Executive Function, Coping, and Behavior in Survivors of Childhood Acute Lymphocytic Leukemia*

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Objective To examine the role of executive function in coping and behavioral outcomes in childhood acute lymphocytic leukemia (ALL) survivors. **Methods** We examined associations among several domains of executive function (working memory, behavioral inhibition, cognitive flexibility, and self-monitoring), coping, and emotional/behavioral problems in 30 children and adolescents ages 10- to 20-years old who completed treatment for ALL and 30 healthy controls matched on age and sex. **Results** We found partial support for our hypothesis that performance on executive function measures is associated with strategies used to cope with stress, and emotional and behavioral problems in ALL survivors. **Conclusions** Findings suggest that executive function impairment may be associated with difficulties in coping and emotion regulation in a subgroup of children treated for ALL. Directions for future research on executive function deficits and coping skills in survivors of pediatric ALL are suggested.

Key words behavior problem; cancer and oncology; coping; neuropsychology.

Acute lymphocytic leukemia (ALL) is the most common form of childhood cancer, accounting for nearly one-third of all diagnoses (American Cancer Society, 2006). An invariably fatal disease prior to 1960 (Mulhern, 1994), ALL now has a 5-year survival rate of over 70% owing to the introduction and ongoing modification of powerful treatment protocols, which not only destroy leukemic cells in the bone marrow, organs, and cerebrospinal fluid (CSF) but also prevent disease metastasis in the central nervous system (CNS). As a result of these advances in treatment, the majority of children diagnosed with ALL are living well into adulthood, and the issue of managing the long-term effects of treatment and preserving quality of life in children treated for ALL has become a major focus of research and clinical practice.

One particularly significant long-term consequence of ALL treatment that has been observed is impaired neurocognitive functioning (see Campbell et al., 2007; Peterson et al., 2008 for meta-analytic reviews). This appears to be true for some survivors of childhood ALL despite the elimination of cranial irradiation in favor of using combined intrathecal and systemic chemotherapy for CNS prophylaxis (Espy et al., 2001; Waber et al., 2000), though most demonstrate good long-term neurocognitive outcomes (Spiegler et al., 2006). For at least a subset of children treated for ALL, chemotherapy is associated with reduced cortical white matter volume, particularly in the right prefrontal cortex (Carey et al., 2008; Reddick et al., 2006). Such white matter differences have been associated with decreased performance in various domains of neurocognitive functioning, including higher order domains of executive function (EF) such as cognitive flexibility and working memory, when compared to children with no cancer history (Carey et al., 2008). Several other studies have also found treatment-related effects in EF in childhood ALL survivors (Anderson, Godber, Smibert, & Ekert, 1997; Campbell et al., 2007; Lesnik et al., 1998).

Neurocognitive sequelae of ALL treatment have clear implications for academic achievement and learning. However, they may also have significant consequences for emotional development and the capacity for coping and emotion regulation. Specifically, EF has been shown to underlie emotion regulation and the utilization of adaptive coping mechanisms in children and adolescents

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(Compas, 2006; Copeland & Compas, 2008). If this is indeed the case, then it is possible that impaired EF associated with ALL treatment could impact the skills needed to regulate emotions and cope with stressful situations. Although most studies report that childhood cancer survivors exhibit positive psychosocial adjustment that is comparable, if not superior, to that of healthy peers (Burgess & Haaga, 1998; Dejong & Fombonne, 2006; Noll et al., 1999; Phipps & Steele, 2002; Phipps, 2007), results from several large-scale studies from the Children's Cancer Group (CCG; Glover et al., 2003) and the Childhood Cancer Survivor Study (CCSS; Hudson et al., 2003; Schultz et al., 2007; Zebrack et al., 2002) examining psychosocial outcomes in adolescent and adult survivors of childhood cancer suggest that a subset, particularly those treated for leukemia, report significant elevations in depressed mood, anxiety, somatic symptoms, and social/interpersonal problems. In fact, in the CCG study (Glover et al., 2003), adolescent leukemia survivors with a history of receiving special education services (and therefore likely neurocognitive sequelae), were up to six times as likely to report significant mood disturbance. Taken together, these studies of long-term childhood ALL survivors suggest that some may be susceptible to psychosocial distress and behavioral problems.

For those who experience differences in EF associated with their treatment, coping with stressful life events may be more difficult, making emotional distress a possible outcome. Previous research has shown that children who are unable to cope effectively with stressful situations are at higher risk for developing emotional and behavioral difficulties (Compas et al., 2001; Skinner & Zimmer-Gembeck, 2007). The aim of the current study was to examine associations among EF, coping, and behavioral outcomes in children and adolescents who have completed chemotherapy treatment for ALL. Our first objective was to compare childhood ALL survivors to a sample of healthy controls on these variables to determine how their neurocognitive and psychosocial functioning compared to same-sex, same-age peers with no cancer history. Our second objective was to examine the relationships among the EF, coping, and behavioral variables within each group. While we expected to find similar relationships among the variables for both groups because we believe EF is associated with the normal development of adaptive coping in children and adolescents, we were also interested in examining between-group differences in these associations.

Our specific hypotheses were: (a) the ALL group will exhibit poorer performance on measures of EF; (b) the ALL group will demonstrate patterns of less adaptive coping strategies (described in more detail in the Methods section); (c) the ALL group will evidence higher levels of emotional/behavior problems; (d) the relationships among the EF, coping, and emotional/behavioral outcome variables will be significantly stronger for the ALL group due to increased heterogeneity in these variables associated with treatment (i.e., we expect the levels of each variable to be distributed more broadly in the ALL group because some of the survivors will be demonstrating treatment-related sequelae); and (e) coping strategies will mediate the relationship between EF and emotional/behavioral problems in the ALL group such that lower EF scores will be related to less adaptive coping, which in turn will be related to higher levels of reported emotional/behavioral problems.

Methods

Participants

Participants included 30 children and adolescents between 10 and 20 years of age who completed treatment for ALL and 30 healthy controls matched on age and sex. We also attempted to match ALL and healthy control participants on family income and parental education; however, once children and adolescents were matched on age and sex, our ability to match on socioeconomic status (SES) variables was very limited. In 76.7% of cases, we were able to match healthy control participants within one income or education category above or below ALL participants. This age range was selected because research suggests that late childhood and adolescence is an important period of continued myelination of the prefrontal cortex and development of EF, and therefore may represent an age range during which children are especially likely to exhibit neurocognitive sequelae related to the development of adaptive coping skills (Klinberg et al., 1999). Children within the specified age range were required to have completed treatment for a diagnosis of standard- or high-risk ALL, be in continuous first remission with no history of disease relapse, and have a working comprehension of the English language. Exclusionary criteria included: (a) history of CNS pathology requiring radiation or surgery; (b) bone marrow transplant, (c) history of other cancer diagnoses or major medical illnesses with known neurocognitive sequelae (e.g., meningitis); (d) known premorbid neurodevelopmental or learning disorders, including ADHD, or a history of very low-birth weight (<1500 g).

Healthy control participants were recruited through peer nomination by ALL participants (17%) and through the Medical Center Trials Office at our institution (83%). The latter method of recruitment was conducted through an e-mail advertisement sent to all medical center faculty and staff regarding participation in a study examining how

specific areas of thinking are related to coping with stress in children and adolescents. Inclusion criteria included working comprehension of the English language and being within our specified age range (10–20 years). Exclusionary criteria included: (a) history of cancer; (b) major medical illnesses; (c) known neurodevelopmental or learning disorders; (d) very low-birth weight (<1500 g).

A total of 63 children and adolescents treated for ALL with chemotherapy only and currently within the study age range were identified, 27 of whom did not have updated contact information and therefore could not be reached. As of the last clinic visits noted in their medical records, the children who could not be reached did not differ from our ALL sample in terms of diagnosis or treatment history or SES. One child relapsed prior to recruitment and was therefore ineligible to participate. Another child had a history of bacterial meningitis, which, like ALL, is associated with impaired EF (Schmidt et al., 2006) and was therefore also ineligible. Four additional children declined participation. Therefore, of the 34 eligible ALL survivors we were able to contact, 30 (88%) consented to participate and completed this study.

Demographic information for the ALL and healthy control groups are provided in Table I. There was no difference between the groups with regard to age at time of testing ($t = .12$, $p = \text{NS}$). Regarding parental education, 60% of the primary caregivers in the ALL group and 93.4% of those in the control group had some college education, a statistically significant difference ($t = -4.03$, $p < .01$). The groups did not differ on household income ($t = 1.15$, $p = \text{NS}$).

Table I. Demographics of ALL Survivors and Healthy Controls

Variables	ALL	Healthy control	χ^2/t (p)
Sex			
Female	15 (50%)	15 (50)	0.02 (0.90)
Male	15 (50%)	15 (50)	
Race/ethnicity, *n* (%)			
White/Caucasian	26 (86.7)	27 (90)	3.00 (.39)
Black/African American	3 (10)	1 (3.3)	
Latino	0	1 (3.3)	
Biracial	1 (3.3)	1 (3.3)	
Main caregiver, *n* (%)			
Biological mother	24 (80)	26 (86.6)	1.60 (.66)
Biological father	4 (13.3)	2 (6.7)	
Stepmother	1 (3.3)	2 (6.7)	
Grandmother	1 (3.3)	0	
Parent education, *n* (%)			
High school graduate	21 (70)	7 (23.4)	12.37 (.00)*
College degree	9 (30)	23 (76.6)	
Household income, *n* (%)			
<$50,000/year	9 (30)	11 (36.6)	1.06 (.59)
≥$50,000/year	21 (70)	19 (63.4)	
Age at assessment (years)			
Mean (*SD*)	14.49 (2.88)	14.31 (2.76)	0.32 (.75)
Range	10.11–20.78	10.27–19.64	
Age at ALL diagnosis (years)			
Mean (*SD*)	5.65 (3.07)	NA	
Range	1.00–14.30	NA	
Time since treatment (years)			
Mean (*SD*)	6.05 (3.35)	NA	
Range	.25–13.96	NA	

Chi-squares are reported for all variables with the exception of age at assessment, for which a *t*-test was performed.
*$p < .01$.

Measures

Executive Function

Four domains of EF, working memory, behavioral inhibition, cognitive flexibility, and self-monitoring were each measured behaviorally and by parent report. Behavioral EF measures included the Working Memory Index (WMI) of the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) or the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III), depending on the age of the participant, and the Color-Word Interference, Sorting, and Tower tests from the Delis–Kaplan Executive Function System (D-KEFS). Parent-reported EF was measured using the Working Memory, Inhibit, Shift, and Monitor subscales of the Behavior Rating Inventory of Executive Function parent questionnaire (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). The D-KEFS is a comprehensive battery of tests designed to examine the primary domains of EF in individuals 8–89 years of age. The BRIEF parent questionnaire is a measure of EF in home and school environments. The Wechsler scales (Wechsler, 2002, 2003), the D-KEFS (Delis, Kaplan, & Kramer, 2001), and the BRIEF (Gioia et al., 2000) all have well-established reliability and validity.

Coping

The self- and parent-report forms of the Social Stress version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000) were administered to assess coping responses related specifically to social stress (e.g., being teased or hassled by other kids; having problems with a friend). In order to compare the ALL and control groups on the RSQ, we chose to measure responses to stress associated with peer interactions and relationships because it is a domain that children with and without a cancer history commonly experience. Additionally, as mentioned earlier, childhood leukemia survivors may

demonstrate social/interpersonal problems associated with treatment (Schultz et al., 2007), making this a particularly relevant stressor to assess.

The RSQ measures both voluntary and involuntary responses to stress; however, the current study focused solely on the three voluntary coping domains: primary control coping (problem solving, emotional modulation, and emotional expression), secondary control coping (acceptance, cognitive restructuring, positive thinking, and distraction), and disengagement coping (avoidance, denial, and wishful thinking). Both primary and secondary control coping responses are associated with lower levels of emotional and behavioral problems in children and adolescents (Compas et al., 2006; Connor-Smith et al., 2000; Thomsen et al., 2002). Disengagement coping responses are characterized by attempts to orient oneself away from a stressor or one's emotional responses. These include avoidance, denial, and wishful thinking. In contrast with the engagement coping responses described above, which appear to be adaptive, disengagement coping responses have been associated with higher levels of emotional and behavioral problems (Connor-Smith et al., 2000). The RSQ coping and stress response items have demonstrated good reliability and validity and the factor structure has been confirmed with several samples of adolescents coping with diverse types of stress (Connor-Smith & Calvete, 2004; Connor-Smith et al., 2000; Wadsworth, Reickman, Benson, & Compas, 2004). In the current sample of child and adolescent ALL and healthy control participants, respectively, internal consistencies were: α (primary control) = .85/.82, α (secondary control) = .81/.79, α (disengagement coping) = .74/.75. Internal consistencies for ALL and healthy control parent reports, respectively were: α (primary control) = 84/.80, α (secondary control) = .72/.74, α (disengagement coping) = .78/.75.

Emotional and Behavioral Problems

The Child Behavior Checklist (CBCL) or The Adult Behavior Checklist (ABCL; Achenbach & Rescorla, 2001), depending on the participant's age, was administered to all parents or caregivers to assess their perceptions of their children's emotional and behavioral functioning over the past 6 months. Similarly, the Youth Self-Report (YSR) or the Adult Self-Report (ASR; Achenbach & Rescorla, 2001), depending on the participant's age, were administered to all children and adolescents participating in the study, in order to determine their perceptions of their own functioning. All of these measures have excellent reliability and validity. For the purpose of this study, only the Total Behavior Problems scale was examined and its internal consistencies were excellent for self- and parent-report versions in both ALL and healthy control groups (α range = .90–.93).

Procedure

This study was approved by the Vanderbilt University Institutional Review Board. Parents or caregivers of ALL survivors were sent a letter from a physician who was not involved in the child's clinical care inviting them to participate in the research study. The physician then placed a follow-up call to the family ~1 week after the letter was sent to ask permission for the research team to contact them with further information and determine their eligibility to participate. If families expressed interest and met eligibility criteria, an appointment was scheduled for the study evaluation.

Upon arriving for the session, informed consent and assent was obtained. At this time, the examiner also asked ALL participants if they would be willing to nominate same-age, same-sex peers who might also be interested in participating in the study as healthy controls. If so, a letter was sent to the parents/caregivers of nominated children and adolescents inviting them to participate. In addition, healthy control participants were also recruited through the Medical Center Clinical Trials Office. Interested individuals who responded to the letters and e-mail messages were administered a screening interview to determine if inclusion and exclusion criteria were met and matched an ALL participant already enrolled in the study in terms of age and sex. Following a brief demographic intake interview, parents were asked to complete questionnaires in a separate room, while the examiner then administered self-report questionnaires and behavioral measures of EF to the child or adolescent. Participants and parents were then debriefed, and each received an honorarium of $25.

Statistical Analysis

After examining descriptive data for each individual measure separately by group, composite scores were computed for each EF, coping, and behavioral domain. As mentioned earlier, each of the four EF domains (working memory, cognitive flexibility, behavioral inhibition, and self-monitoring) were measured through behavioral assessment and parent-report measures. Similarly, the three coping domains and total behavior problems were measured using self- and parent-report questionnaires. Composite scores were computed by converting all raw scores to *z*-scores and summing the two *z*-scores for each EF, coping, and behavior domain. Between-group analyses were then conducted using independent sample *t*-tests. Pearson product moment correlations were conducted to

examine associations among the independent and dependent variables for each group. In order to determine whether the strengths of correlations differed significantly between the groups, Fisher's *z*-tests were performed. Finally, in order to determine if coping mediates the relationship between EF and total behavior problems, we followed the methodology discussed by Baron and Kenney (1986). Specifically, statistically significant correlations were required among EF and coping, EF and behavior problems, and coping and behavior problems. When all three criteria were met, stepwise forward linear regression was performed by adding the EF domain in step 1 and the coping domain in step 2. Evidence for a fully mediated model occurred when EF was no longer a significant predictor when coping is added to the equation and significantly predicts total behavior problems. Evidence for a partially mediated model occurred when both EF and coping remain significant predictors of emotional problems in the second step. When either form of mediation was demonstrated through regression analyses, a Sobel test was performed in order to test the indirect effect of the independent variable on the dependent variable through the mediator using the following equation (Sobel, 1982). An α-level of .01 was considered statistically significant for more conservative interpretation of all data analyses.

Power analyses using G*Power (Buchner, Erdfelder, & Faul, 1997) indicated that the current sample of 30 participants in each group produced power to detect medium effects ($d \geq .5$) of 61% and 92% to detect large effects ($d \geq .8$) for *t*-tests. With regard to within-group correlations among the independent and dependent variables, each group of 30 participants produced power of 48% to detect correlations of.40 or greater at the $p < .01$ level of significance.

Results

Descriptive Statistics

Means scores and *SD*s for each EF, coping, and behavioral problem measure, as well as the results of *t*-tests based on the composite scores, are reported in Table II. All mean EF scores (WISC/WAIS WMI, BRIEF, and D-KEFS) for both groups fell within the average range compared to normative samples. Outliers, which were defined as scores falling to 2 or more *SD*s above or below the mean, were examined in both groups, and the analyses were run with and without these variables present. The ALL group had one participant with a WISC-IV WMI score 2 *SD*s above the mean (135) and two with WISC-IV WMI scores 2 *SD*s below the mean (62 and 65), and the Healthy Control groups had one participant with WISC-IV WMI scores 2 *SD*s above the mean (133). No other outliers were identified for our other independent or dependent variables. Because the between- and within-group analyses did not differ significantly when the outliers were removed, we retained these data to maximize statistical power and variability.

Demographic, medical, and cognitive variables were examined separately for each group to determine if they were significantly correlated with the independent or dependent variables, and should therefore be controlled for in the regression analyses. Sex and age at the time of the evaluation, as well as parent education level, were examined in both groups, and age at time of diagnosis and number of years since treatment were also examined in the ALL group. None of these variables were significantly correlated with EF, coping, or total behavior problems in either group and were therefore not included as covariates in the analyses.

Between-group Analyses

Comparisons between the ALL and healthy control groups were made using independent sample *t*-tests (Table II). With regard to the EF composite scores, the only significant between-group difference that emerged was working memory ($t = -2.61$, $p < .01$), with the ALL group scores falling significantly below those of the control group. The between-group effect size was $-.75$, indicating a medium effect according to Cohen (1988). Because we were interested in determining whether the between-group difference in parental education impacted this significant finding, we conducted a univariate analysis of variance (ANOVA) including parent education level as a covariate. The ALL working memory composite remained significantly lower than the healthy control group ($F = 3.49$, $p < .01$). As mentioned earlier, however, it should be noted that the scores that comprise the working memory composite were well within the average range for both groups. No significant between-group differences were detected for any of the other EF, coping, or behavior problem composites.

Correlations Among EF, Coping, and Behavioral Outcomes

ALL Group

All correlations among the EF, coping, and behavioral composite scores for the ALL group that reached statistical significance ($p < .01$) were in the expected directions (Table III). All four EF composite scores were positively associated with primary control coping. With the exception of the inhibit composite score, all of the other EF composites were also positively associated with secondary control coping. As expected, all EF composites were negatively

Table II. Mean Scaled Scores and Standard Deviations for Executive Function, Coping, and Behavioral Variables

Executive function domains	ALL group mean (*SD*)	Healthy control group mean (*SD*)	*t* (*p*)
WISC-IV/WAIS-III WMI	97.27 (16.32)	106.38 (13.01)	−2.61 (0.00)*
BRIEF working memory scale	51.75 (13.37)	46.81 (7.82)	
D-KEFS color-word interference test	10.57 (2.08)	10.40 (2.27)	−0.19 (0.43)
BRIEF inhibit scale	47.82 (13.00)	46.74 (6.30)	
D-KEFS sorting test	10.60 (3.04)	11.83 (2.07)	−1.15 (.13)
BRIEF shift scale	52.14 (18.32)	47.81 (8.29)	
D-KEFS tower test	10.34 (2.27)	10.57 (2.45)	−0.21 (0.42)
BRIEF monitor scale	51.18 (15.62)	48.30 (9.37)	
RSQ scales	Self/parent	Self/parent	
Primary control engagement	0.20 (0.04)/0.22 (0.05)	0.20 (0.04)/0.23 (0.04)	−0.27 (0.40)
Secondary control engagement	0.26 (0.05)/0.25 (0.05)	0.27 (0.04)/0.26 (0.05)	−0.94 (0.18)
Disengagement	0.14 (0.03)/0.15 (0.03)	0.15 (0.03)/0.15 (0.03)	−0.46 (0.33)
Behavioral problems	Self/parent	Self/parent	
Total problems	50.48 (9.94)/50.39 (12.62)	51.94 (8.23)/50.34 (9.36)	−.03 (.49)

WISC-IV standard scores ($M = 100$, $SD = 15$), D-KEFS scaled scores ($M = 10$, $SD = 3$), and *T*-Scores for the BRIEF and CBCL/YSR are reported. Mean proportion scores and *SD* are reported for the RSQ; higher scores on the BRIEF indicate poorer performance; *t*-tests and *p*-based on composite scores.
*$p \leq .01$.

Table III. Correlations Among Executive Function, Coping, and Total Behavioral Problem Composite Scores

	1	2	3	4	5	6	7	8
1. Working memory		.33	.05	.14	.16	.20	−.00	−.41
2. Behavioral inhibition	.61*		.43*	−.04	−.15	.12	.10	−.12
3. Cognitive flexibility	.63*	.41		−.04	−.16	−.03	.08	−.41
4. Self-monitoring	.73 *	.72*	.57*		.26	−.06	−.12	−.47*
5. Primary control coping	.52*	.43*	.49*	.46*		.09	−.74*	−.17
6. Secondary control coping	.52*	.30	.45*	.45*	.54*		−.35	−.26
7. Disengagement coping	−.63*	−.49*	−.37	−.50*	−.73*	−.70*		.12
8. Total behavior problems	−.56*	−.42*	−.55*	−.59*	−.52*	−.80*	.56*	

Healthy control correlations are on the top right.
*$p < .01$.

associated with disengagement coping and total behavior problems. With regard to the correlations between the coping and behavior variables, both primary and secondary control coping were negatively associated with total behavior problems, while disengagement coping was positively associated with total behavior problems.

Health Control Group

With the exception of negative correlations between the shift and monitor composites and total behavior problems, no other correlations between the independent and dependent variables met statistical significance at the .01 level.

Between-group Comparisons of Correlations

Correlations among the EF, coping, and behavioral outcome variables were expected to be significantly stronger for the ALL group due to greater heterogeneity in variance associated with their exposure to neurotoxic treatment. Fisher's *z*-tests were computed to compare the groups on each correlation coefficient. Out of 28 possible correlations, 26 correlations were significantly greater for the ALL group at the .01 level of significance [e.g., the correlations between working memory and secondary control coping for the ALL group ($r = .52$) and the healthy control group ($r = .20$) were significantly different ($z = 3.32$, $p < .01$)]. None of the healthy control correlations was significantly greater than the correlations for the ALL group. It is also notable that 89.29% of the ALL correlations were significant or approached significance, compared to only 3.57% of the healthy control correlations.

Regression Analyses Examining Coping as a Mediator Between EF and Behavioral Outcomes

Stepwise forward linear regression analyses were conducted to predict behavior problems from each EF composite and coping composite and to determine whether there

Table IV. Regression Equations Testing for Evidence of Mediation Among EF, Coping, and Total Behavior Problems in ALL Survivors

Predictors	β	R^2	R^2-change	*F*	*F*-change
1. Step 1: Working memory composite	−.56	.32		11.57*	
Step 2: Primary control coping	−.31	.39	.07	7.60	2.80
2. Step 1: Working memory composite	−.56	.32		11.57*	
Step 2: Secondary control coping	−.70	.67	.36	24.78*	26.30[a]
3. Step 1: Working memory composite	−.56	.32		11.57*	
Step 2: Disengagement coping	.34	.39	.07	7.54	2.72
4. Step 1: Behavioral Inhibition composite	−.42	.42		5.70*	
Step 2: Primary control coping	−.41	.56	.14	5.77	4.98
5. Step 1: Behavioral inhibition composite	−.42	.42		5.70*	
Step 2: Disengagement coping	.46	.34	.16	6.47	6.11
6. Step 1: Cognitive flexibility composite	−.55	.30		11.38*	
Step 2: Primary control coping	−.32	.38	.08	7.76	3.19
7. Step 1: Cognitive flexibility composite	−.55	.30		11.38*	
Step 2: Secondary control coping	−.70	.83	.38	26.81*	29.69[a]
8. Step 1: Self-monitoring composite	−.59	.35		13.49*	
Step 2: Primary control coping	−.30	.42	.07	8.79	3.00
9. Step 1: Self-monitoring composite	−.59	.35		13.49*	
Step 2: Secondary control coping	−.63	.66	.31	23.75*	22.44[a]
10. Step 1: Self-monitoring composite		−.59	.35	13.49*	
Step 2: Disengagement coping	.24	.40	.05	7.88	1.83

β = Standardized Beta.

*$p < .01$.

[a]Full mediation.

is evidence to suggest that coping mediates the relationship between EF and behavior problems. Criteria for testing mediation (Baron & Kenney, 1986) were required to be met before regression analyses were conducted. A total of 10 sets of correlations in the ALL group met these criteria (Table IV) and were therefore eligible to be examined in regression analyses. Specifically, all three coping composites as mediators of the EF domains working memory and self-monitoring and total behavior problems, adding up to six regression equations. In addition, the criteria were met for testing primary control and disengagement coping as mediators of the relationship between behavioral inhibition and total behavior problems, and for testing primary and secondary control coping as mediators of the relationship between cognitive flexibility and total behavior problems, adding up to another four regression equations. No sets of correlations met eligibility requirements for testing mediation for the healthy control group and therefore no regression analyses were conducted for this group.

The regression analyses provided evidence that secondary control coping mediates the relationship between EF and total behavior problems for Working Memory, Cognitive Flexibility, and Self-Monitoring (Fig. 1). Sobel tests (Sobel, 1982), which were conducted to determine if these indirect effects were significant, confirmed that secondary control coping fully mediates the relationship between working memory ($z = 3.02$, $p < .01$), cognitive flexibility ($z = 2.46$, $p < .01$), and self-monitoring ($z = 2.39$, $p < .01$).

Discussion

This study examined associations among several domains of EF, coping with stress, and emotional/behavioral problems in childhood ALL survivors and a matched healthy control sample. First, based on previous literature that provides evidence of treatment-related differences in EF (Anderson et al., 1997; Campbell et al., 2007; Carey et al., 2008; Lesnik et al., 1998) and differences in emotional/behavioral outcomes (Glover et al., 2003; Schultz et al., 2007; Zebrack et al., 2002) in at least some adolescents and young adults treated for ALL, we hypothesized that our sample of ALL survivors would exhibit poorer EF, less adaptive patterns of coping, and possibly greater emotional/behavioral problems than a healthy control sample. The data partially support these hypotheses in that ALL survivors had significantly lower composite working memory scores when compared to the control group. Of note, these scores, as well as those for the other EF domains, fell within the average range for both groups suggesting that despite the one between-group difference

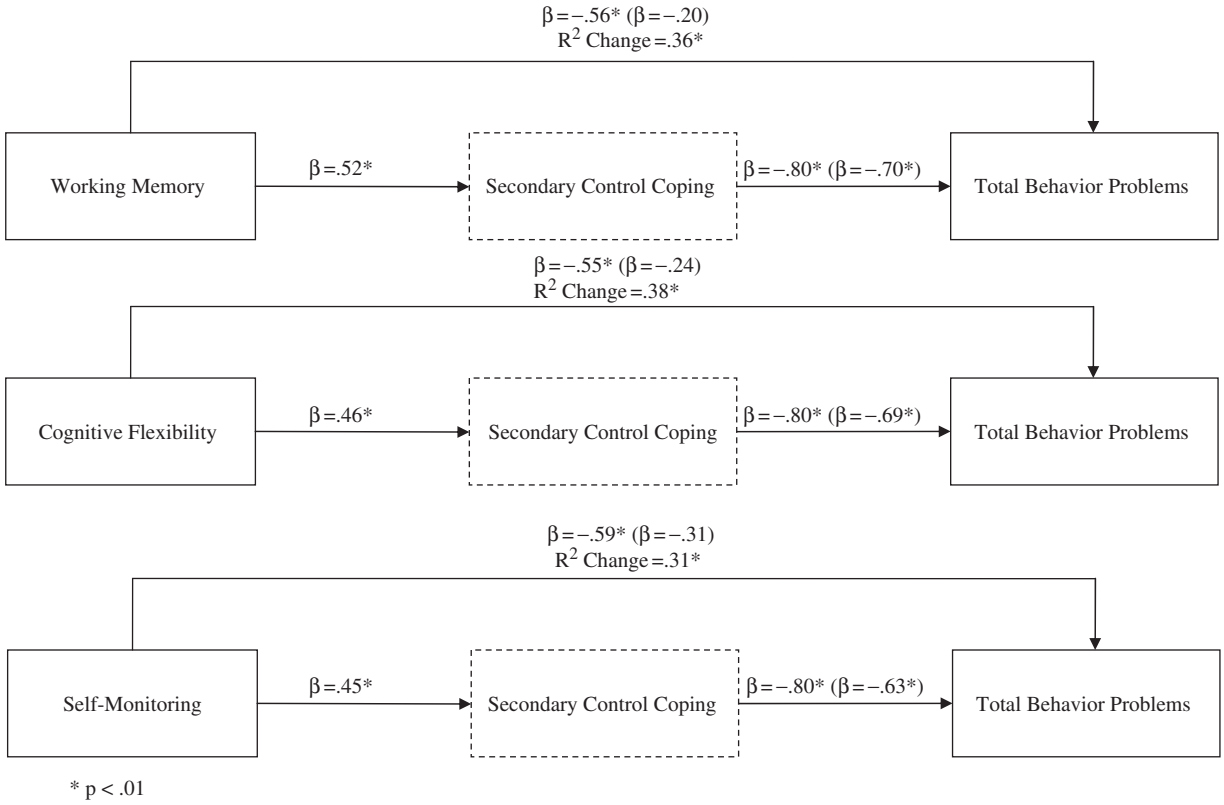

Figure 1. Secondary control coping fully mediated the relationship between three of the four EF domains (working memory, cognitive flexibility, and self-monitoring) and total behavior problems in the ALL group.

in working memory, childhood ALL survivors generally demonstrate intact EF abilities.

Likewise, contrary to our hypotheses, no statistically significant between-group differences were found for any of the coping and emotional/behavioral outcome variables. This may not seem surprising considering that numerous studies in the literature have reported findings indicating that children with cancer do not exhibit clinically significant symptoms of distress, and in fact, report even lower levels of depression and anxiety than control samples (Burgess & Haaga, 1998; Phipps & Steele, 2002). Although most childhood cancer survivors are indeed well-adjusted during and after treatment, the results from CCG and CCSS studies suggest that some adolescent and adult survivors of childhood leukemia report elevated levels of emotional distress, such as symptoms of depression and anxiety, as well as social/interpersonal issues (Glover et al., 2003; Hudson et al., 2003; Schultz et al., 2007; Zebrack et al., 2002). Psychosocial sequelae appear to be a late effect of treatment for some ALL survivors.

We also hypothesized that the correlations among EF, coping, and emotional/behavioral outcomes would be significantly stronger for the ALL group compared to the healthy control group because we predicted that the variability in each domain would be greater for ALL survivors, and therefore make finding significant correlations among the variables more likely. The data did support this hypothesis, as the majority of correlations were stronger for the ALL group compared to the control group and there were many more statistically significant correlations in the ALL group. It is also possible, however, that the range was relatively restricted in our healthy control sample, decreasing our likelihood of finding significant associations among the variables.

Finally, we hypothesized that coping would mediate the relationship between EF and emotional/behavioral outcomes. Regression analyses could not be performed in the healthy control sample because the data did not satisfy Baron and Kenney's (1986) criteria for testing mediation. With regard to the ALL group, the data partially supported our hypothesis such that secondary control coping fully mediated the relationship between three domains of EF (working memory, cognitive flexibility, and self-monitoring) and emotional/behavioral outcomes. That is, the higher order abilities to retain and manipulate information simultaneously, think flexibly and shift cognitive set, and observe one's own mental processes appear to be related to the use of adaptive coping strategies, such as acceptance

and cognitive restructuring, in response to social stress, which in turn is related to one's level of emotional/behavioral outcomes. Lower EF abilities could make it difficult for children and adolescents to adapt well in the face of social stress, such as an argument with a friend or being rejected by peers, and be associated with increased emotional distress. In contrast, a child or adolescent with good EF may be better able to adapt to the stress (e.g., think that things will soon get better) and feel less distressed. In our sample of ALL survivors, it appears that even though many report good adjustment and have intact EF, those who did have lower scores on EF did in fact also exhibit less use of secondary control coping and greater total behavioral problems. Because our study was cross-sectional, we are not able to infer a causal relationship among these variables, but it does appear that EF, coping, and emotional/behavioral outcomes are associated in our sample of ALL survivors.

The current study addresses some of the methodological problems of previous studies by employing well-normed measures of EF, collecting data using multiple methods and informants, and selecting a control sample matched on age and sex. However, this study also had limitations that must be considered when interpreting the data. First, the sample size of 30 participants in each group limited power to detect small but potentially meaningful effects between groups and in the correlations among the variables within each group. It should be noted, however, that this study's sample of childhood ALL survivors is on par with or larger than over 50% of the published papers included in a meta-analysis reviewing the neurocognitive effects of childhood ALL treatment (Campbell et al., 2007). In addition, no behavioral measures were included for coping and emotional/behavioral problems and instead child and parent self-report data were collected for each variable. However, we believe we overcame the issue of potential method effects by creating composite variables. Finally, as mentioned earlier, this study was cross-sectional and therefore no causal inferences can be made regarding the associations among the variables.

Overall, the results from this study suggest important associations among EF, coping with stress, and emotional/behavioral outcomes in children and adolescents who received ALL treatment, which may accentuate individual differences and increase variability in samples of survivors. A great many ALL survivors will experience positive long-term neurocognitive and psychosocial outcomes, while some may demonstrate differences in specific domains, such as EF, which may be associated with their ability to adaptively cope with stress and increased emotional distress. This study paves the way for continued research on the psychosocial correlates of neurocognitive impairment in children treated for ALL. Future research should focus on the neurophysiological underpinnings of the associations among EF, coping, and emotion regulation.

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