ONLINE EXCLUSIVE

Impact of Childhood Leukemia Treatment on Attention Measured by the Continuous Performance Test Factor Structure

Kari M. Koerner, MPH, CHES, Kathleen C. Insel, PhD, RN, Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN, Lynnette L. Harris, PhD, Olga A. Taylor, MPH, and Ida M. (Ki) Moore, PhD, RN, FAAN

OBJECTIVES: To describe the impact of central nervous system–directed treatment on attention and its relation to academic outcomes in childhood acute lymphoblastic leukemia (ALL) survivors.

SAMPLE & SETTING: 51 children diagnosed with ALL at two pediatric oncology treatment centers in the southwestern United States.

METHODS & VARIABLES: A prospective, longitudinal design measured attention after a child was in remission, two years after the start of treatment, and at the end of treatment. Attention measures from the Conners' Continuous Performance Test were grouped into composite subdomains based on a factor structure describing focused attention, hyperactivity/impulsivity, sustained attention, and vigilance.

RESULTS: Children treated for ALL exhibited decreased focused attention, sustained attention, and vigilance during and at the end of treatment when compared to age- and gender-normed references.

IMPLICATIONS FOR NURSING: Pediatric oncology nurses are in a position to ask patients and parents about neuropsychological difficulties during ALL treatment. Patients who experience these effects are at risk for decreased academic abilities after treatment.

KEYWORDS attention; childhood leukemia; pediatric oncology; survivors
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The population of young adults who have survived cancer is growing, with 1 in 530 young adults aged 20 to 39 years having had cancer (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). Among childhood cancer survivors, acute lymphoblastic leukemia (ALL) is the most frequent diagnosis (Turcotte et al., 2017). Prior to the use of central nervous system (CNS)–directed therapy, the brain was the primary site of initial relapse among children with ALL who achieved a bone marrow remission (Pui & Evans, 2006; Pui et al., 1998). CNS-directed treatment with intrathecal (IT) and high-dose systemic chemotherapy, primarily methotrexate, is essential for long-term survival, which approaches 90% (Pui, 2003; Pui et al., 1998). As many as 60% of these children experience CNS treatment–related cognitive problems (Buizer, de Sonneville, & Veerman, 2009; Insel et al., 2017; Kanellopoulos et al., 2016; Krull et al., 2008; Krull, Hockenberry, Miketova, Carey, & Moore, 2013) that negatively affect academic success (Insel et al., 2017; Krull et al., 2013; Moore et al., 2016), behavioral adjustment (Patel & Carlson-Green, 2005; Stenzel et al., 2010), and quality of life (van der Plas et al., 2015). Attentional regulation is one neurobehavioral domain that is commonly noted to be vulnerable among children with ALL (Ashford et al., 2010; Bava, Johns, Kayser, & Freyer, 2018; Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Cheung & Krull, 2015; Jacola et al., 2016; Richard, Hodges, & Heinrich, 2018), and there is some evidence that the frequency of problems is associated with younger age and female sex (Jacola et al., 2016; Krappmann et al., 2007). Buizer et al. (2005) found subtle deficits in attention and information processing in children following CNS-directed chemotherapy, and that attentional problems were predominantly among children with intermediate- and high-risk disease who received intensified treatment. Cumulative IV methotrexate dose was greater in the intensified treatment group, suggesting that this could be a risk factor for attentional problems (Buizer et al., 2005). Compared to normative expectations on measures of sustained attention, a cohort of 393 ALL survivors had a significantly higher frequency of below-average performance two years after completion of treatment (Jacola et al., 2016). Measures of attention, inhibition of impulsivity, and variability in reaction time obtained from a retrospective sample of 24 childhood ALL survivors ranged from 1.4 to 1.6 standard deviations (SDs) below the normative mean, and scores in visual attention and response control accounted for a significant amount of variance in math performance (Richard et al., 2018).

Continuous performance tests (CPTs) are one of the most commonly used measures of attention and have been used in a variety of clinical populations, including those with attention-deficit/hyperactivity disorder (Wasserstein, 2005), youth with autism spectrum disorders (Chien et al., 2014), adolescent offspring of women with type 1 diabetes (Bytoft et al., 2017), and children with ALL (Bava, Johns, Freyer, & Ruccione, 2017; Jacola et al., 2016). The Conners' CPT (CCPT) is a computerized CPT that scores performance with 12 variables (Conners, 2004). Researchers usually do not report all 12 variables, but vary in which of the 12 measures they report. However, there are other ways to operationalize the multiple variables reported. For instance, in a heterogeneous clinical sample of 376 adults ($\bar{X}$ age = 32.9 years, SD = 13.8) referred for a neuropsychological assessment, Egeland and Kovalik-Gran (2010) tested the factor structure of the CCPT (2nd ed.) to determine if the CCPT measures distinct dimensions of attention. Results yielded a five-factor model that explained 74% of the variance in CCPT performance.

The purpose of the current study is to assess which subdomains of attention are more vulnerable to leukemia treatment and the association of these dimensions with academic abilities. The authors used the CCPT to assess the impact of treatment for ALL on attention using a prospective study design. The authors applied the factor structure developed by Egeland and Kovalik-Gran (2010) to investigate those attentional subdomains within this clinical population, both to determine if they were significantly different than normative data and if they were predictive of academic abilities. As Egeland and Kovalik-Gran (2010) concluded, the CCPT measures several different aspects of attention, and applying their findings to a sample of children who have been treated for ALL may increase understanding of the attentional difficulties that these children exhibit.

Methods

Sample and Setting

Children with ALL and their parents were recruited from two pediatric oncology treatment centers: the Banner University Medical Center Tucson at the University of Arizona and the Texas Children's Cancer Center at Texas Children's Hospital in

FIGURE 1. CCPT Factor Structure

Factor 1: Focus
Ability to respond correctly to targets and degree of variability in reaction time to targets; includes the traditionally used omission errors (failing to respond to targets), hit reaction time standard errors, variability, and perseverations

Factor 2: Hyperactivity/Impulsivity
Indiscriminate response style is based on fast reaction time and commission errors (responding to nontargets), therefore, commission errors, reaction time, and response style

Factor 3: Sustained Attention
Decline in performance as test progresses over time (test length is 14 minutes for CCPT and 8 minutes for K-CPT); composed of 2 block change measures and change in omission errors

Factor 4: Vigilance
Ability to sustain performance over time; includes a tendency to respond slower when the ISI is longer (periods of infrequent stimuli); composed of 2 measures of ISI changes

Factor 5: Change in Control
Changes in mental control characterize individuals who become more impulsive over time; composed of change in commission and block change; not available for measure in this study

CCPT—Conners' Continuous Performance Test; ISI—interstimulus interval; K-CPT—Conners' Kiddie Continuous Performance Test
Note. Based on information from Conners, 2004; Egeland & Kovalik-Gran, 2010.

Houston. Institutional review board approval was received from both sites. Consent from parents and assent from children aged 7 years or older at the time of ALL diagnosis were obtained. Study staff, who were not responsible for providing treatment to potential participants, approached the families in the treatment centers after receiving a referral from the oncologist. The following were eligibility criteria:

- Being recently diagnosed with pre–B cell or pre–T cell ALL
- Receiving treatment according to Children's Oncology Group protocols for low-, standard-, high-, or very high–risk disease

The exclusion criterion was having a history of other neurologic injury causes, including developmental disabilities (e.g., Down Syndrome), traumatic brain injury, or seizures. CNS-directed treatment for these children included high- or intermediate-dose IV and IT methotrexate administered at specific intervals during the 2.5 to 3 years of ALL therapy. Participant demographic information was collected from caregivers during a baseline assessment when the child was medically stable. Attentional abilities were assessed after the child was in disease remission and medically stable (baseline), two years later (year 2), and about one year after the end of ALL treatment (end of treatment); academic abilities were assessed at the end of treatment. Participants received a check for $50 after completing each assessment. Study staff followed up with participants when they were due for a yearly assessment; however, some attrition occurred. Only participants who completed year 2 and end-of-treatment assessments are reported in this article.

TABLE 1. Sample Characteristics (N = 51)

Characteristic	$\bar{X}$	SD
Age at diagnosis (years)	6.22	2.92
Age at year 2 assessment (years)	8.57	2.91
Age at EOT assessment (years)	9.61	2.93
Months from diagnosis to year 2 assessment	28.14	2.5
Months from diagnosis to EOT assessment	40.65	3.15
Characteristic		**n**
Race		
Caucasian		21
Not Caucasian		30
Ethnicity		
Hispanic		28
Not Hispanic		21
Unknown		2
Gender		
Female		31
Male		20
Acute lymphoblastic leukemia risk group		
Low		1
Standard		37
High		11
Very high		2

EOT—end of treatment

Cognitive Measures

Attention was measured by CCPT (2nd ed.) for children aged 6 years or older; the Conners' Kiddie CPT (K-CPT) (1st ed.) was used for children aged 4 and 5 years. Both tests are computer-based and assess subdomains of attention, including vigilance, impulsivity, and inattention. Simple pictures are used in the test for younger children, and letters are used in that for older children (Conners, 2004). Each time children see a stimulus, they are instructed to press the space bar, except when they see the letter X (CCPT) or a soccer ball (K-CPT). Raw scores are converted by the CCPT software to age- and gender-normed t scores with a mean of 50 and an SD of 10. Higher scores are indicative of worse performance. The CCPT varies the time between stimuli, which is often referred to as the interstimulus interval (ISI). Measuring a change in a participant's response as the ISI changes introduces more opportunities for assessing attention rather than simply counting errors alone (e.g., errors of omissions or commissions). In addition, the CCPT takes 14 minutes to complete, allowing for assessment of the responses over the length of the measure, or eight minutes in the case of the K-CPT. Test-retest reliability reported for the CCPT is acceptable, with significant correlations ranging from 0.43 to 0.92; however, some scores did not have significant test-retest correlations in a sample of 23 participants (Conners, 2004).

The authors computed composite attention scores (focus, hyperactivity/impulsivity, sustained attention, and vigilance) based on the factor structure created by Egeland and Kovalic-Gran (2010). Figure 1 summarizes the dimension of attention measured. The focus factor includes the omission score, which frequently has been reported in longitudinal studies with survivors of childhood leukemia (Conklin et al., 2012). Although Egeland and Kovalic-Gran (2010) included

TABLE 2. Attention Composite and Component Scores Compared to the Normal Reference Values

Attention Measure	Year 2		1-Sample Test Versus Value = 50		End of Treatment		1-Sample Test Versus Value = 50	
	$\bar{X}$	SD	t	p	$\bar{X}$	SD	t	p
Focus composite	56.86	10.61	4.61	< 0.001	54.91	11.53	3.04	0.004
Variability	56.05	9.37	4.62	< 0.001	55.02	11.44	3.13	0.003
Hit reaction time SE	56.06	10	4.32	< 0.001	56.25	12.8	3.49	0.001
Perseverations	61.11	22.82	3.48	0.001	58.94	22.95	2.78	0.008
Omissions	54.2	11.43	2.63	0.011	54.75	13.98	2.43	0.019
Hyperactivity/impulsivity composite	50.6	5.12	0.84	0.403	51.43	6.48	1.57	0.122
Commissions	50.95	10.3	0.66	0.513	49.44	7.98	–0.5	0.621
Hit reaction time	49.26	9.94	–0.53	0.595	53.92	13.07	2.14	0.037
Response style	51.61	6.9	1.66	0.102	50.92	7.56	0.87	0.391
Sustained attention composite	54.92	10.87	3.23	0.002	53.04	10.71	2.03	0.048
Hit reaction time block change	55.34	12.9	2.96	0.005	55.29	12.77	2.96	0.005
Hit SE block change	54.5	10.01	3.21	0.002	50.8	10.59	0.54	0.591
Vigilance composite	57.59	10.53	5.15	< 0.001	57.37	12.34	4.26	< 0.001
Hit reaction time ISI change	58.55	12.33	4.95	< 0.001	59.78	15.7	4.45	< 0.001
SE of hit reaction time ISI change	56.64	10.12	4.68	< 0.001	54.96	9.97	3.55	0.001

ISI—interstimulus interval; SE—standard error

Note. Values are t scores, with the expected mean being 50 and the expected SD being 10. Higher mean scores are indicative of worse performance.

change in omissions and change in commissions as part of their factor analysis, these measures were not available for the current sample because the CCPT software used did not calculate scores for these variables. Accordingly, the sustained attention composite instead consists of block change and block change standard error, and the change in control factor was not analyzed.

Two measures from Woodcock, McGrew, and Mather (2007), calculation and letter-word identification, were used to measure academic abilities. The calculation subtest measures math skills, and the letter-word identification subtest measures basic reading skills. Test-retest reliability for the measures are 0.94 and 0.95, respectively (McGrew, Schrank, & Woodcock, 2007).

Data were analyzed using IBM SPSS Statistics, version 20.0. Descriptive statistics were used to summarize sample characteristics and performance on attention and academic abilities measures. Mean scores on the attention composite scores were compared to age-adjusted standardized norms using one-sample t tests. Associations between attention measures and academic abilities were examined using Pearson correlations. Finally, forced-entry multiple linear regression was used to identify attention factors at year 2 that predicted academic outcomes at the end of treatment. Statistical significance was set at $p < 0.05$.

Results

Demographic Characteristics

Table 1 summarizes demographic and clinical characteristics of the sample. The sample included 51 children with ALL. Mean age at the time of diagnosis was 6.22 years (range = 2.85–12.61, SD = 2.92). There were 20 males and 31 females. Most participants were diagnosed with standard-risk (n = 37) or high-risk (n = 11) ALL. Mean age at the time of the year 2 assessment was 8.57 years (range = 5.34–15.37, SD = 2.91); mean age at the end-of-treatment assessment was 9.61 years (range = 6.4–16.4, SD = 2.93). Mean maternal education attainment was 13.34 years (range = 7–20, SD = 2.568), and mean paternal education attainment was 13 years (range = 10–20, SD = 2.341).

Attention Abilities

Performance on the CCPT at year 2 and end of treatment and results from the one-sample t test comparing mean attention composite scores with standardized norms are summarized in Table 2.

TABLE 3. Correlation Coefficients Among the Attention Composites

Time Point	Focus	H/I	Sustain
Year 2			
Focus	–	–	–
H/I	0.601**	–	–
Sustain	0.212	0.278*	–
Vigilance	0.655**	0.372**	0.361**
End of treatment			
Focus	–	–	–
H/I	0.912**	–	–
Sustain	0.532**	0.646**	–
Vigilance	0.754**	0.773**	0.498**

* $p < 0.05$; ** $p < 0.01$
HI—hyperactivity/impulsivity

Children undergoing treatment for ALL had significantly worse scores at the year 2 assessment on the focus ($p < 0.001$), sustained attention ($p = 0.002$), and vigilance ($p < 0.001$) composites. The mean score on the hyperactivity/impulsivity composite was not different from an expected score of 50. Scores at the end of treatment were similar to year 2 scores, with participant scores being significantly worse than norm values for the focus ($p = 0.004$), sustained attention ($p = 0.048$), and vigilance ($p < 0.001$) composites; the hyperactivity/impulsivity composite was not different from 50.

Table 3 summarizes correlations among the CCPT composites. At year 2, focus was significantly correlated with hyperactivity/impulsivity and vigilance. Hyperactivity/impulsivity was significantly correlated with sustained attention and vigilance; sustained attention was significantly correlated with vigilance. All composites were significantly correlated with each other at the end of treatment.

Academic Abilities

Participant scores in letter-word identification and calculation were within expectations for norm references. The means were 100.08 (SD = 14.75) and 100.44 (SD = 15) for letter-word identification and calculation, respectively. Reading and math abilities were not significantly different from 100 ($p = 0.97$ and $p = 0.837$, respectively), indicating that academic abilities were, on average, close to peers' scores. Associations between attention at year 2 and academic abilities at the end of treatment were examined with Pearson correlations (see Table 4). Reading abilities were significantly correlated with the focus, hyperactivity/impulsivity, and vigilance composites at both year 2 and the end of treatment. Math abilities were significantly correlated with the year 2 hyperactivity/impulsivity composite.

To examine whether attention after two years of ALL treatment predicts academic abilities at the end of treatment, the year 2 attention composites were entered into a regression equation using the forced-entry method (see Table 5). Although the overall model significantly predicts 20% of variance in letter-word identification scores, none of the attention composites was individually significant predictors. The relatively small sample size may have affected the predictive ability of the regression.

Discussion

CPTs are widely used measures of attention, with studies often selecting specific subdomains of the measure rather than all the aspects provided in the CPT (Cheung & Krull, 2015). Using exploratory data analysis, Egeland and Kovalik-Gran (2010) reduced the number of measures in the CCPT to five factors, supporting the claim that no one overall measure of attention exists within the CCPT, but rather there are several aspects or subdomains that have different meanings. Creating composite scores that reflect their factor structure provides an opportunity to make full use of the aspects of attention that could be differentially affected by treatment among children with ALL.

Findings from the current study indicate significant differences among children treated for ALL

TABLE 4. Correlation Coefficients Between Attention Composite Scores and Academic Outcomes

Time Point	Letter-Word	Calculation
Year 2		
Focus	–0.437**	–0.117
H/I	–0.447**	–0.375**
Sustain	–0.007	0.031
Vigilance	–0.31*	–0.048
End of treatment		
Focus	–0.395**	–0.216
H/I	–0.47**	–0.269
Sustain	–0.165	–0.167
Vigilance	–0.321*	–0.154

* $p < 0.05$; ** $p < 0.01$
H/I—hyperactivity/impulsivity

in composite scores reflecting decreased focused attention, sustained attention, and vigilance on the CCPT compared to age-normed references at both year 2 and the end of treatment. The authors found no difference in scores of the composite reflecting hyperactivity/impulsivity when compared to norm values, indicating average attentional abilities in this area. To the authors' knowledge, this is the first time the Egeland and Kovalik-Gran (2010) factor structure has been applied to a sample of children who have received cancer treatment.

The subdomains composing Egeland and Kovalik-Gran's (2010) focus factor include omission errors (failing to respond to a target), hit reaction time standard error, variability in reaction time to targets, and perseverations. These aspects occurred throughout the test rather than being differentially decreased block by block or in relation to the interstimulus interval. Therefore, this factor reflects focused attention across the course of the task, and the authors showed vulnerability in this subdomain among the ALL sample. In other studies of this patient population, two of the focus factor loadings (omissions and variability) are often referred to as reflecting "sustained attention" (Conklin et al., 2012; Edelmann et al., 2014). However, Egeland and Kovalic-Gran's (2010) model yielded another distinct factor composed of hit reaction time and hit standard error block change, both of which more specifically reflect the ability to sustain focus; therefore, they labeled this the focus factor. The authors found that the children in the current sample were also vulnerable to problems in this subdomain. The vigilance factor was viewed as reflecting the consistency or inconsistency of response speed across different ISIs, and the sample had scores lower than normative expectations as well. The final Egeland and Kovalik-Gran (2010) factor that the authors applied, hyperactivity/impulsivity, was composed of commission errors and response style. The sample did not differ from the age-normed reference in this domain.

KNOWLEDGE TRANSLATION

- Focused attention, hyperactivity/impulsivity, sustained attention, and vigilance have not been explored in a sample of children who have been treated for leukemia.
- Using a composite structure to understand a widely used measure of attention may be meaningful to understand which dimensions of attention may be vulnerable to leukemia treatment and the impact on the child's academic abilities.
- Children with attentional problems are also more likely to have difficulties with reading skills.

Another goal was to determine if any attention subdomains could predict academic difficulties one year later. Entering all the factor composites simultaneously did significantly predict letter-word identification scores. However, none of the individual composites rose to the level of significance when taking all the composites into account. Therefore, it is possible that children who are lower in their performance across all aspects of the CCPT are particularly affected in relation to achievement, whereas difficulty in a single composite was less robust. The regression model using the composites to predict calculation scores was not significant ($p = 0.051$), suggesting that problems in these specific attention skills may be less important for future basic math achievement.

A study by Bava et al. (2018) examining outcomes among Latino survivors of childhood ALL concluded that, although most cognitive functions were within the average range, there were lower scores in specific areas that could reflect mild, but potentially clinically important, weakness for children with ALL. The sample performed better than norm reference values in CCPT (3rd ed.) commission errors, but was not significantly different from norm values on other reported CCPT (3rd ed.) scores (Bava et al., 2018).

TABLE 5. Simultaneous Regression Results for Attention Composites Predicting Reading Ability

Measure	R^2	Adjusted R^2	F	β	p
Overall model	0.262	0.196	3.989	–	0.007
Focus	–	–	–	−0.2	0.312
H/I	–	–	–	−0.319	0.068
Sustain	–	–	–	0.164	0.25
Vigilance	–	–	–	−0.105	0.547

H/I—hyperactivity/impulsivity

In a study analyzing the CCPT in a sample of adolescent offspring of mothers with type 1 diabetes mellitus, Bytoft et al. (2017) discovered nearly identical factors as those identified by Egeland and Kovalik-Gran (2010). Their results concluded that children of mothers with diabetes did not have decreased attention skills when compared to children of mothers without diabetes. The factor structure, first reported by Egeland and Kovalik-Gran (2010), and reproduced by Bytoft et al. (2017), is a useful tool in interpreting specific attentional deficits as measured by the CCPT.

Limitations

Although the factor structure that was developed by Egeland and Kovalic-Gran (2010) is of interest, it must be noted that the sample they used was a clinical sample. Even the "normal" group was referred for neuropsychological testing because of possible exposure to toxins or trauma. Therefore, the factor loadings need to be replicated in a larger sample that includes children who are developing normally—that is, those who are not experiencing obvious signs of attention difficulty. In addition, the factors were obtained on a largely adult sample, and findings may not be generalizable to children. Some children did not complete all measures because of scheduling issues or disinterest, which resulted in missing data. Only children who completed both year 2 and end-of-treatment attention measures were presented in this article.

Implications for Nursing

Childhood leukemia survivors and their parents may complain of diminished attention abilities during and after treatment, and difficulties within the broad category of attention, including focus, inhibitory control, and vigilance, are associated with decreased academic achievement. Nurses who detect signs of lower attentional abilities or hear concerns regarding attention should seek follow-up. Follow-up may include referral to neuropsychologists or school psychologists to help determine the presence and impact of attentional difficulties. Treatment could include educational interventions. Early intervention is important to help children remain on track and achieve academic success during and after treatment.

Conclusion

Applying a previously identified factor structure and using it to guide composite formation provides a more detailed approach to deciphering the grouping of subdomains in attention. Taking a commonly used computerized measure of attention and using its component processes may allow more targeted intervention for any identified areas of difficulty. The current authors found vulnerability in some but not all subdomains of attention within a pediatric ALL sample. Egeland and Kovalik-Gran (2010) argued that the use of one CCPT variable is reductionistic and running all the CCPT variables individually runs the risk of type 1 error. Potential for tailoring interventions is improved when a more thoughtful approach to deciphering the components of attention is taken.

Compared to normative data, children who have been treated for ALL demonstrate reduced skills in focused attention, sustained attention, and vigilance two years after diagnosis and at the end of treatment. Difficulties with attentional regulation (i.e., focus, impulsivity, concentration, and vigilance) during treatment are associated with lower reading abilities at the end of treatment. ALL survivors who experience these specific attention problems may benefit from additional support to maximize academic achievement.

Kari M. Koerner, MPH, CHES, is a senior research specialist in the Department of Family and Community Medicine in the College of Medicine and **Kathleen C. Insel, PhD, RN,** is the Biobehavioral Health Science Division Interim Chair and a professor in the College of Nursing, both at the University of Arizona in Tucson; **Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN,** is a professor of pediatrics in the College of Medicine at Baylor University in Houston, TX, and the Bessie Baker professor emeriti in the School of Nursing at Duke University in Durham, NC; **Lynnette L. Harris, PhD,** is an associate professor and **Olga A. Taylor, MPH,** is a clinical research manager, both in the College of Medicine at Baylor University; and **Ida M. (Ki) Moore, PhD, RN, FAAN,** is the Anne Furrow endowed professor and interim dean in the College of Nursing at the University of Arizona. Koerner can be reached at kkoerner@arizona.edu, with copy to ONFEditor@ons.org. (Submitted October 2018. Accepted January 29, 2019.)

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