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Executive Function Late Effects in Survivors of Pediatric Brain Tumors and Acute Lymphoblastic Leukemia

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Abstract

BACKGROUND—Survivors of pediatric brain tumors (BT) and acute lymphoblastic leukemia (ALL) are at risk for neurocognitive late effects related to executive function.

PROCEDURE—Survivors of BT (48) and ALL (50) completed neurocognitive assessment. Executive function was compared to estimated IQ and population norms by diagnostic group.

RESULTS—Both BT and ALL demonstrated relative executive function weaknesses. As a group, BT survivors demonstrated weaker executive functioning than expected for age. Those BT survivors with deficits exhibited a profile suggestive of global executive dysfunction, while affected ALL survivors tended to demonstrate specific rapid naming deficits.

CONCLUSION—Findings suggest that pediatric BT and ALL survivors may exhibit different profiles of executive function late effects, which may necessitate distinct intervention plans.

Keywords

pediatric; leukemia; brain tumor; executive function; late effects

Over the last 40 years, the 5-year survival rate for children with cancer has increased from 58% to 83% (American Cancer Society, 2013). The two most common cancers in children are acute lymphoblastic leukemia (ALL) and brain tumors (BT), with current 5-year survival rates of 84% and 75%, respectively (American Cancer Society, 2013). Despite the excellent trend toward increased survivorship, the same treatments that improve survival can damage the developing central nervous system. Late effects are negative and lasting changes to healthy developing tissue caused by disease and treatment (American Cancer Society, 2013).

BT and ALL survivors appear to be particularly susceptible to neurocognitive late effects due to their exposure to aggressive cancer treatments. Risk factors for more severe neurocognitive late effects include cranial radiation therapy (CRT), high dose and intrathecal chemotherapy, younger age at diagnosis, and female gender (Campbell et al., 2007; Peterson et al., 2008; Ris & Noll, 1994; Robinson et al., 2010). Injury to healthy brain tissue due to tumor location and size, tumor resection, and shunt placement is also associated with worse neurocognitive outcomes in brain tumor patients (Doxey, Bruce, Sklar, Swift, & Shapiro, 1999; Grill et al., 2004).

Neurocognitive late effects in survivors of BT and ALL have been well documented. These include global intellectual decline (i.e., IQ) as well as declines in specific neurocognitive domains, including attention, executive function, processing speed, working memory, memory, visual-spatial, visual-motor, and fine motor skills (Armstrong, 2006; Armstrong & Briery, 2004; Ashford et al., 2010; Buizer, de Sonnevile, & Veerman, 2009; Conklin et al., 2013; Conklin, Ashford et al., 2012; Kahalley et al., 2013; Langer et al., 2002). Structural alteration of white matter tracts (e.g., damage to existing tracts, disruption of developing tracts) in the developing brain is considered a primary cause of cognitive late effects (Mulhern et al., 2004; Schatz, Kramer, Ablin, & Matthay, 2000). Research has linked white matter disruptions with specific neurocognitive deficits, including IQ, working memory, and processing speed, in survivors of pediatric cancer (Aukema et al., 2009; Reddick et al., 2003).

Executive functions are an interrelated group of cognitive skills responsible for the implementation of purposeful, goal directed behavior. Executive functions include both higher- and lower-level skills that work in tandem. Higher-level skills include inhibition, cognitive flexibility, working memory, planning, and problem solving (Denckla, 1996; Gioia, Isquith, & Guy, 2001; Welsh, Pennington, & Groisser, 1991). Executive functions also include lower-level skills such as processing speed and cognitive efficiency/fluency, which are core executive functions subserving those higher-level skills (Baron, 2004). Executive functions are essential for completion of daily academic, adaptive, and social functions. Neurologically, the frontal lobes and their connections throughout the brain, including white matter tracts/integrity, are of integral importance to executive function. Not surprisingly, survivors of pediatric cancer have been found to be at risk for impaired executive functions, including both higher- and lower-level skills (Campbell et al., 2009; Conklin, Krull et al., 2012; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Mabbott et al., 2011; Schatz et al., 2000).

The role of executive function and processing speed deficits in measured IQ deficits and decline has been examined in pediatric cancer survivors. A study by Reddick et al. (2003) examined neurocognitive late effects and white matter volumes in a sample of BT survivors treated with CRT. A significant association between white matter volume and IQ was explained by attentional, but not memory, deficits in that sample. The authors concluded that impaired attentional abilities in BT survivors treated with CRT were responsible for post-treatment IQ and academic impairments. Similarly processing speed was found to contribute uniquely to IQ in a group of posterior fossa tumor survivors, even after treatment had been statistically controlled (Mabbott, Penkman, Witol, Strother, & Bouffet, 2008). The authors

concluded that IQ declines following CRT may be related to processing speed deficits. These studies could indicate that survivors' general reasoning abilities are more resilient to treatment, while specific executive deficits may represent the heart of neurocognitive changes identified in this population.

While executive function deficits are fairly well documented in pediatric oncology samples, less research has examined the inter-relationship among executive function skills in the pediatric cancer population. Of note, Schatz et al. (2000) demonstrated that working memory (a higher-level executive function), but not processing speed (a lower-level executive function), emerged as an influential predictor of IQ in a group of ALL survivors treated with CRT. Processing speed, however, was found to moderate the relationship between working memory and CRT. This paper highlighted the complexity of the relationship between CRT and processing speed, working memory, and IQ. Importantly, it highlights that executive function is not a single ability, but rather a set of inter-related skills.

Given the vulnerabilities for cognitive late effects in survivors of BT and ALL, we aimed to examine both higher-level (inhibition and cognitive flexibility) and lower-level (processing speed) executive functions in both diagnostic groups. Specifically, we compared executive function performance to normative means and to measured estimated IQ (EIQ) scores. We expected that both ALL and BT would demonstrate executive function performance that was lower than EIQ and normative means, with particular vulnerability anticipated in BT performance due to the cognitive risks associated with BTs and their treatment. We also examined clinical characteristics associated with the distribution of scores in both groups. Additionally, we examined the interrelationships between upper- and lower-level executive functions.

Method

Participants

The data examined in the present study are part of a larger study examining cognitive functioning and health behaviors in survivors of pediatric cancer. Detailed sample descriptions have been reported elsewhere (Kahalley et al., 2010; Kahalley et al., 2011; Kahalley et al., 2012). Eligibility criteria for this study included: (a) diagnosis of ALL or BT; (b) completed treatment at least 1 year prior to study enrollment; (c) no evidence of active disease; (d) between the ages of 12 and 17 years (inclusive); (e) English speaking; and (f) accompanied by a parent or legal guardian. Patients with documentation of intellectual impairment (e.g. IQ <70) in the medical record were excluded to ensure that all participants could complete relevant study measures. Participant groups were stratified based on diagnosis (ALL, BT), gender, and age (12-14, 15-17).

One hundred survivors (50 ALL, 50 BT) participated in this study. Two BT participants were excluded from the current analyses due to significant visual impairments that precluded their completion of particular measures examined in the present study. Demographic and clinical characteristics for participants are reported in Table 1.

Procedure

Data were collected at a large pediatric cancer hospital following approval from the Institutional Review Board and informed consent/assent. Eligible survivors, identified by medical record review in order of consecutive clinic visits, were contacted about the study. Research appointments were scheduled in coordination with routine medical visits. Of the 114 eligible survivors approached, most (87.7%) agreed to participate, and no demographic or clinical differences were identified between survivors who participated and declined. Participants completed a comprehensive neurocognitive evaluation. Scores from a selection of measures from that battery are examined here.

Measures

Delis-Kaplan Executive Function System (DKEFS) – Color-Word Interference (CWI) Subtest

The DKEFS is a battery of executive function tests (Delis, Kaplan, & Kramer, 2001). The DKEFS CWI subtest was used in this study to provide measures of processing speed and executive function. Very good test-retest reliability ($r = .90$) has been reported for individuals ages 9 – 19. The first two trials of this subtest (*Color Naming* and *Word Reading*) provide measures of processing speed, which are lower-level skills that subserve higher-level executive function. The *Color Naming* trial requires the examinee to name swatches of colors quickly and accurately. The *Word Reading* trial requires the examinee to read color words (e.g. “blue,” “red”) printed in black ink quickly and accurately. The DKEFS also provides a normed *processing speed Composite* score (also called *Combined Naming + Reading*), which is calculated from the combined performance on both the *Color Naming* and *Word Reading* trials. The second two trials (*Inhibition* and *Inhibition/Switching*) provide measures of higher-level executive function. The *Inhibition* trial requires the examinee to look at a series of color words printed in a different color of ink and name the ink color (thus inhibiting the prepotent tendency to read the word). The *Inhibition/Switching* trial measures cognitive flexibility, requiring the examinee to switch between reading the word and naming the color of ink, depending on a rule. An age-normed scaled score is derived for each trial ($M=10$, $SD=3$). In current analyses, significant positive correlations were found across all four CWI trials in this sample for both diagnostic groups (BT: $r = .65 - .73$, all $p < .05$; ALL $r = .57 - .71$, all $p < .05$).

Wechsler Abbreviated Scale of Intelligence (WASI) Two-Subtest Estimated IQ (EIQ)

The WASI is a brief standardized, normed assessment of intellectual ability (Wechsler, 1999a). Our measure of general reasoning ability in this study was based on the WASI IQ score, estimated from two WASI subtests, Vocabulary and Matrix Reasoning. In standardization samples, this score is highly correlated with the more comprehensive Full Scale IQ scores derived from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), $r = .82$, and the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), $r = .87$ (Wechsler, 1999b; Wechsler, 2003). EIQ scores derived from age norms were converted to standard scores ($M=100$, $SD=15$). Of note, the Vocabulary and Matrix Reasoning subtests used to calculate the EIQ score do not impose time limits or speed demands. As such, this measure of general reasoning ability should be minimally influenced by a child’s reasoning speed.

Statistical Analyses

As previously reported, statistically significant clinical differences between BT and ALL groups were identified in this sample (Kahalley et al., 2013). Specifically, more BT survivors received CRT than ALL survivors, ALL survivors received chemotherapy more often than BT survivors, and ALL survivors were younger at diagnosis and had been off treatment longer at study enrollment compared to BT survivors. Due to these differences, BT and ALL were analyzed separately in the present study. No statistically significant differences were found between diagnostic groups on sex, race/ethnicity, or age at study participation. Descriptive information by diagnosis group is provided in Table 1.

Clinically significant scores were identified on EIQ and CWI scales. Clinically significant impairment was defined as 1.5 standard deviations below the normative mean. In a normal distribution, 1.5 standard deviations below the mean is equal to a standard score of 77.5, a scaled score of 5.5, and a percentile ranking of 7. Individuals with global deficits were defined as those with clinically low performance on at least 3 out of 4 CWI trials.

Paired samples t-tests compared processing speed and executive function scores to EIQ scores. The distribution of EIQ in this sample is described in detail in Kahalley et al., 2013. One-sample t-tests compared processing speed and executive function scores to the test population mean. Paired samples t-tests compared processing speed and executive function scales. Bivariate (t-test, Pearson correlation) and multivariate (multiple regression) analyses examined demographic and clinical characteristics associated with processing speed, executive function, and EIQ for both BT and ALL groups.

Because our analyses involved multiple comparisons, we used the false discovery rate (FDR) approach (Benjamini & Hochberg, 1995) to adjust our results for the proportion of false positives expected among significant associations ($p < .05$) using an FDR threshold of 10%. Associations with p values $< .05$ but FDR values > 0.1 are reported as trends. Effect size estimates are reported for all statistically significant comparisons. We used the following conventions to guide our interpretation of small, medium, and large effect sizes, respectively: Pearson's r (.1, .3, .5) and Cohen's d (0.2, 0.5, 0.8; Cohen, 1992). After applying the FDR threshold procedure, no test scores were significantly associated ($p < .05$ and $FDR < 0.1$) with multiple demographic and clinical characteristics. Thus, only bivariate comparisons are reported.

Results

Table 2 shows the means, standard deviations, and ranges for processing speed, executive function, and EIQ scores by diagnosis group.

Processing Speed and Executive Function Scores in BT Survivors

Deficient performance on processing speed and executive function trials (scaled scores < 5.5) was relatively frequent in the BT group. One third (33.3%) of BT survivors exhibited deficient performance on one or more DKEFS CWI trials. Clinically significant processing speed deficits were identified in 16.67% of BT survivors on *Color Naming* and 18.75% on *Word Reading* trials. Similarly, clinically significant executive function deficits on

Inhibition and *Inhibition/Switching* were identified in 16.67% and 18.75% of BT survivors, respectively.

We examined those BT survivors who obtained one or more DKEFS CWI scores that fell in the clinically significant range ($n = 16$). Most (62.5%) exhibited deficient performance on multiple processing speed and/or executive function trials. Within this group, nearly one third (31.25%) exhibited global deficits, with clinically low performance on three or more trials. Of those with deficient processing speed scores ($n = 10$), most (70%) were deficient on both processing speed trials. Similarly, of those with deficient executive function scores ($n = 11$), many (54.6%) were deficient on both executive function trials.

Performance on each DKEFS CWI trial was compared to the test population mean of 10. BT survivors obtained scores on both trials that were significantly lower than the normative mean (*Color Naming*: $t(47) = -2.33$, $p < .05$, $d = -0.34$; *Word Reading*: $t(47) = -2.66$, $p < .05$, $d = -0.38$). On the executive function trials, BT survivors' *Inhibition/Switching* scores were significantly lower than the normative mean, $t(47) = -3.84$, $p < .01$, $d = -0.55$, while a trend was identified between survivors' *Inhibition* scores and the normative mean, $t(47) = -2.02$, $p = .049$, $d = -0.29$, $FDR > 0.1$.

When BT survivors' DKEFS CWI scores were compared to EIQ scores, significant relative weaknesses were identified. In paired samples t-tests, BT survivors' processing speed scores were significantly lower than their EIQ scores on both the *Color Naming*, $t(47) = 2.58$, $p < .05$, $d = 0.75$, and *Word Reading*, $t(47) = 3.35$, $p < .01$, $d = 0.98$, trials. Executive function scores on both trials were also significantly lower than their EIQ scores (*Inhibition*: $t(47) = 2.28$, $p < .05$, $d = 0.67$; *Inhibition/Switching*: $t(47) = 3.99$, $p < .01$, $d = 1.16$).

Similar to the DKEFS CWI contrast scores used clinically to examine discrepancies across combinations of trials for an individual examinee, we used paired samples t-tests to examine score discrepancies across processing speed and executive function trials. In the BT group, scores on the *Inhibition/Switching* trial were significantly lower compared to *Processing Speed Composite* scores, $t(47) = 2.63$, $p < .05$, $d = 0.77$. Scores on the *Inhibition/Switching* trial were also significantly lower than scores on the *Inhibition* trial, $t(47) = 2.50$, $p < .05$, $d = 0.73$. No other significant differences were identified in comparisons across all other processing speed and executive function trials for the BT group.

In bivariate analyses within the BT group, no significant associations were found between processing speed or executive function scores and demographic or clinical variables, including gender, age, age at diagnosis, years since diagnosis, years since treatment, history of CRT, craniospinal irradiation (CSI), chemotherapy, neurosurgery, and shunt. Having a score in the clinically significant range on DKEFS CWI trials was significantly associated with lower EIQ in the BT group, $t(46) = 4.30$, $p < .01$, $d = 1.35$, but not with any other demographic or clinical variables.

Processing Speed and Executive Function Scores in ALL Survivors

More than one quarter of ALL survivors (28%) in this sample exhibited deficient performance on one or more DKEFS CWI trials. Some variability was observed in the

proportion of ALL survivors that obtained clinically low scores across trials (in contrast to the relatively even proportions observed in the BT group across trials). Specifically, on processing speed trials, 18% of ALL survivors obtained clinically low scores on the *Color Naming* trial, and 12% were clinically low on the *Word Reading* trial. On executive function trials, only 6% of survivors obtained clinically low scores on the *Inhibition* trial while 14% were clinically low on the *Inhibition/Switching* trial.

We examined those ALL survivors with one or more clinically low DKFES CWI scores ($n = 14$). While most (57.1%) exhibited deficient performance on multiple processing speed and/or executive function trials, only 21.4% exhibited global deficits across most or all trials. Of those with deficient processing speed scores ($n = 12$), half (50%) were deficient on the *Color Naming* trial only, while only 21.4% were deficient on both processing speed trials. Of those with deficient executive function scores ($n = 9$), two-thirds (66.67%) were deficient on the *Inhibition/Switching* trial only, while only one survivor (7.1%) was deficient on both executive function trials.

In the ALL group, scores on the *Color Naming* trial were lower than the test population mean of 10, $t(49) = -2.57$, $p < .05$, $d = -0.36$. Scores did not differ from the test population mean across all other DKEFS CWI trials (including *Word Reading*, *Inhibition*, and *Inhibition/Switching*).

Paired samples t-tests compared DKEFS CWI scores to EIQ scores in the ALL group. Scores on both processing speed trials were significantly lower than EIQ scores in this subsample (*Color Naming*: $t(49) = 3.35$, $p < .01$, $d = 0.96$; *Word Reading*: $t(49) = 2.68$, $p < .05$, $d = 0.77$). Similarly, on executive function trials, both *Inhibition* scores, $t(49) = 2.37$, $p < .05$, $d = 0.68$, and *Inhibition/Switching* scores, $t(49) = 2.15$, $p < .05$, $d = 0.61$, were significantly lower than EIQ scores.

Paired samples t-tests were used to compare scores across all processing speed and executive function trials in the ALL group. No significant differences were identified.

Having a history of CRT was significantly associated with lower *Word Reading* scores $t(48) = -3.48$, $p < .01$, $d = 1.45$ (CRT $M = 5.57$; No CRT $M = 9.74$). No other statistically significant associations were found between processing speed or executive function scores and any other demographic or clinical variables, including gender, age, age at diagnosis, years since diagnosis, and years since treatment. Still, several statistical trends were identified (all FDR > 0.1). Lower *Color Naming* scores were associated with longer time since diagnosis ($r = -.35$, $p = .014$), younger age at diagnosis ($r = .29$, $p = .043$), and longer time since treatment ($r = -.31$, $p = .029$). Lower *Inhibition* scores were associated with male gender, $t(48) = -2.10$, $p = .041$, $d = 0.61$ (Female: $M = 10.12$, Male: $M = 8.52$), time since diagnosis ($r = -.29$, $p = .041$) and younger age at diagnosis ($r = -.28$, $p = .049$), all FDR > 0.1 . Lower *Inhibition/Switching* scores were associated with history of CRT, $t(48) = -2.65$, $p = .011$, $d = 1.10$ (CRT: $M = 8.00$, No CRT: $M = 9.53$), longer time since diagnosis ($r = -.29$, $p = .045$), and longer time since treatment ($r = -.32$, $p = .025$), all FDR > 0.1 . Additionally, having a score in the clinically significant range on DKEFS CWI trials was significantly associated with lower EIQ in the ALL group, $t(48) = 3.14$, $p < .01$, $d = 1.01$.

Discussion

Survivors of both BT and ALL in this sample demonstrated vulnerabilities in executive functioning. Both BT and ALL survivors demonstrated weaker than expected executive function performance, on both higher- and lower-level executive function tasks, for general reasoning ability. However, it should be noted that, while means were generally within normal age expectations, subsets of individuals with specific executive weaknesses were identified for both the BT and ALL groups. Discrepancies identified between EIQ and processing speed in this study are consistent with a previous report from this sample that found similar discrepancies when processing speed was measured with the Wechsler Processing Speed Index (PSI), a measure that includes notable graphomotor and visual-motor demands (Kahalley et al., 2013). Taken together, these similar findings suggest processing speed is broadly affected in this sample, impacting survivors' ability to efficiently and accurately process information in a range of contexts and independent of the motor deficits associated with some diagnoses and treatments. While both BT and ALL survivors demonstrated relative weaknesses in higher-order executive function as compared to EIQ, the BT group exhibited weaker performance across most lower- and higher-order executive function tasks compared to population norms, suggestive of global executive function difficulties in this group. In contrast, the ALL group seemed to have a particular vulnerability in lower-level executive function skills (i.e., rapid naming). Although statistically significant differences did not emerge between BT and ALL groups on measures of processing speed and executive function in this sample, the differing patterns of score discrepancies between these two groups are compelling. If supported by further investigation, these differences may have implications for late effects intervention planning.

As a group, BT survivors exhibited processing speed and executive function performance that was significantly weaker than expected as compared to both group EIQ and test norms. While BT group means were at the low end of the Average range across CWI subtests, it should be noted that one-third of BT survivors obtained at least one clinically significant CWI score. Cognitive flexibility was particularly impacted in the BT group as evidenced by inter-trial statistical comparisons. On tasks of greatest complexity, BT survivors appear to have greatest difficulty engaging executive function skills to perform quickly and accurately.

In addition to relative weaknesses in processing speed and executive function, evidence for a pattern of global deficits emerged in a subset of BT survivors. Most survivors with clinically low processing speed scores performed poorly on both processing speed trials, and many with clinically low executive function scores performed poorly on both executive function trials. Taken together, these findings suggest the presence of consistent, global processing speed and executive function deficits in a vulnerable subset of BT survivors. Additionally, the processing speed and executive function deficits in this sample were significantly associated with EIQ. Therefore, it stands to reason that those with impaired EIQ also show similar deficits in processing speed and executive function skills. In the current BT sample, no other demographic or clinical variables other than EIQ were found to be associated with executive function and processing speed. These findings might suggest that BT survivors are

at risk for global cognitive impairment post-treatment, further suggesting the presence of executive function difficulties may be less likely to represent an isolated deficit.

While ALL survivors, like BT survivors, demonstrated processing speed and executive function performance that was lower than expected for group EIQ, performance across most processing speed and executive function trials was within normal limits relative to test norms. For the ALL group, the most common deficit was on the lowest-order task of rapid naming (CWI *Color Naming*). Of the four CWI trials, *Color Naming* was the only scale that was lower than expected for both EIQ and age. Additionally, it emerged as the most frequently identified clinically significant deficit in the ALL group (in 64.29% of those with one or more clinically significant score). This vulnerability for rapid naming is noteworthy. In another ALL sample, Conklin et al. (2007) also identified an isolated impairment in ink color naming on the Stroop Word-Color Association Test. In the present study, *Inhibition/Switching*, the most complex task of the CWI trials, was the next most frequently identified clinically significant deficit for ALL survivors, identified in 50% of individuals with one or more clinically significant score. In addition to particular vulnerability related to rapid naming, ALL survivors with clinically low performance on any of the CWI measures demonstrated much more intra-individual score variability; the proportion of deficits across CWI trials in this affected group of ALL survivors was more variable than observed in the affected BT group. Further, few ALL survivors with identified deficits on CWI tasks demonstrated both processing speed and executive function deficits. Taken together, the emergence of rapid naming deficits, along with intra-individual score variability, may be consistent with primary difficulties related to attention in a subset of ALL survivors. Rapid naming has been found to be a vulnerable neurocognitive skill that is specifically impaired in children with Attention Deficit/Hyperactivity Disorder (ADHD) (Arnett et al., 2012; Rucklidge & Tannock 2002; Yanez-Tellez et al., 2012). Color naming and object naming have been specifically identified as impaired in children with ADHD, whereas rapid naming of letter and numbers remain unaffected in these children (Tannock, Martinussen, & Frijters, 2000). With regard to intra-individual variability, children with attentional disorders frequently present with inconsistent intra-individual performance and a “moment to moment variability” (Castellanos & Tannock, 2002). Further, attentional deficits have been well documented in children treated for ALL (Brouwers, Riccardi, Poplack, & Fedio, 1984; Buizer, de Sonnevile, van den Heuvel-Eibrink, & Veerman, 2005; Buizer et al., 2009; Conklin et al., 2012; Jain, Brouwers, Okcu, Cirino, & Krull, 2009; Krull et al., 2008; Langer et al., 2002; Lofstad, Reinfjell, Hestad, & Diseth, 2009; Reddick et al., 2006).

Unlike in the BT group, trends indicating demographic and clinical risk factors of weaker executive function performance were identified in the ALL group. Of note, male gender was associated with weaker executive function in the current study. This is notable as female gender has been found to be a risk factor for the presence of neurocognitive late effects in other research (Buizer et al., 2005; Buizer et al., 2009; Ellenberg et al., 2009). However, some studies have found males to be more vulnerable to neurocognitive late effects (Conklin, Li, Xiong, Ogg, & Merchant, 2008; Jain et al., 2009). Since gender’s relationship to neurocognitive late effects is not consistently investigated, future research should aim to clarify gender’s role as a potential risk factor for late effects. Consistent with previous

research showing cognitive vulnerability in younger children (Buizer et al., 2005; Buizer et al., 2009; Ellenberg et al., 2009), trends emerged indicating that younger age at diagnosis was associated with weaker processing speed and executive functioning in ALL survivors. Lastly, trends indicated that longer time since diagnosis and completion of treatment are risk factors for weaker processing speed and executive function performance, also consistent with previously reported findings (Moore, Kramer, Wara, Halberg, & Ablin, 1991). Notably, gender, age, and timing were associated with outcomes for only the ALL group, while the diagnosis of a BT itself appeared to be the greatest risk factor for neurocognitive late effects in the BT group. Additionally, having an EF score in the clinically significant range was associated with IQ; those participants with higher IQ appear to suffer less impairment related to processing speed and executive functioning, indicating generally better global functioning.

This study, like many other studies with similar populations, utilized multiple statistical analyses and comparisons in order to explore the hypotheses, including associations among test performance and demographic and medical factors. However, multiple comparisons can be problematic, as they increase the rate of false positives. Therefore, we utilized the FDR approach to balance retaining enough power to detect true associations while recognizing that there may be a chance that some significant results could be false positives. This is a common problem in research with populations that are rare and medically complex. However, our trend findings are in the direction that would be expected based on previous literature, and we expect that these associations are likely clinically meaningful, although our sample was too small and heterogeneous to detect these associations with adequate power.

Intervention for Executive Function and Processing Speed Deficits

Across the measures of executive function and processing speed in survivors of BT and ALL, group means were generally within normal limits. However, for both groups, there are subsets of survivors with significant difficulties. This subset of ALL and BT survivors are at risk for neurocognitive difficulties post-treatment. Both BT and ALL survivors are vulnerable to slower processing speed which will necessitate accommodation for many children. Importantly, children with processing speed difficulties may be misidentified as lazy, inattentive, or defiant. In the classroom, they are often among the last to complete work and turn in tests, and they may not finish classwork or homework. Fortunately, simple classroom accommodations, including extended time on exams, reduced items on rote homework and assignments, providing the student with class notes, and offering the student alternative methods of demonstrating knowledge in class and on exams (e.g. type, dictation) can be helpful. Since processing speed difficulties are more of a universal area of potential difficulty across BT and ALL, both diagnostic groups would benefit from accommodations to offset slower speed of information processing.

In contrast to more universal processing speed difficulties, affected BT survivors (i.e. those with 1 deficit on executive functioning tasks) tended to exhibit global executive function deficits, while affected ALL survivors exhibited variable performance across higher-order executive function tasks. These differing performance patterns may indicate that a

divergence in intervention planning is needed for these two groups. Specifically, BT survivors may need a more intensive intervention plan that includes supports for higher- and lower-level executive function (including attention) as well as broader supports due to more global dysfunction. ALL intervention plans may be more focused to offset specific processing speed and attention difficulties. Again, although we describe differences in the patterns of scores obtained by ALL and BT survivors in this sample, no statistically significant differences were identified between group means on executive function subtest in this study.

Survivors of ALL and BT are known to be at risk for attention difficulties (Brouwers et al., 1984; Buizer et al., 2005; Butler et al., 2013; Langer et al., 2002; Moyer et al., 2012; Reddick et al., 2006). Our findings suggest that attention is the primary deficit in affected survivors of ALL, while attentional difficulties appear to be part of a more global deficit profile in affected survivors of BT. Many educators and interventionists are familiar with the signs of typical attentional disorders (i.e., ADHD), and there are some similarities between post-treatment attentional deficits in ALL survivors and symptoms of ADHD. However, ALL and BT survivors with attention problems and children diagnosed with ADHD do not share exactly the same cognitive profile (Kahalley et al., 2010), with survivors being more likely to exhibit inattentive symptoms versus hyperactive/impulsive symptoms.

With regard to treatment for attentional problems, there has been much research on evidence-based intervention for children with ADHD, including stimulant medication, parent management training, and behavioral classroom management (Barkley, 2006; Pelham, Jr. & Fabiano, 2008). Recent research has applied evidenced-based intervention for ADHD to pediatric cancer survivors with attentional difficulties. Conklin and colleagues (2007) found significant benefits of methylphenidate in survivors of ALL and BT on a measure of attention, cognitive flexibility, and processing speed that is similar to the CWI. Further, methylphenidate produced lasting benefits on attention symptoms in survivors of both pediatric ALL and BT (Conklin et al., 2010). Therefore, stimulant medication may be a suitable treatment option for ALL and BT survivors with attentional deficits. Additionally, environmental accommodations for inattention may be helpful. These may include preferential seating, reduced distraction environments (e.g. testing in a separate, quiet room), frequent teacher check-ins, having an adult use nonverbal signals such as a tap on the desk to redirect the individual to pay attention, allowing for brief breaks (with the expectation of immediately returning to work after the break), and reminders to double check classwork and exams for careless errors.

With regard to higher-level executive dysfunction, such as cognitive inflexibility, survivors may exhibit difficulty with mentally taxing activities, which academically can affect note-taking, planning assignments and projects, studying for exams, multi-tasking, and generalizing knowledge to new situations. Social implications include interpreting environmental cues and responding to incoming social stimuli in a flexible manner. Environmental supports for cognitive flexibility problems may include presenting information one part at a time, using external organizers (e.g. specific visual schedules, folders with distinct locations for different items), and providing extra time. Interventions

may include teaching these individuals how to organize information (e.g. via use of graphic organizers) and strategies to generalize previously learned information.

Although ALL survivors' performance on inhibition and cognitive flexibility tasks appears to be less impacted than on processing speed tasks, higher-order executive function remains an area of potential relative weakness in both BT and ALL survivor groups. Even subtle weaknesses could have an impact on educational and daily functioning. Educational planning for these individuals may include apprising caregivers and educators of the signs of executive function difficulty in daily and school settings. Additionally, sequential monitoring of academic growth and progress is essential, as attention and executive deficits may manifest in academic difficulties. This way, if a child is demonstrating difficulties, necessary changes may be implemented as soon as possible. Additionally, due to the association between longer time since treatment and weaker executive function, the implementation of early intervention, even prior to the emergence of significant executive difficulties, may be an important consideration in intervention planning. While there are differences in the neurocognitive profiles of BT and ALL survivors, they both require careful interval monitoring and updated intervention plans throughout childhood and adolescence. Measurement of executive function and known processing speed limitations are important to consider, as many instruments used to measure higher-level executive functions include time limits. It stands to reason that slower processing speed may impact the measurement of other executive functions given time constraints. Therefore, in addition to administering tasks that measure processing speed, it may be useful to administer both timed and untimed measures of other executive function skills (e.g. inhibition, cognitive flexibility, problem solving, planning, etc.) in future research and in clinical evaluations with survivors. Untimed measures may partially eliminate the impact of processing speed on executive function, whereas timed measures provide valuable information about the potential interplay of processing speed and executive function. For instance, while a child may be much better able to perform a task of cognitive flexibility without time constraints, a measure with time constraints may paint a more realistic picture of how the child may get along in everyday academic and daily living activities. A problem with timed measures may be a possible underestimate of other executive function skills, whereas a problem with untimed measures may be an overestimation of executive function that is unrealistic and incompatible with daily demands. Therefore, administration of both timed and untimed executive function measures is best practice to obtain information about executive function for treatment planning.

Limitations

Limitations of the current study must be considered. First, the lack of a control group resulted in the use of normative means within the test populations of the study measures. The cross sectional study design limited the current analyses to one time point, restricting our ability to understand how processing speed and executive function change over time post-treatment. Future studies should aim to collect data from multiple points in time to better capture the trajectory of executive and other late effects. An additional sample limitation is the exclusion of those individuals with IQ below 70. By excluding these individuals, we may have missed information about a group of individuals who are

particularly vulnerable to neurocognitive late effects and who would require the most extensive intervention planning. This limitation may be especially salient for BT survivors, with their more general, pervasive neurocognitive impairments. Additionally, given the heterogeneous nature of the BT sample (difference in tumor type/location, treatment type, location, and dosage), significant associations with demographic and medical predictors may have been undetected in this relatively small sample, particularly in light of the wealth of research that shows associations between radiation therapy and poor cognitive outcomes (Alvarez et al., 2007; Merchant, Conklin, Wu, Lustig, & Xiong 2009; Merchant, Pollack & Loeffler, 2010; Packer al., 1999; Saury & Emanuelson, 2011). This sample included survivors within a limited age range (12-17 years). Future studies should include a larger age range, ranging from early childhood to adulthood to capture and study the complete developmental span. However, this adolescent sample represents the developmental period when the frontal lobes experience a growth spurt allowing for intense development of executive functions, making this an ideal age range to examine these outcomes. This is also the period of development that executive dysfunction often becomes more apparent as the daily and academic demands requiring executive skills increase (e.g. independent completion of tasks, more complex planning and organization). Additionally, it should be noted that this sample's performance amongst survivors of BT may represent a higher functioning BT group than is typical (i.e., BT group mean EIQ = 100.5). Further, group means were within normal limits (within the average range of performance) across all subtests in both groups, even when significant differences were found relative to group EIQ and/or normative means. While there are clear impairments experienced by a subset of survivors in both groups, the clinical significance of these areas of relative weakness for BT and ALL survivors as a whole remains unclear and should be studied further. Study measure limitations were present as well. All executive function measures were timed, so the outcomes may be influenced, at least partially, by processing speed. The lack of untimed executive function measures also made it difficult to fully parcel out the effect of processing speed on higher-order executive functions. Additionally, only one measure of executive function and an abbreviated measure of intelligence were given in this study. Future studies and clinical assessments should aim to use a fuller, more detailed battery with complete intelligence batteries and multiple measures of executive function.

Another important limitation that warrants discussion is the use of multiple comparisons. The False Discovery Rate (FDR) method was implemented in order to control for the use of multiple statistical comparisons. We chose a value of 10% in order to retain power to detect true associations while reducing the rate of false positives. Controlling for use of multiple comparisons is a common problem with a population that is rare, requiring consideration of many demographic and medical variables. However, our findings that were trends (as opposed to statistically significant findings) were all in the expected direction, given previous literature. Additionally, all but one of the findings that were statistically significant had $FDR > 0.1$, indicating medium to large effect sizes and were therefore worth interpreting. This indicates that the trends we found may be clinically meaningful, while the sample was too small and heterogenous to detect the findings with adequate power.

Conclusion

The current study confirms that both ALL and BT survivors demonstrate relative and normative weaknesses in executive function. A subset of BT survivors demonstrate global deficits in processing speed and executive function, while affected ALL survivors' most salient deficit was in rapid naming, a lower-order executive function skill. ALL survivors with clinically significant deficits also demonstrated more variable executive function profiles. Together, these findings may be suggestive of differing neurocognitive profiles between ALL and BT groups, which could have implications for intervention planning. Accommodations for ALL survivors are likely to require more focus on processing speed and attention, while plans for BT survivors will likely focus on a broader set of cognitive skills, including both higher-and lower-level executive functions. Still, both ALL and BT survivors appear to be at risk for cognitive late effects and require interval monitoring.

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Abbreviations

BT	Brain Tumor
ALL	Acute Lymphoblastic Leukemia
EIQ	Estimate IQ
PS	Processing Speed
DKEFS	Delis Kaplan Executive Function System
CWI	Color-Word Interference
CSI	Cranio-Spinal Irradiation
CRT	cranial radiation therapy

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Table 1
Demographic and Clinical Characteristics of Survivors by Diagnostic Group

Characteristic	BT Survivors		ALL Survivors	
	<i>n</i>	%	<i>n</i>	%
Total	48	100.00	50	100.00
Sex				
Female	24	50.00	25	50.00
Male	24	50.00	25	50.00
Race/ethnicity				
White, non-Hispanic	41	85.42	43	86.00
Non-White	7	14.58	7	14.00
Cranial radiation therapy				
No	9	18.75	43	86.00
Yes	39	81.25	7	14.00
CSI				
No	30	62.50	48	96.00
Yes	18	37.50	2	4.00
Chemotherapy				
No	23	47.92	0	0.00
Yes	25	52.08	50 ^a	100.00
Neurosurgery				
No	4	8.33	50	100.00
Yes	44	91.67	0	0.00
Shunt				
No	35	72.92	50	100.00
Yes	13	27.08	0	0.00
	<i>M ± SD</i>	<i>Range</i>	<i>M ± SD</i>	<i>Range</i>
Age at study participation	14.91 ± 1.79	12.06-17.99	14.95 ± 2.00	12.16-17.99
Age at diagnosis	8.12 ± 3.61	1.95-15.21	4.97 ± 3.09	0.65-12.95
Years from diagnosis	6.79 ± 4.02	1.74-16.02	9.98 ± 3.04	4.64-16.93
Years off treatment	5.60 ± 3.66	1.11-16.02	7.07 ± 3.28	1.52-15.48

Note. Some survivors are represented in more than one treatment category. Cranial radiation therapy includes any irradiation to the brain (i.e., focal, whole brain, and craniospinal). CSI = craniospinal irradiation.

^a All ALL survivors received intrathecal chemotherapy.

Table 2
Estimated IQ and DKEFS CWI Scores by Diagnostic Group

Score	BT (<i>n</i> = 48)		ALL (<i>n</i> = 50)	
	<i>M</i> ± <i>SD</i>	<i>Range</i>	<i>M</i> ± <i>SD</i>	<i>Range</i>
EIQ ^a	100.52 ± 15.62	58-131	101.86 ± 11.38	85-129
DKEFS CWI Trials ^b				
Color Naming	8.88 ± 3.34	1-14	8.80 ± 3.30	1-14
Word Reading	8.67 ± 3.48	1-14	9.16 ± 3.26	1-14
PS Composite	9.02 ± 3.24	1-14	9.26 ± 3.08	3-14
Inhibition	8.96 ± 3.58	1-15	9.32 ± 2.78	1-15
Inhibition/Switching	8.04 ± 3.53	1-15	9.38 ± 3.20	1-14

Note. EIQ = Estimated IQ. DKEFS CWI = Delis-Kaplan Executive Function System Color-Word Interference subtest.

^aStandard score (*M* = 100, *SD* = 15).

^bScaled score (*M* = 10, *SD* = 3)