

Brief Report: Sluggish Cognitive Tempo Among Pediatric Survivors of Acute Lymphoblastic Leukemia

Cara B. Reeves,¹ PhD, Shawna Palmer,² PhD, Alan M. Gross,³ PhD, Susan J. Simonian,⁴ PhD, ABPP, Lloyd Taylor,^{1,5} PhD, Elizabeth Willingham,⁶ EdS and Raymond K. Mulhern,² PhD

¹Division of Clinical Services, Medical University of South Carolina, ²Division of Behavioral Medicine, St Jude Children's Research Hospital, ³Department of Psychology, University of Mississippi, ⁴Department of Psychology, The College of Charleston, ⁵Department of Psychology, The Citadel, and ⁶Department of Counseling and Psychological Services, Georgia State University

Objective The purpose of the present study was to assess sluggish cognitive tempo (SCT) behavioral symptoms among pediatric survivors of acute lymphoblastic leukemia (ALL) and to determine the relationship of these behaviors with cognitive late effects. **Methods** ALL survivors ($n = 80$) and a sibling control group ($n = 19$) were administered intelligence (IQ) testing, achievement testing and SCT behavioral items. Group differences (patients vs. siblings) were examined on the SCT behaviors and partial correlations were conducted to explore the relationship of the SCT behaviors with IQ and achievement, while controlling for age at treatment and time since treatment. **Results** ALL survivors exhibited significantly more SCT symptoms than the sibling control group and increased SCT symptoms were associated with lower IQ and achievement scores. **Conclusions** ALL survivors are vulnerable to SCT symptoms and these behaviors are associated with cognitive late effects. SCT symptoms may represent a behavioral component of cognitive late effects.

Key words academic achievement; ADHD; behavior problems; leukemia.

Leukemia is the most common form of childhood cancer, comprising 30% of new diagnoses (Pui & Evans, 1998). Although there are different subtypes of leukemia that vary in their histological mechanisms and chronicity, the most common form found in children is acute lymphoblastic leukemia (ALL). ALL is a cancer of the white blood cells, or lymphoid cells, that work to protect the body from infection (National Cancer Institute, 2002). During the 1960s, the 5-year survival rate for children diagnosed with ALL was <5% (National Cancer Institute, 2002). The dismal prognosis was due not to the primary disease itself, but to metastatic spread into the central nervous system. However, with substantial improvements in available treatments the survival rate has now increased to 85%. The most common treatment regimens for children diagnosed with ALL include prophylactic whole brain and spinal irradiation (CRT) and chemotherapy administered directly into the central nervous system

(intrathecal chemotherapy; IT) to prevent metastasis (Pui & Evans, 1998).

Though successful in reducing meningeal relapse, prophylactic therapy has some marked drawbacks. In particular, intellectual (IQ) and academic declines have consistently been documented among ALL survivors, with younger age at treatment and time since treatment identified as significant risk factors (Anderson, Godber, Smibert & Ekert, 1997; Espy et al., 2001; Mulhern et al., 1987). The cognitive deficits are significant, with estimates of a 10 to 15 point drop in intellectual and academic functioning over time (Anderson et al., 1997; Cousens, Waters, Said & Stevens, 1988). Some evidence suggests that these deficits are at least partially attributable to impairments in more basic cognitive skills including attention, processing speed, and working memory (Schatz, Kramer, Ablin & Matthay, 2000).

All correspondence concerning this article should be addressed to Cara B. Reeves, Division of Clinical Services, Medical University of South Carolina, 151-B Rutledge Avenue, PO Box 250962, Charleston, South Carolina 29425-0962, USA. E-mail: reeve@musc.edu

Journal of Pediatric Psychology 32(9) pp. 1050–1054, 2007

doi:10.1093/jpepsy/jsm063

Advance Access publication October 12, 2007

Journal of Pediatric Psychology vol. 32 no. 9 © The Author 2007. Published by Oxford University Press on behalf of the Society of Pediatric Psychology. All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org

In working clinically with survivors of childhood ALL, there are significant similarities with the subset of children with attention deficit hyperactivity disorder (ADHD) described in the literature as exhibiting a sluggish cognitive tempo (SCT). ADHD patients with SCT behavioral symptoms are described as lethargic, always daydreaming, frequently staring, and unorganized (Barkley, DuPaul, & McMurray, 1990; Carlson & Mann, 2002; Hartman, Willcutt, Rhee, & Pennington, 2004; McBurnett, Pfiffner, & Frick, 2001). These children also have documented cognitive and achievement deficits. It may be that SCT behavioral symptoms are not unique to ADHD, but instead exist among other pediatric populations including survivors of ALL.

Therefore, the purpose of the present study was to be the first to assess SCT behavioral symptoms among survivors of ALL and to determine the association of these behaviors with cognitive late effects. It was predicted that (a) ALL patients would exhibit more SCT symptoms than expected in a group of sibling control subjects and that (b) SCT behavioral symptoms would be associated with lower intelligence scores and poorer academic achievement.

Method

Participants

The nature of the present study was retrospective and the project was granted approval by the Institutional Review Board at St Jude Children's Research Hospital (SJCRH). Patients were considered for the present study from a larger cohort participating in screening for National Cancer Institute (NCI) funded investigation of the effectiveness of methylphenidate in treating the cognitive late effects observed among child cancer survivors (Principal Investigator: R.K. Mulhern). All patients with histologically diagnosed ALL and who were 1-year postcompletion of treatment with no signs of progressive disease, or were a sibling of an ALL patient, were approached for screening. Exclusion criteria included previous diagnoses of depression, anxiety, ADHD, Tourette's syndrome, substance abuse, or uncontrolled seizure disorder. Those excluded did not participate in the screening testing. Parents or legal guardians who were of legal age gave written informed consent and child participants gave written assent. Since patients for the present study were drawn from the screening pool of the NCI study, no patients were receiving psychotropic medication at the time of the investigation and no patients were previously treated for ADHD.

Patient Group ($n = 80$)

Patients enrolled in the current investigation had a mean age at the time of treatment of 3.8 years ($SD = 2.3$; range = 6 months to 11 years). There were 43 males (53.8%) and 37 females (46.3%). Seventy-four patients were Caucasian (92.5%), five were African American (6.3%), and one was of Hispanic decent (1.3%). Thirteen patients (16.3%) received whole-brain CRT and 67 (83.8%) patients were treated with chemotherapy alone.

Sibling Control Group ($n = 19$)

Among the sibling group, there were 10 males (52.6%) and 9 females (47.4%). Fifteen were Caucasian (78.9%), one was African American (5.35%), none were of Hispanic decent (0%), and three were of "other" decent (15.8%). No statistically significant differences were found between the ALL survivors and siblings on gender ($\chi^2 = 0.018$; ns). Although parametric statistical analyses could not be conducted on ethnicity due to asymmetrical data (no siblings of Hispanic decent), examination of descriptive data suggest relative similarity in ethnic representation between groups.

Psychological Evaluation

The psychological evaluation data for the current investigation was obtained from the screening phase of the parent NCI study; thus, patients and siblings evaluated at this time point were not required to exhibit attention problems nor had they started on the methylphenidate drug trial. At the time of testing, patients were a mean of 12.4-years old ($SD = 3.3$; Range = 6.6 to 18.2 years) and were 6.0 years since the completion of treatment ($SD = 3.6$; Range = 1.4 to 13.8years). Siblings were a mean of 12.6-years old ($SD = 3.6$; Range = 6.8 to 18.6 years) at the time of testing. No statistically significant difference was found between patients and siblings on age at the time of testing [$t(97) = 0.21$; ns]. Patients and siblings received measures of SCT, intelligence, and academic achievement.

The SCT was assessed using the Child Behavior Checklist (Achenbach, 1991; CBCL). Recent studies have identified behavioral items consistent with SCT (Carlson & Mann, 2002; Hartman et al., 2004). Specifically, Hartman and colleagues (2004) identified five items from the CBCL that loaded onto the SCT factor in exploratory factor analyses and described these items as indicators of SCT. These five CBCL items included item 13 "confused or in a fog," item 17 "daydreams or gets lost in his or her thoughts," item 54 "overtired," item 80 "stares blankly," and item 102 "underactive, slow moving, or lacks energy." Scores from each of these five items

(0 = not true, 1 = sometimes true, 2 = often true) were combined to create a SCT total score (range = 0–10).

Patients were evaluated with an age-appropriate measure of intelligence using the Wechsler Intelligence Scale for Children, third edition (WISC-III; Wechsler, 1991) or the Wechsler Adult Intelligence Scale (Wechsler, 1997). All patients and siblings completed at least three subtests (information, similarities, and block design) allowing an estimation of global functioning (EIQ) to be calculated using a special short-form procedure (Sattler, 1992, p. 1034).

Patients and siblings were also evaluated with regard to academic achievement using the Wechsler Individual Achievement Test (WIAT; The Psychological Corporation, 1992). Measures of basic reading skills, reading comprehension, spelling, mathematical reasoning, and numerical operations were obtained.

Results

Prior to conducting the statistical analyses, the data set was examined for missing values and outliers. No participants were eliminated from the analyses as a result of missing data or outliers. Data were analyzed using SPSS statistical software.

Primary Analyses

Patients versus Siblings

A multivariate analysis of variance was conducted to determine group differences (patients vs. siblings) within the domains of behavior (SCT total score), intelligence (EIQ), and academic achievement (basic reading skills, reading comprehension, spelling, mathematical reasoning, and numerical operations; Table I). Results revealed that patients had significantly lower basic reading skills [$F(1,99) = 4.89, p = .029$] and significantly higher SCT total scores [$F(1,99) = 5.26, p = .024$]. Although EIQ approached significance [$F(1,99) = 3.24, p = .075$], no other significant differences were found.

Associations of SCT with Intelligence and Academic Achievement

SCT was examined in relation to both intelligence and academic achievement within the ALL patient group. Because younger age at treatment and increased time since treatment have both been associated with poorer cognitive outcome following ALL treatment, the variance associated with these variables was controlled for using partial correlations (Meadows et al., 1981). With the exception of spelling, higher scores on SCT were found to be significantly related to poorer performance on all

Table I. Group Differences on Measures of SCT Behaviors, Intelligence and Achievement

Test	ALL Patients		Siblings		F	p
	Mean	SD	Mean	SD		
Estimated IQ	93.06	18.25	101.37	17.23	3.25	.075
Basic reading	95.83	13.93	103.79	14.85	4.89	.029
Math reasoning	97.10	16.05	100.42	17.55	0.64	.428
Spelling	96.24	14.96	100.79	17.63	1.33	.252
Reading comprehension	97.45	14.15	102.16	16.38	1.60	.209
Numerical operations	94.24	17.92	93.26	16.58	0.05	.829
SCT composite score	1.74	2.15	0.58	0.90	5.26	.024

outcome measures including EIQ ($r = -.302, p = .007$), basic reading ($r = -.26, p = .022$), numerical operations ($r = -.29, p = .01$), reading comprehension, ($r = -.272, p = .016$), and math reasoning ($r = -.364, p = .001$).

Post-hoc Analyses

Previous literature has demonstrated that an interruption to the normal development of processing speed and working memory is a significant variable in cognitive deficits among pediatric patients surviving ALL (Schatz et al., 2000). In an effort to better understand the significant group differences in reading skills that occurred in the present study, we investigated whether SCT total score could be considered a mediator of reading skills. Using a simultaneous regression analysis, basic reading was significantly predicted by group (patients vs. siblings) and SCT [$F(2, 96) = 5.50, p = .005$] and β -weights for group and SCT were .165 and $-.242$, respectively. Consistent with a mediating model, the only significant predictor was SCT ($t = -2.42, p = .017$). After statistically controlling for SCT, group was no longer found to be significantly related to basic reading skills ($p > .05$). This suggests that group differences between patients and siblings on basic reading performance may be at least partially explained by differences in SCT total score.

Discussion

The purpose of the present study was to provide initial data regarding SCT behavioral symptoms among pediatric ALL survivors and to evaluate the relationship of the SCT symptoms with cognitive late effects. Consistent with our hypothesis, ALL patients evidenced significantly more SCT symptoms than the sibling control group. Additionally, these behaviors were related to cognitive late effects in that the presence of SCT behaviors was associated with impaired intellectual functioning and

New model of late effects including cognitive and behavioral symptoms.

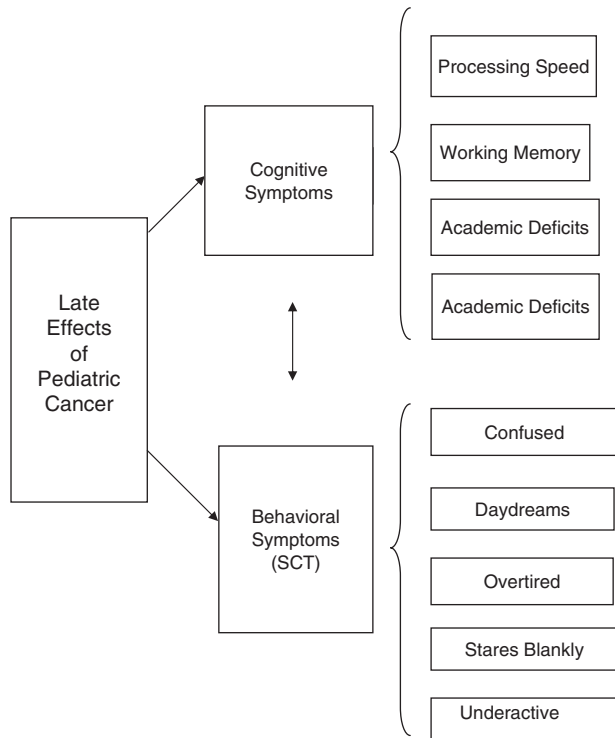


Figure 1. Conceptual framework of late effects following ALL treatment and including behavioral symptoms associated with documented cognitive deficits.

reading ability. The lack of group differences in math and spelling ability may be attributable to the insensitivity of the WIAT in assessing subtle differences within these domains.

The observation that ALL survivors exhibit SCT symptoms is clinically meaningful and suggests that ALL survivors are vulnerable to this behavioral symptom cluster. One explanation is that the SCT symptoms represent a behavioral component of cognitive late effects that until now has been overlooked in the literature (Figure 1). Supporting this theory is the post-hoc observation that SCT symptoms mediated the relationship between group membership (patients vs. siblings) and basic reading. It also is possible that SCT is the behavioral manifestation of reduced processing speed, which has previously been shown to underlie deficits associated with cognitive late effects (Schatz et al., 2000). Monitoring SCT behaviors provide parents, caregivers, and teachers the opportunity to identify children at risk for cognitive late effects. Early screening of at-risk patients would allow for identification of those individuals who may benefit from a more thorough assessment. This model is consistent with the two-step screening-assessment model first proposed in psychiatric epidemiology and would allow for

appropriate intervention planning and implementation (Simonian, 2006).

Given that this investigation is the first to examine the relationship between these cognitive and behavioral outcome variables among ALL survivors, additional research is needed. Specifically, future studies should explore the impact of radiation dosimetry (Merchant, 2006) on the manifestation of SCT symptoms. Additionally, the association of other psychosocial variables (e.g., emotional stressors, family environment, internalizing behavior problems, and community support of the family) with the SCT symptoms observed among ALL survivors need to be considered so as to provide insight into the multifaceted nature of cognitive late effects and to explore possible risk and resiliency factors. Additionally, the inclusion of multiple measures of cognitive and achievement functioning will allow a more thorough assessment of these abilities.

Several limitations of the present study should be considered when interpreting and generalizing the results. First, the present study was limited to parent report of behavior and did not utilize cross-situational assessment of behaviors. Future research should involve multiple informants (i.e., parent and teacher) to assess behavior across different environments. Additionally, examination of other cognitive, social, parenting and coping style variables within the context of a developmental model of risk, and resiliency for cognitive late effects is warranted. Future studies should also include treatment modality within the primary hypotheses to determine its etiological role in observed deficits.

This investigation is important as it the first to identify SCT behavioral symptoms among pediatric cancer survivors and to link these symptoms to cognitive late effects. These data support using the five SCT behavioral items as a marker for identifying ALL patients vulnerable to intellectual and achievement deficits, thereby enabling future researchers and clinicians to tailor inventions to ameliorate these problems in an empirically supported fashion.

Conflict of interest. None declared.

Received November 14, 2006; revisions received July 5, 2007; accepted July 17, 2007

References

- Achenbach, T. M. (1991). Integrative guide for the 1991 CBCL/4-18, YSR & TRF Profiles. Burlington, VT: University of Vermont Department of Psychiatry.

- Anderson, V., Godber, T., Smibert, E., & Ekert, H. (1997). Neurobehavioural sequelae following cranial irradiation and chemotherapy in children: An analysis of risk factors. *Pediatric Rehabilitation, 1*(2), 63–76.
- Barkley, R. A., DuPaul, G. J., & McMurray, M. B. (1990). Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. *Journal of Consulting and Clinical Psychology, 58*(6), 775–789.
- Carlson, C. L., & Mann, M. (2002). Sluggish cognitive tempo predicts a different pattern of impairment in the attention deficit hyperactivity disorder, predominantly inattentive type. *Journal of Clinical Child and Adolescent Psychology, 31*(1), 123–129.
- Cousens, P., Waters, B., Said, J., & Stevens, M. (1988). Cognitive effects of cranial irradiation in leukemia: A survey and meta-analysis. *Journal of Child Psychology and Psychiatry, 29*(6), 839–852.
- Espy, K. A., Moore, I. M., Kaufmann, P. M., Kramer, J. H., Matthay, K., & Hutter, J. J. (2001). Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: A prospective study. *Journal of Pediatric Psychology, 26*(1), 1–9.
- Hartman, C. A., Willcutt, E. G., Rhee, S. H., & Pennington, B. F. (2004). The relation between sluggish cognitive tempo and DSM-IV ADHD. *Journal of Abnormal Child Psychology, 32*(5), 491–503.
- McBurnett, K., Pfiffner, L. J., & Frick, P. J. (2001). Symptom properties as a function of ADHD type: An argument for continued study of sluggish cognitive tempo. *Journal of Abnormal Child Psychology, 29*(3), 207–213.
- Meadows, A. T., Massari, D. J., Fergusson, J., Gordon, J., Littman, P., & Moss, K. (1981). Declines in IQ and cognitive dysfunctions in children with acute lymphoblastic leukemia treated with cranial irradiation. *Lancet, 2*, 1015–1018.
- Merchant, T. E. (2006). Craniopharyngioma radiotherapy: Endocrine and cognitive effects. *Journal of Pediatric Endocrinology and Metabolism, 19*(Suppl 1), 439–446.
- Mulhern, R. K., Ochs, J., Fairclough, D., Wasserman, A. L., Davis, K. S., & Williams, J. M. (1987). Intellectual and academic achievement status after CNS relapse: A retrospective analysis of 40 children treated for acute lymphoblastic leukemia. *Journal of Clinical Oncology, 5*(6), 933–940.
- National Cancer Institute. (2002). Acute lymphoblastic leukemia in children. Retrieved September 15, 2003 from <http://www.nci.nih.gov/newscenter/all3>.
- Pui, C., & Evans, W. E. (1998). Acute lymphoblastic leukemia. *The New England Journal of Medicine, 339*(9), 605–613.
- Sattler, J. M. (1992). Assessment of children (pp. 1034). San Diego, CA: Jerome M. Sattler, Publisher, Inc.
- Schatz, J., Kramer, J. H., Albin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: A developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14*, 189–200.
- Simonian, S. (2006). Screening and identification in pediatric primary care. *Behavioral Modification, 30*(1), 114–131.
- The Psychological Corporation (1992). *The Wechsler individual achievement test*. New York: Harcourt, Brace, Jovanovich.
- Wechsler, D. (1991). *Wechsler intelligence test for children, third edition*. New York, NY: The Psychological Corporation.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-III*. San Antonio, TX: The Psychological Corporation.