interest.

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