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Adaptive Functioning and Academic Achievement in Survivors of Childhood Acute Lymphoblastic Leukemia: Associations with Executive Functioning and Socioeconomic Status

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ADAPTIVE FUNCTIONING AND ACADEMIC ACHIEVEMENT IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: ASSOCIATIONS WITH EXECUTIVE FUNCTIONING AND SOCIOECONOMIC STATUS

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ABSTRACT

This study examined the associations of functional outcomes (adaptive functioning and academic achievement) with executive functioning and neighborhood-specific variables (area deprivation and child opportunity) and individualized education plan (IEP) support in survivors of childhood acute lymphoblastic leukemia (ALL). From a retrospective database, 44 patients (38.6% female, 72.7% non-Hispanic White, ages 6-17) previously diagnosed with low-risk or standard-risk pre-B cell ALL and treated with chemotherapy-only were identified. Participants were evaluated on performance-based measures of executive functioning and academic achievement, and parent-ratings of executive and adaptive functioning. Within adaptive functioning, 45.5% of patients showed impairment (≥ 1 SD above the normative mean) in activities of daily living and leadership. Adaptive functioning was significantly positively correlated with parent-rated, but not performance-based, executive functioning ($p<0.001$). Compared to female survivors, male survivors were at increased risk for adaptive functioning difficulties ($p<0.05$). Impairments for word reading and math calculation were 25% and 41.7%, respectively. Greater math calculation was associated with better performance-based executive functioning ($p<0.05$), and survivors with older age at evaluation and those without IEP support showed better word reading ($p<0.05$). Functional outcomes were not associated with neighborhood-specific variables. Overall, findings suggest that a subset of ALL survivors are at risk for reduced functional outcomes, and these outcomes may be more strongly related to executive functioning than neighborhood-specific variables or IEP support. Long-term goals include translating findings into practice to remediate adaptive or academic difficulties in ALL survivors.

Keywords: Acute lymphoblastic leukemia, Adaptive Functioning, Academic Achievement, Executive Functioning, Socioeconomic Status

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer (Kaatsch, 2010), accounting for 26% of all childhood malignancies (Ward et al., 2014). With the advancement of modern treatment protocols, the current estimated probability of 15-year survival among patients who have survived five years is approximately 95% (Ward et al., 2014). As a result of this increase in survivorship, greater research efforts are being devoted to understanding health issues arising months or years after treatment that may be due to ALL and/or its treatment, also known as late effects (Stein et al., 2008). One frequently reported late effect involves neurocognitive functioning (Cheung & Krull, 2015; Kesler et al., 2018; Krull et al., 2013; Krull et al., 2018; Liu et al., 2018). The replacement of prophylactic cranial radiation therapy with intrathecal methotrexate has resulted in reduced neurotoxicity and improved neurocognitive outcomes. Nevertheless, survivors of childhood ALL treated with chemotherapy-only protocols (e.g., consisting of intrathecal methotrexate) continue to show higher rates of neurocognitive difficulties compared to population norms and healthy controls (Hunger & Mullighan, 2015; Krull et al., 2018).

Among patients treated only with chemotherapy, demographic and clinical risk factors for greater neurocognitive late effects include younger age at therapy, higher intensity of central nervous system (CNS)-directed therapy, greater time since treatment, lower socioeconomic status, and certain genetic alterations (Hardy et al., 2017; L. M.

Jacola et al., 2016; Krull et al., 2018; Von der Weid et al., 2003). Historically, female sex has been associated with worse neurocognitive outcomes, although recent evidence suggests a potential moderating effect of sex and that male survivors may be at higher risk for some neurocognitive late effects (van der Plas et al., 2021). Moreover, proposed mechanisms for chemotherapy-induced neurotoxicity include direct neurotoxicity, in which chemotherapeutic agents readily cross the blood-brain barrier and lead to apoptosis of healthy cells and white matter demyelination (Sleurs et al., 2016); immune dysregulation and neuroinflammation (Alexander et al., 2018; Wen et al., 2018); hormonal changes and suppression of the hypothalamic-pituitary-adrenal (HPA) axis involved in stress (Sleurs et al., 2016); damage to DNA of healthy cells leading to decreased neurogenesis; and the production of oxidative stress causing neurodegeneration (Ahles & Saykin, 2007; Alexander et al., 2018; Sleurs et al., 2016). Notably, markers of neurological injury associated with neurocognitive impairment in survivors of childhood ALL and animal models treated with chemotherapy-only include decreased white matter volume (Montour-Proulx et al., 2005); protein alterations in the cerebrospinal fluid (CSF; Cheung et al., 2018); increased CSF nerve growth factor (Cheung et al., 2018); elevated levels of glial fibrillary acidic protein (Cheung et al., 2018); elevated tau and phosphorylated tau observed in CSF (Cheung et al., 2018); decreased cell density in the corpus callosum; decreased glucose metabolism (Seigers et al., 2010); and decreased hippocampal cell proliferation (Seigers et al., 2010). In turn, these markers of neurological injury are associated with altered neurocognitive development and neurocognitive late effects even among survivors of childhood ALL treated without cranial radiation (Alexander & Krull, 2021). Thus, our proposed conceptual model for neurocognitive late effects in survivors of childhood ALL treated with chemotherapy-only includes demographic risk factors (e.g., age at diagnosis and sex), treatment risk factors (e.g., intensity), and physiological effects (e.g., decreased white matter volume, reduced glucose metabolism, etc.). Continued research is essential to delineate the impact of neurocognitive late effects long-term outcomes in this population.

Executive functioning is the most commonly cited neurocognitive late effect in survivors of ALL (Krull et al., 2018). Executive functioning refers to cognitive processes involved in goal-directed behavior and includes cognitive flexibility, working memory, processing speed, and verbal fluency (Best & Miller, 2010). Reports indicate that between 20% and 60% of survivors of childhood ALL demonstrate deficits in executive functioning (Krull et al., 2018). Moreover, the frequency of severe impairment (defined as two standard deviations below the age-based population mean) is eight times higher in survivors of childhood ALL compared to the general population (Krull et al., 2013).

Importantly, executive functioning impairment increases with time since diagnosis in ALL survivors (Krull et al., 2013) and is associated with age-appropriate adaptive skills and academic achievement, collectively referred to as functional outcomes hereafter (Best et al., 2011; King et al., 2015; Reem A Tarazi et al., 2007; Treble-Barna et al., 2017). Adaptive skills are conceptual, practical, and social skills that are needed for daily life. Collectively, these skills constitute adaptive functioning, defined as one’s ability to independently perform developmentally appropriate adaptive skills (e.g., activities of daily living, functional communication, and social skills; Tasse et al., 2012). Executive functioning facilitates the acquisition of adaptive skills and is positively correlated with increased independence in these skills throughout development (Reem A

Tarazi et al., 2007). Early childhood disruption of executive functioning may negatively impact adaptive functioning, as appropriate executive functioning skills are needed to carry out age-appropriate skills. As such, adaptive functioning may be challenging for children and adolescents who lack the prerequisite executive functioning skills (Gardiner & Iarocci, 2018; Reem A Tarazi et al., 2007). Prior studies have shown robust associations between executive and adaptive functioning in populations with executive dysfunction (King et al., 2015; Treble-Barna et al., 2017). In the only study to examine adaptive functioning in survivors of childhood high-risk B-lineage ALL, Jacola et al. (2021) found significantly higher rates of at-risk impairment than expected in global adaptive functioning, with particular deficits in the practical domain.

Specific to academic achievement, executive functioning is associated with both reading and math across age in typically developing children and adolescents (Best et al., 2011; Kendeou et al., 2014). A broad set of executive functioning skills including planning, self-monitoring, working memory, and inhibition, relate to performance in both reading and math as both subjects require the coordination of these individual skills (Blair & Razza, 2007; Bull et al., 2008; Bull & Scerif, 2001; Kendeou et al., 2014). Specifically, math problem solving involves self-monitoring as well as strategy formulation and implementation, while calculation relies primarily on working memory (Best et al., 2011). Reading comprehension is also associated with performance-based executive functioning, particularly working memory, inhibition, and inference making (Cirino et al., 2019; Gathercole et al., 2006; Kendeou et al., 2014; Messer et al., 2016). The contribution of executive functioning to single word reading (i.e., decoding) is more ambiguous, with some studies demonstrating relationships with working memory and inhibition (Arrington et al., 2014; Christopher et al., 2012; Jacobson et al., 2017; Locascio et al., 2010), and others placing more emphasis on lower-level skills such as phonological processing (Cirino et al., 2019; Sesma et al., 2009). Prior studies investigating academic achievement have shown performance similar to same-aged peers (Kingma et al., 2001; Spiegler et al., 2006) as well as lower achievement and educational attainment in survivors of childhood ALL (Lisa M Jacola et al., 2016; Krull et al., 2013). However, little is known about academic achievement and its relationship with executive functioning in survivors of childhood ALL.

Variation in neurocognitive and functional outcomes post-treatment in survivors of childhood ALL may be explained by the cognitive reserve hypothesis, which proposes that functioning post-brain injury is impacted by factors that are intrinsic (e.g., pre-injury cognition) and extrinsic (e.g., socioeconomic status; Kesler et al., 2010) to the individual. Thus, those with higher reserve show better outcomes after brain injury due to greater intrinsic and extrinsic resources, and subsequent higher threshold of brain injury needed for neurocognitive and functional deficits to manifest. Consistent with the cognitive reserve hypothesis, survivors of childhood ALL with higher socioeconomic status, a component of cognitive reserve, may show better neurocognitive and functional outcomes post-treatment. Socioeconomic status is a multifaceted construct including insurance status, family income, parental education, neighborhood-specific variables (e.g., area deprivation and child opportunity), and access to resources (Cheng et al., 2015; Jacola et al., 2021). Higher socioeconomic status provides children with greater learning opportunities and a more enriched environment, which further contribute to cognitive development (Kesler et al., 2014). The research thus far has demonstrated socioeconomic status, specifically maternal education, to be positively correlated with executive functioning in survivors of childhood ALL (Kesler et al., 2010). Given that adaptive functioning and academic achievement are largely dependent on executive functioning (Blair & Razza, 2007; Bull et al., 2008; Bull & Scerif, 2001; Cirino et al., 2019; Kendeou et al., 2014; Reem A Tarazi et al., 2007), socioeconomic variables may similarly predict low functional outcomes. Indeed, ALL survivors with US public health insurance are at greater risk for adaptive functioning difficulties and lower academic achievement than those with US private or military insurance (Jacola et al., 2021). However, further work is needed to explore the relationships of neighborhood-specific variables, area deprivation and child opportunity, and access to resources such as provision of academic supports (e.g., individualized education plan [IEP]), to adaptive functioning and academic achievement. Neighborhoods with reduced poverty and increased resources such as housing, education, employment, access to healthy environments, social enrichment opportunities (i.e., indicators of area deprivation (Kind & Buckingham, 2018) and child opportunity (Acevedo-Garcia et al., 2014)), and access to academic supports, may promote cognitive development while simultaneously providing increased opportunities for children to practice adaptive and academic skills. As such, evaluation of these factors may add evidence of the impact of socioeconomic status on functional outcomes.

The prior studies mentioned above contribute valuable insights regarding functional outcomes (adaptive functioning and academic achievement) and their associated risk factors in children treated for ALL (Jacola et al., 2021; Tremolada et al., 2019). However, the associations among functional outcomes, executive functioning, and neighborhood-specific variables and IEP support have yet to be investigated in survivors of childhood low-risk and standard-risk B-lineage ALL treated with chemotherapy-only protocols. Consequently, the current study aims to address these gaps in the literature. Specifically, we aimed to examine the association of functional outcomes and executive functioning, and the association of functional outcomes with neighborhood-specific variables and IEP support, in survivors of childhood ALL. We hypothesized that 1) survivors of childhood ALL would show low functional outcomes and performance-based and parent-rated executive functioning compared to population norms, 2) survivors with low performance-based and parent-rated executive functioning would show low functional outcomes, and 3) high area deprivation and low child opportunity (neighborhood-specific variables) and fewer IEP provisions (academic resources) would predict low functional outcomes.

METHODS

Participants

Pediatric survivors of childhood ALL were identified from a retrospective database of patients seen for neuropsychological evaluation by a licensed clinical neuropsychologist in the Division of Hematology/Oncology at Children's of Alabama Hospital. Inclusion criteria included the following: Pediatric survivors of childhood ALL ages 6-18; designated as low-or standard-risk during treatment; treated with chemotherapy-only protocols; at least one-year post-treatment; evaluated on performance-based measures of intelligence, executive functioning, and academic achievement (word reading and math calculation), and parent-ratings of executive and adaptive functioning; and English-speaking. Exclusion criteria included: high-risk or very high-risk (e.g., due to older age at diagnosis or high minimal residual disease); treated with prophylactic cranial radiation or bone marrow transplant; experienced cancer relapse or secondary malignancy; or diagnosed with intellectual disability (Full-Scale IQ less than standard score of 70), neurodevelopmental disorder, neurological condition, and/or genetic disorder. This study was approved by the UAB Institutional Review Board. The review was in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services

Procedure

103 patients previously diagnosed with B-lineage ALL who received a neuropsychological evaluation between the years of 2014-2021 were identified through retrospective medical record review. Of these 103 participants, 44 met the eligibility criteria stated previously. See Figure 1 for study enrollment. The performance-based executive functioning skills that were assessed included cognitive flexibility, verbal fluency, working memory, and processing speed. In addition to examining the role of each performance-based executive functioning skill individually, scores were also combined to create an executive functioning average T-score (transformed score with M=50 and SD=10) and a global deficit score (GDS; see Table 1). GDS was used to represent an individual's overall impairment in the executive functioning domain (Murdaugh et al., 2020; Sharafeldin et al., 2018; Sharafeldin et al., 2022). Scores for word reading and math calculation were abstracted for academic achievement.

Measures

Performance-based measures and parent-ratings of neurocognition were collected for analyses. Performance-based measures included tests of intellectual functioning (full-scale IQ and verbal IQ [VIQ]) and executive functioning (cognitive flexibility, verbal fluency, working memory, and processing speed). Each executive functioning skill was evaluated individually as well as combined to form an average T-score and a GDS. Performance-based academic achievement scores were also collected for word reading and math calculation. Parent-ratings of executive and adaptive functioning were collected using the Behavior Rating Inventory of Executive Functioning (BRIEF) and Behavior Assessment System for Children (BASC; Reynolds, 2010) respectively. Scores on the

BRIEF are represented as T-scores, in which higher scores indicate greater difficulty. See Appendix Table 1 for all other measures used. For the purpose of this study, other scores including performance-based executive functioning, adaptive functioning, and academic achievement were also converted to T-scores and reverse coded so that higher scores indicated greater difficulty.

Intellectual Functioning

Overall intellectual functioning from the following tests were used to screen participants: Wechsler Intelligence Scale for Children (WISC) 4th and 5th Editions; Wechsler Adult Intelligence Scale (WAIS) 4th Edition; Stanford-Binet Intelligence Scale – 5th Edition (SB-5); and Differential Ability Scales (DAS) 1st and 2nd Editions. The verbal composites from the same tests were used to control for verbal IQ (VIQ) in analyses.

Performance-Based Executive Functioning

Cognitive Flexibility. Overall achievement scores from the following tests were used as measures of cognitive flexibility: Trails B; Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test Condition 4; Test of Everyday Attention in Children (TEA-Ch) Opposite Worlds; TEA-Ch 2nd Edition Red & Blues, Bags & Shoes; and Developmental Neuropsychological Assessment (NEPSY) and NEPSY-II Animal Sorting.

Verbal Fluency. Overall achievement scores from the following tests were used as measures of verbal/semantic fluency: D-KEFS Category Fluency; NEPSY and NEPSY-II Word Generation Semantic; and Controlled Oral Word Association Test (COWAT) Animals.

Working Memory. Overall achievement scores from the following tests were used as measures of working memory: WISC-IV, WISC-V, and WAIS-IV Working Memory Index; SB-5 Working Memory Index; and DAS-II Recall of Digits Forward.

Processing Speed. Overall achievement scores from the WISC-IV, WISC-V, and WAIS-IV Processing Speed Index were used as measures of processing speed.

Academic Achievement

Word Reading. Overall achievement scores from the WIAT-III Word Reading and WJ-IV Letter-Word Identification were used as measures of word reading.

Math Calculation. Overall achievement scores from the WIAT-III Numerical Operations and WJ-IV Calculation were used as measures of math calculation.

Parent-Rated Executive Functioning

Parent-rated executive functioning was measured using the BRIEF and BRIEF-2. The BRIEF and BRIEF-2 are parent-rating scales that assess children's everyday executive functioning in the home and school settings. Caregivers are asked to read a series of statements that each describes an executive functioning behavior (e.g., "has trouble finishing tasks") and rate the frequency (i.e., never, sometimes, or often) with which their child has had difficulties with the behavior in the past six months. The BRIEF-2 consists of nine theoretically and empirically derived scales: Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task-Monitor, and Organization of Materials. These nine scales are aggregated into three indices, including the Behavioral Regulation Index (BRI; consists of Inhibit and Self-Monitor), the Emotion Regulation Index (ERI; consists of Shift and Emotional Control), and the Cognitive Regulation Index (CRI; consists of Initiate, Working Memory, Plan/Organize, Task-Monitor, and Organization of Materials). These three indices form a summary score known as the Global Executive Composite (GEC). The first edition of the BRIEF combines the Self-Monitor and Task-Monitor scales into one domain known as Monitor. There are two broader indices in the BRIEF: The Behavioral Regulation Index (BRI; consists of Inhibit, Shift, and Emotional Control) and the Metacognition Index (MI; consists of Initiate, Working Memory, Plan/Organize, Monitor, and Organization of Materials). In the current study, the Self-Monitor and Task-Monitor scales were averaged to form one overall Monitor score for participants who were administered the BRIEF-2. Like the BRIEF-2, the two indices in the BRIEF form the GEC. Scores on the BRIEF and BRIEF-2 are represented as T-scores, in which higher scores indicate greater difficulty.

Parent-Rated Adaptive Functioning

Parent-rated adaptive functioning was measured using the BASC-2 and BASC-3. The BASC-2 and BASC-3 are parent-rating scales that assess children's adaptive functioning in the home and school settings. Caregivers are asked to read a series of statements that each describes an adaptive skill (e.g., "organizes chores or other tasks well") and rate the frequency (i.e., never, sometimes, often, or almost always) with which their child independently performs the skill. The BASC-2 and BASC-3 consist of five adaptive domains including Activities of Daily Living, Adaptability, Functional Communication, Leadership, and Social Skills. Together, the five domains form the Adaptive Skills Composite. Scores on the BASC-2 and BASC-3 Adaptive scales are represented as T-scores, in which lower scores indicate greater difficulty.

Additional Data

Demographic, socioeconomic, and medical/treatment data were abstracted from medical records. Demographic data included sex, age at evaluation, and race/ethnicity. Socioeconomic data included area deprivation index, child opportunity index, and individualized education program (IEP) status at the time of evaluation. Area deprivation index was based on participants' census block groups, defined as the smallest geographic unit used by the US Census Bureau, and includes income, education, employment, and housing quality. Scores range from 1-10, with lower scores indicating lower disadvantage (Kind & Buckingham, 2018). Child opportunity index was based on participants' census tracts, defined as statistical subdivisions of a county, and includes 29 indicators of child opportunity across three domains (education, health and environment, and social and economic) combined into a composite score. Five categories are used to represent child opportunity indiex (*very high, high, moderate, low,* and *very low*). These categories were represented on a scale from 1-5, with higher scores indicating less child opportunity (Mast & Din, 2021). IEP status was coded dichotomously (i.e., with or without IEP). Medical/treatment information included the following: age at diagnosis, years post-diagnosis, and years off-treatment.

Statistical Analyses

All data were analyzed using IBM SPSS 27.0 statistical software, with an alpha level set to 0.05. Prior to conducting primary study analyses, descriptive statistics and frequencies were analyzed. *A priori* power analyses were completed during initial study design and planning.

To examine functional outcomes and executive functioning performance in pediatric ALL survivors compared to the normative sample, group means, 95% confidence intervals and the standard error were calculated for each measure and scale. Percentages of participants showing impairments were calculated using a cutoff of ≥ 1 SD above the normative mean for adaptive functioning, performance-based executive functioning, and academic achievement T-scores (T-score ≥ 60); ≥0.5 for performance-based executive functioning deficit scores and GDS; and T-score ≥ 65 (defined as clinical significance) for parent-rated executive functioning.

Partial correlations were conducted to examine whether participants with low performance-based and parent-rated executive functioning would show reduced functional outcomes. Power analyses indicated at least 80% power to detect a population partial correlation ≥ 0.5 as statistically significant assuming a one-tailed test, an alpha level of 0.05, and a sample size of at least 23 participants. Prior to conducting partial correlation analyses, test assumptions including normality of residuals, homoscedasticity, independence, linearity, and absence of collinearity, were tested. All test assumptions were satisfied.

Multiple regression analyses were conducted to evaluate whether neighborhood-specific variables (area deprivation and child opportunity) and IEP status would predict functional outcomes and executive functioning. Power analyses indicated at least 80% power to detect a population partial R^2 of 0.13 as statistically significant assuming an alpha level of 0.05 and a sample size of at least 44 participants. Prior to conducting multiple regression analyses, test assumptions including normality of residuals, homoscedasticity, independence, linearity, and absence of collinearity, were tested. All assumptions, except for absence of collinearity, were satisfied. Area deprivation and child opportunity indices were collinear (*r* = 0.705). Thus, child opportunity index was removed from the regression models in follow-up analyses. Finally, all partial correlations and multiple regression analyses included age at evaluation, age at diagnosis, sex, and VIQ as covariates to control for neurocognitive risk factors.

RESULTS

Results of descriptive and frequency analyses are presented in Table 2. Forty-four participants previously diagnosed with B-cell ALL were included in the study. Seventeen (38.6%) were female and 32 (72.7%) were non-Hispanic White. Mean age at diagnosis ranged from less than 1 year to 9 years of age (M=3.34, SD=2.199); mean age at evaluation ranged from 6 to 17 years (M=11.11, SD=2.879). Survivors were on average 7.32 years post-diagnosis and 4.64 years post-treatment. Frequencies of neighborhood-specific variables, area deprivation and child opportunity, are presented in Figure 2. Area deprivation ranged from 1 to 10 (M=5.30, SD=2.62), and child opportunity ranged from 1 to 5 (M=3.39, SD=1.28). 27.3% of participants (n=12) had an IEP at the time of evaluation.

Functional Outcomes and Executive Functioning Performance

As stated previously, impairments were defined as ≥ 1 SD above the normative mean for adaptive functioning, performance-based executive functioning, and academic achievement, ≥0.5 for performance-based executive functioning deficit scores and GDS, and T-score ≥ 65 for parent-rated executive functioning. Compared to population norms, all T-scores of adaptive functioning (M=55.91; 95% CI, 52.78-59.04), word reading (M=54.64; 95% CI, 50.91-58.36), math calculation (M=57.67; 95% CI, 54.06-61.27; Figure 3A), performance-based executive functioning average (M=56.72; 95% CI, 54.46-58.98; Figure 3B), performance-based executive functioning GDS (M=0.68; 95% CI, 0.43-0.93; Figure 3C), and parent-rated executive functioning (M=61.91; 95% CI, 58.18-65.64; Figure 3D) indicated impairment, although mean scores fell within normal limits. Within adaptive functioning domains, all skill areas with the exception of Social Skills also showed impairment compared to population norms. Cognitive flexibility T-scores fell within the range of impairment for the overall group on average (M=60.43; 95% CI, 56.86-64.02). Mean global deficit of performance-based executive functioning fell above the 0.5 impairment cutoff. (M=0.68; 95% CI, 0.43-0.93; Figure 3C). Across all performance-based executive functioning skills, deficit score means ranged from 0.39 to 1.12 with the least deficit demonstrated in working memory (M=0.39; 95% CI, 0.15-0.62) and the greatest deficit demonstrated in cognitive flexibility (M=1.12; 95% CI, 0.65-1.58). Parent-rated working memory fell within the range of clinical significance (M=65.41; 95% CI, 61.68-69.13). Percentages of participants showing impairments were as follows: adaptive functioning (38.6%), word reading (25%), math calculation (41.7%), performance-based executive functioning average (31.8%) performance-based executive functioning global deficit (52.3%), and parent-rated executive functioning (52.3%). Rates of impairment within adaptive functioning domains were as follows: social skills (34.1%), adaptability (40.9%), functional communication (43.2%), activities of daily living (45.5%), and leadership (45.5%).

Relationship Between Functional Outcomes and Executive Functioning

Significant partial correlation results are presented in Table 3. Adaptive functioning was significantly correlated with parent-rated executive functioning, $r_{\text{partial}}(41) = 0.694$, $p<0.001$. In this model, male sex was significantly associated with lower adaptive functioning, $t(41)= 2.697$, $p<0.05$. Each adaptive skill domain was significantly positively correlated with parent-rated executive functioning ($p<0.05$). See Figure 4 for scatterplots of significant partial correlations between math calculation and performance-based executive functioning. Math calculation scores were significantly correlated with verbal fluency, $r_{partial}$ (32) = 0.378, $p<0.05$, and processing speed, $r_{partial}$ (31) = 0.439, $p < 0.05$, while controlling for age at evaluation, age at diagnosis, sex, and VIQ. Correlation coefficients were weaker when excluding covariates in analyses. Other associations among performance-based or parent-rated executive functioning were not significant.

Relationship Between Neighborhood-Specific Variables, Academic Resources, and Functional Outcomes

Neighborhood-specific variables, area deprivation and child opportunity, and IEP status did not predict adaptive functioning or math calculation. However, multiple regression analyses examining the associations among neighborhood-specific variables, IEP status, and demographic variables revealed significant effects for word reading, see Table 4. There were significant main effects of age at evaluation, β = -0.580, $t(28) = 4.51$, $p<0.001$, and IEP status $t(28) = 2.993$, $p<0.05$, in the prediction of word reading, indicating better word reading in older survivors at the time of evaluation and those with an IEP. Regression coefficients were weaker when excluding covariates in analyses.

Relationship Between Neighborhood-Specific Variables, Academic Resources, and Executive Functioning

Multiple regression analyses examining the associations among neighborhood-specific variables, IEP status, and demographic variables revealed significant effects for performance-based executive functioning, specifically verbal fluency, see Table 5. There were significant main effects of sex $t(35) = 2.281$, $p<0.05$, and IEP status $t(35) = 2.206$,

$p<0.05$, indicating better verbal fluency in female survivors and those without IEP support. In this model, ADI approached significance, $\beta = 0.386$, $t(35) = 2.017$, $p=0.051$. Due to collinearity between child opportunity and area deprivation ($r = 0.705$), follow-up analyses were conducted with child opportunity removed from the model. Results of follow-up analyses indicated a significant effect of area deprivation with child opportunity removed, $\beta = 0.282$, $t(36) = 2.118$, $p = 0.041$. Regression coefficients were weaker when excluding covariates in analyses.

DISCUSSION

The current study examined the relationship among functional outcomes (adaptive functioning and academic achievement), executive functioning, and socioeconomic status, including neighborhood-specific variables and IEP support, in survivors of childhood low-risk and standard-risk B-lineage ALL treated with chemotherapy-only. Although findings from other populations show strong support for the contribution of executive functioning to functional outcomes (Best et al., 2011; Blair & Razza, 2007; Bull et al., 2008; Bull & Scerif, 2001; Cirino et al., 2019; Gardiner & Iarocci, 2018; Kendeou et al., 2014; Reem A Tarazi et al., 2007), this is the first study to examine this association in survivors of childhood ALL, a population with high rates of executive functioning difficulties compared to population norms (Cheung & Krull, 2015; Krull et al., 2013; Krull et al., 2018). Additionally, this is the first study within this population to examine the association between neighborhood-specific variables and IEP support with functional outcomes. Strengths of the study include a homogenous sample of survivors of childhood ALL, evaluation of performance-based as well as parent-reported executive functioning, and innovative measures of neighborhood-specific socioeconomic variables (area deprivation and child opportunity indices).

In the current study, all skill areas of adaptive functioning, with the exception of social skills, indicated impairment compared to population norms. Specifically, 38.6% of participants showed impairment in overall adaptive skills, with impairment defined as ≥ 1 SD above the normative mean. Rates of impairment within adaptive functioning domains were highest for activities of daily living and leadership, with 45.5% of the sample showing impairment in each domain. These results are consistent with the findings of Jacola et al. (2021) who found overall adaptive functioning in the average range but significantly higher rates of at-risk impairment compared to population norms. Rates of at-risk impairment in their study were particularly high in the practical domain, which includes adaptive skills such as activities of daily living or self-care. The literature suggests that children and adolescents with chronic health conditions and concurrent weaknesses in executive functioning may be especially prone to difficulties in self-care or practical adaptive skills (R. A. Tarazi et al., 2007). In contrast, the high rate of leadership difficulties in this population represents a new finding in the literature. Given that items on the BASC leadership scale may tap into facets of social functioning (Reynolds, 2010), it is possible that this finding is related to reduced social outcomes in pediatric cancer survivors that is correlated with the intensity of CNS-directed treatment (Vannatta et al., 2007).

Further, we found that overall adaptive functioning and adaptive skill domains were significantly positively correlated with parent-rated, but not performance-based, executive functioning. This finding is expected given that adaptive functioning is also parent-rated. Moreover, prior studies have found modest correlations between performance-based measures and rating scales of executive functioning, and have proposed that the two measure different constructs of executive functioning (Miranda et al., 2015; Toplak et al., 2013). Specifically, performance-based measures indicate processing efficiency and measure the cognitive component of executive functioning, while parent-ratings indicate difficulty in goal pursuit and measure the behavioral component of executive functioning (Miranda et al., 2015; Toplak et al., 2013). Thus, it is possible that adaptive functioning relates to the behavioral component of executive functioning to a greater extent than its cognitive component, and may explain the strong positive correlation between the two.

Male biological sex emerged as a significant risk factor for adaptive functioning difficulties, similarly to what was shown by Jacola et al. (2021). This finding is supported by recent literature indicating that risk of neurocognitive impairment is sex-dependent when accounting for treatment exposures and chronic conditions (van der Plas et al., 2021). In male survivors, dexamethasone exposure increases risk for memory impairment, while chronic neurological or pulmonary conditions increase risk for executive dysfunction (van der Plas et al., 2021). Thus, our findings of reduced adaptive functioning in male survivors may be explained in light of underlying treatments and chronic conditions. Children with chronic health conditions who have atypical self-care demands and executive dysfunction may be at heightened risk for adaptive functioning difficulties compared to peers with typical self-care needs (Reem A Tarazi et al., 2007). Survivors of childhood cancer are at-risk for developing various chronic health conditions (Hudson et al., 2013), including pulmonary, cardiac, endocrine, and nervous system diseases (Diller et al., 2009; Hudson et al., 2003; Hudson et al., 2013; Oeffinger et al., 2006; Oeffinger et al., 2003; Oeffinger et al., 2008), and may subsequently show differential patterns of adaptive functioning based on the condition and its severity, and typical versus atypical self-care needs.

Similarly to adaptive functioning, academic achievement performance indicated impairments compared to population norms, although mean performance fell within the average range in the overall sample, as previously shown in the literature (Jacola et al., 2021; Kingma et al., 2001; Spiegler et al., 2006). 25% and 41.7% of participants showed impairments in word reading and math calculation, respectively. Math calculation was significantly positively correlated with performance-based executive functioning including verbal fluency and processing speed. Two underlying processes of verbal fluency tasks include processing speed (Delgado-Álvarez et al., 2021) and the facilitation of information retrieval from memory (Delgado-Álvarez et al., 2021; Patterson, 2011), both of which have been implicated in math calculation performance. In the general population, processing speed has consistently emerged as a significant predictor of math calculation skills, particularly as it interacts with working memory to increase available short-term storage space necessary for performing mental operations (Berg, 2008). Further, processing speed and calculation ability are more robustly related early on in arithmetic development, when greater emphasis is placed on the automaticity of number representations. As children advance in their calculation skills, the influence of processing speed subsides, and other cognitive abilities such as working memory become of greater importance for performing calculation problems (Berg, 2008). These differential contributions of processing speed and working memory throughout math development may explain the lack of a relationship between calculation performance and working memory in our study. Of our sample, 41.7% showed impairment in math calculation, perhaps suggesting that much of our sample is in the early stages of arithmetic development. Moreover, our findings may suggest reduced automaticity in calculation skills in ALL survivors, indicated by greater contributions of processing speed and information retrieval from memory as opposed to other cognitive skills such as working memory.

In contrast, word reading was not related to performance-based or parent-rated measures of executive functioning, consistent with studies conducted in the general population (Sesma et al., 2009). Although there is strong evidence for the influence of executive functioning in reading comprehension (Arrington et al., 2014; Christopher et al., 2012; Jacobson et al., 2017; Locascio et al., 2010; Messer et al., 2016), the literature regarding the contribution of executive functioning to word reading is mixed (Haft et al., 2019; Sesma et al., 2009). Rather, lower-level skills such as phonological processing may play a greater role in single word reading given that it is inherently a less complex task than comprehension of a passage (Sesma et al., 2009). Studies also suggest that executive functioning may contribute to word reading to a greater extent in kindergarten during the early stages of reading development, when word decoding is a highly effortful task (Haft et al., 2019). As decoding becomes more automatic throughout reading development, greater mental resources are made available for higher-level processes necessary for reading comprehension such as inference making, reasoning, and organization of information within working memory (Cirino et al., 2019; Kendeou et al., 2014). Overall, these findings are in line with previous work demonstrating that executive functioning is not predictive of word reading in school-aged children (Sesma et al., 2009). Moreover, we found that being without IEP support and older age at evaluation were correlated with greater word reading scores, and survivors without an IEP as well as female survivors showed better verbal fluency. These results can be explained by the finding that struggling readers and children with greater cognitive and/or academic difficulties are more likely to be provided with IEP support (O'connor & Yasik, 2007). Additionally, reading achievement generally improves with age (Guo et al., 2015), and male and female survivors of ALL may differ in the neurocognitive domains that are affected (van der Plas et al., 2021), potentially explaining our finding of better verbal fluency in female survivors.

Contrary to hypotheses, neighborhood-specific variables were not associated with adaptive functioning. One possibility for this finding may be that adaptive functioning is associated with other indices of socioeconomic status that were not explored in this study, such as parental education (Kesler et al., 2010) or insurance status (Jacola et al., 2021). Alternatively, adaptive functioning may develop independently of socioeconomic status, and is instead related to parent-rated executive functioning, as shown in the current study, or other factors such as chronic health conditions (van der Plas et al., 2021) or parenting styles (Long & Marsland, 2011). As previously mentioned, children with executive functioning deficits and atypical self-care needs in the presence of a chronic health condition, a so-called "double-deficit," are at greatest risk for adaptive functioning concerns (Reem A Tarazi et al., 2007). Parenting factors may also influence the degree to which caregivers offer their children opportunities to engage in and develop age-appropriate adaptive skills. A descriptive study of psychosocial adjustment to childhood cancer found that the majority of parents place fewer household demands on their children with cancer and allow greater leniency when compared to siblings (Chao et al., 2003); other quantitative and qualitative work has also found increased overprotection and setting fewer limits among parents of children with cancer (Hillman, 1997; Pelcovitz et al., 1998). However, neighborhood-specific variables, specifically area deprivation, did predict verbal fluency in follow-up analyses when child opportunity was removed from the model. Consistent with the broader literature on the impact of early life stress and socioeconomic status, greater neighborhood-level deprivation has been shown to adversely predict neurocognitive functioning and neurodevelopment of brain regions subserving executive functioning during key developmental periods in school-aged children (Vargas et al., 2020). Our findings provide preliminary evidence for the potential effects of area deprivation in survivors of childhood ALL, and further research is encouraged to expand on these findings with neuroimaging methods.

Lastly, we found that performance-based and parent-rated T-scores (cognitive flexibility, verbal fluency, working memory, and processing speed) fell within normal limits. However, mean performance-based global deficit fell above the 0.5 impairment cutoff, consistent with prior studies indicating scores above 0.5 to be a valid indicator of impairment in cancer survivors (Sharafeldin et al., 2018; Vardy et al., 2007). Interestingly, the least deficit was shown in working memory and the greatest deficit in cognitive flexibility, which is in contrast to prior reports indicating high rates of working memory impairments in survivors of childhood ALL (Krull et al., 2013; Krull et al., 2018). Further, contrary to working memory deficit scores on performance-based measures, parent-rated working memory fell within the range of clinical significance. Moreover, it is noteworthy that rates of impairment on performance-based executive functioning global deficit and parent-rated executive functioning were equal, with 52.3% of participants demonstrating impairment in each domain compared to the expected 16% showing impairment in the normal population. This provides further evidence for the notion that performance-based measures and parent ratings assess different constructs of executive functioning, although both complementary to one another and valuable for fully understanding one's cognitive and behavioral functioning (Miranda et al., 2015; Toplak et al., 2013).

Our study is not without limitations. First, we had a relatively small and homogenous sample with regard to disease and treatment factors, which limits generalizability of our findings to other survivors of childhood ALL (e.g., high-risk survivors) or pediatric cancer. Second, our sample may have been biased given that many participants were referred for neuropsychological assessment due to neurocognitive concerns. Third, we used neighborhood-specific variables and academic/IEP support as proxies of socioeconomic status, which provided a less comprehensive measure of socioeconomic status. Similarly, the performance-based measures of executive functioning used in this study (cognitive flexibility, verbal fluency, working memory, and processing speed) may be associated with adaptive functioning and academic achievement to a lesser extent than other aspects of executive functioning. Despite these limitations, the current study represents an important first step in examining the link between functional outcomes, executive functioning, and socioeconomic status. Proposals for future research include investigating functional outcomes in survivors of childhood ALL using larger samples, more comprehensive measures of socioeconomic status and additional areas of executive functioning, examining patterns of adaptive functioning in relation to chronic health conditions within ALL survivors, and integrating neuroimaging methods.

In conclusion, the current study expanded on prior work investigating functional outcomes (adaptive functioning and academic achievement) in survivors of childhood ALL to examine the associations with executive functioning and socioeconomic status. Impairments were shown across all functional outcomes for the overall group; however, group mean performance fell within normal limits. Within adaptive functioning, highest rates of impairments were shown in activities of daily living and leadership. Adaptive functioning was significantly positively correlated with parent-rated but not performance-based measures of executive functioning, potentially indicating that adaptive functioning draws more on the behavioral component of executive functioning than its cognitive component. Further, consistent with prior reports, male survivors were at increased risk for adaptive difficulties. With regards to academics, math calculation was significantly positively correlated with performance-based executive functioning, specifically verbal fluency and processing speed. Older survivors at the time of evaluation and those without IEP support also showed better word reading. Functional outcomes were not found to be related to socioeconomic factors. These findings add important insights to the growing literature on functional outcomes in survivors of childhood ALL. In the long-term, research and clinical efforts should focus on early screening of adaptive and academic difficulties, targeted intervention, and neuropsychological monitoring to support pediatric survivors' neurocognitive and psychosocial development.

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Tables

Table 1. Conversion of T-Scores to Deficit Scores.

T-Score	Deficit Score	Impairment
≥40	0	Normal
39-35	1	Mild
34-30	2	Mild-to-Moderate
29-25	3	Moderate
24-20	4	Moderate-to-Severe

Global deficit score (GDS) is calculated by averaging deficit scores across each measure.

Table 2. Participant Demographic and Clinical Characteristics.

	N=44
	Mean (Range, SD)
Age at Evaluation (years)	11.11 (6-17, 2.879)
Age at Diagnosis (years)	3.34 (0-9, 2.199)
Years Post-Diagnosis	7.32 (3-16, 3.190)
Years Post-Treatment	4.64 (1-15, 3.293)
Gender	**N (%)**
Male	27 (61.4)
Female	17 (38.6)
Ethnicity	
Non-Hispanic White	32 (72.7)
African American	7 (15.9)
Hispanic	5 (11.4)
Risk Group	
Low Risk	3 (6.8)
Standard Risk	41 (93.2)
CNS Status	
CNS 1	43 (97.7)
CNS 2	1 (2.3)
Treatment	
IT MTX	44 (100)
School Supports	
IEP Support	12 (27.3)

Abbreviations: CNS, central nervous system; IT MTX, intrathecal methotrexate; IEP, Individualized Education Plan.

Table 3. Significant Partial Correlation Results among Executive Functioning and Functional Outcomes.

Outcome Variable	Predictor Variable	Unstd Beta	SE	Std Beta	Partial Correlation Coefficient	*p* Value
Adaptive Skills Composite	GEC	0.545	0.092	0.648	0.694	**<0.001**
Adaptability	GEC	0.547	0.105	0.589	0.645	**<0.001**
Social Skills	GEC	0.434	0.119	0.466	0.508	**<0.001**
Leadership	GEC	0.393	0.120	0.459	0.469	**0.002**
ADL	GEC	0.657	0.086	0.771	0.778	**<0.001**
FC	GEC	0.356	0.103	0.456	0.490	**0.001**
Math Calculation	Verbal Fluency	0.394	0.180	0.441	0.378	**0.036**
Math Calculation	Processing Speed	0.527	0.204	0.493	0.439	**0.015**

Predictor variables are significant at $p<0.05$, while controlling for age at evaluation, age at diagnosis, sex, and VIQ. Parent-rated executive functioning (GEC) is significantly correlated with adaptive functioning. Performance-based executive functioning (verbal fluency and processing speed) is significantly correlated with math calculation. Abbreviation: ADL, activities of daily living; FC, functional communication; GEC, global executive composite.

Table 4. Demographic and Socioeconomic Predictors of Word Reading.

Predictor Variable	Unstd Beta	SE	Std Beta	t	*p* Value
ADI	-0.357	0.806	-0.085	-0.442	0.662
COI	1.049	1.532	0.128	0.685	0.499
IEP	11.272	3.766	0.465	2.993	**0.006**
Age Evaluation	-2.213	0.491	-0.580	-4.510	**<0.001**
Age Diagnosis	-0.997	0.823	-0.196	-1.211	0.236
Sex	2.646	2.927	0.121	0.904	0.374
VIQ	-0.176	0.127	-0.187	-1.384	0.177

Predictor variables are significant at $p<0.05$, while controlling for age at evaluation, age at diagnosis, sex, and VIQ. IEP status and age at evaluation significantly predict word reading. Abbreviations: ADI, area deprivation index; COI, child opportunity index; IEP, individualized education plan; VIQ, verbal IQ.

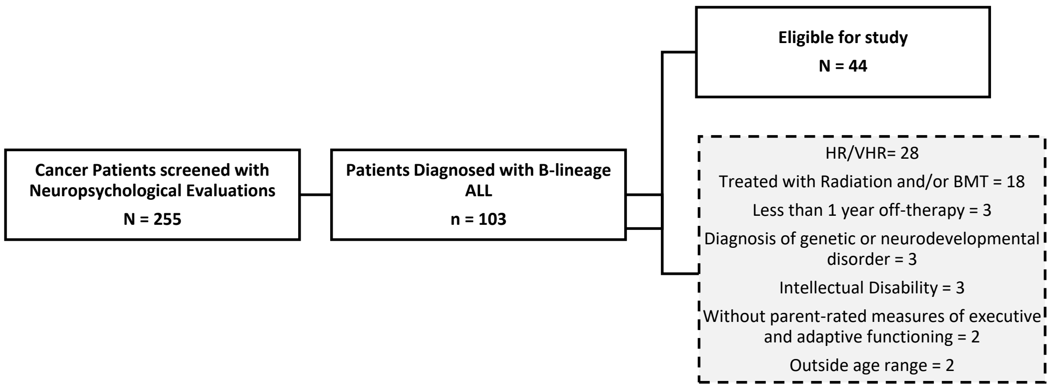
Table 5. Demographic and Socioeconomic Predictors of Verbal Fluency.

Full model					
Predictor Variable	Unstd Beta	SE	Std Beta	t	*p* Value
ADI	1.767	0.876	0.386	2.017	0.051
COI	-1.384	1.815	-0.143	-0.763	0.451
IEP	8.927	4.048	0.337	2.206	**0.034**
Age Evaluation	-0.486	0.546	-0.117	-0.889	0.380
Age Diagnosis	0.171	0.802	0.031	0.213	0.832
Sex	-7.340	3.218	-0.302	-2.281	**0.029**
VIQ	-0.151	0.154	-0.136	-0.981	0.334
Model with COI excluded[a]					
ADI	1.289	0.609	0.282	2.118	**0.041**
IEP	9.830	3.848	0.371	2.554	**0.015**
Age Evaluation	-0.420	0.536	-0.102	-0.782	0.439
Age Diagnosis	-0.010	0.762	-0.002	-0.013	0.990
Sex	-7.252	3.198	-0.298	-2.268	0.029
VIQ	-0.149	0.153	-0.135	-0.978	0.335

Predictor variables are significant at $p<0.05$, while controlling for age at evaluation, age at diagnosis, sex, and VIQ. IEP status and sex significantly predict verbal fluency in the full model.
[a] Significant effect of area deprivation when child opportunity was removed from the model.
Abbreviations: ADI, area deprivation index; COI, child opportunity index; IEP, individualized education plan; VIQ, verbal IQ.

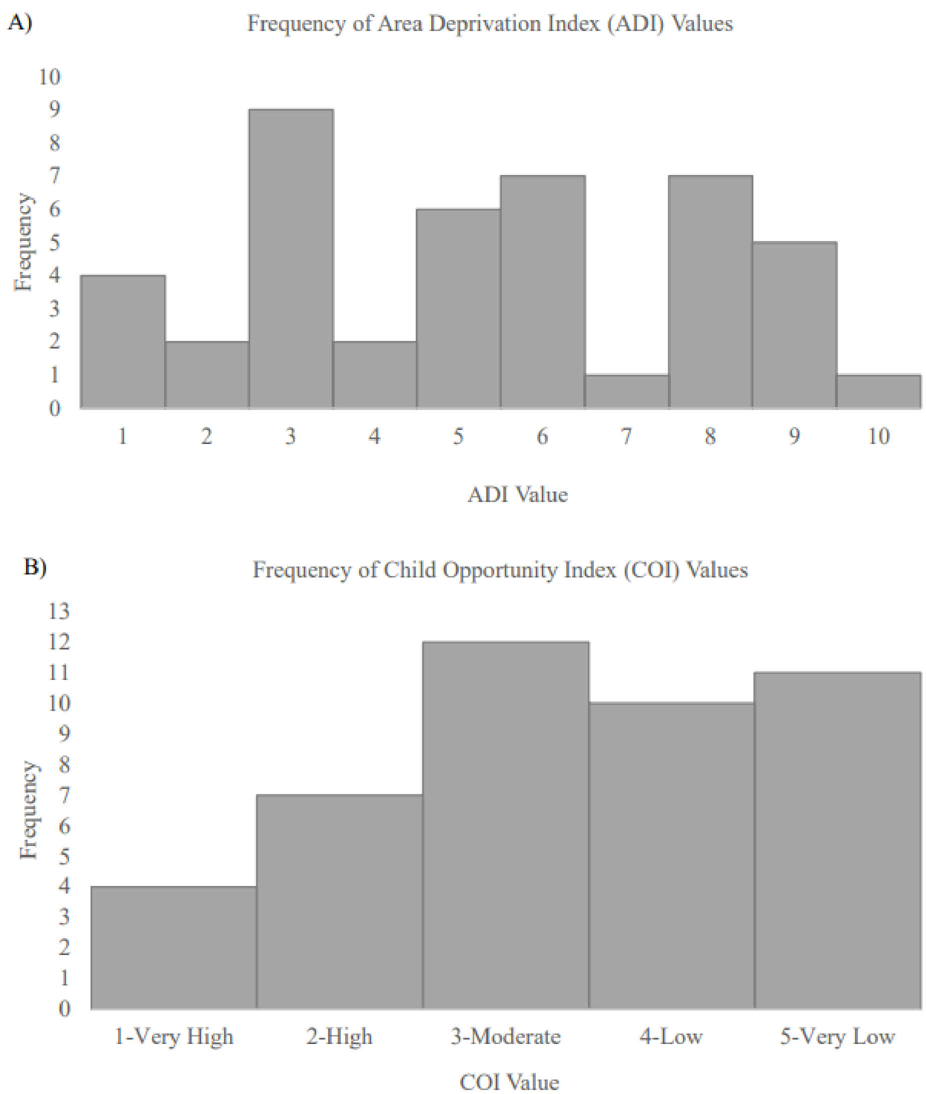
Figures

Figure 1. Study Enrollment.



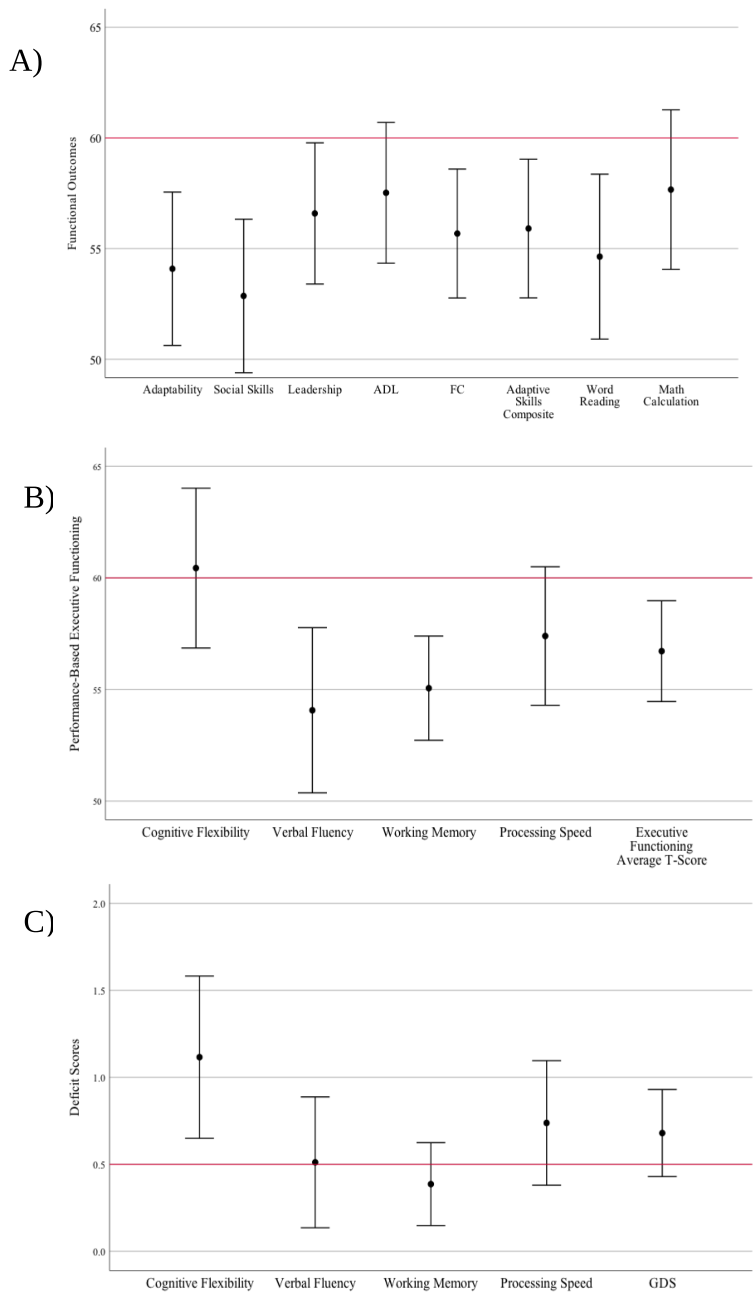
Abbreviations: HR/VHR, high risk/very high risk; BMT, bone marrow transplant

Figure 2. Area Deprivation and Child Opportunity Frequencies.

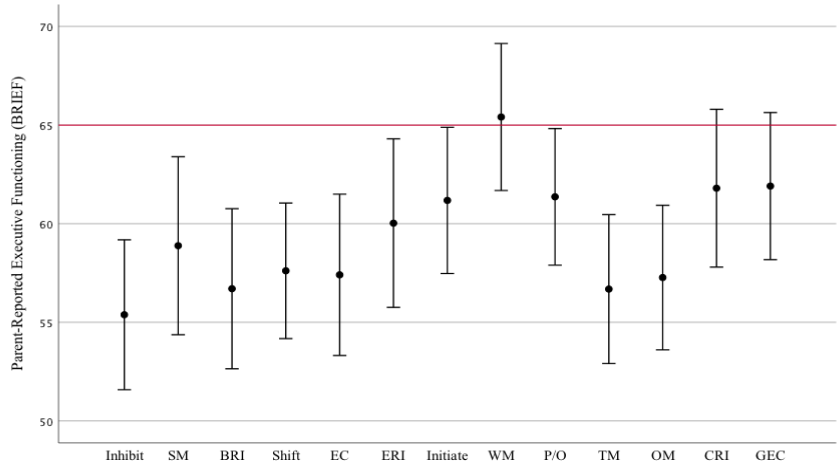


Frequency of A) ADI and B) COI (N=44). ADI ranges from 1-10 and COI ranges from 1-5; lower scores indicate lower disadvantage and greater opportunity.

Figure 3. Means and 95% Confidence Intervals of Functional Outcomes and Executive Functioning.



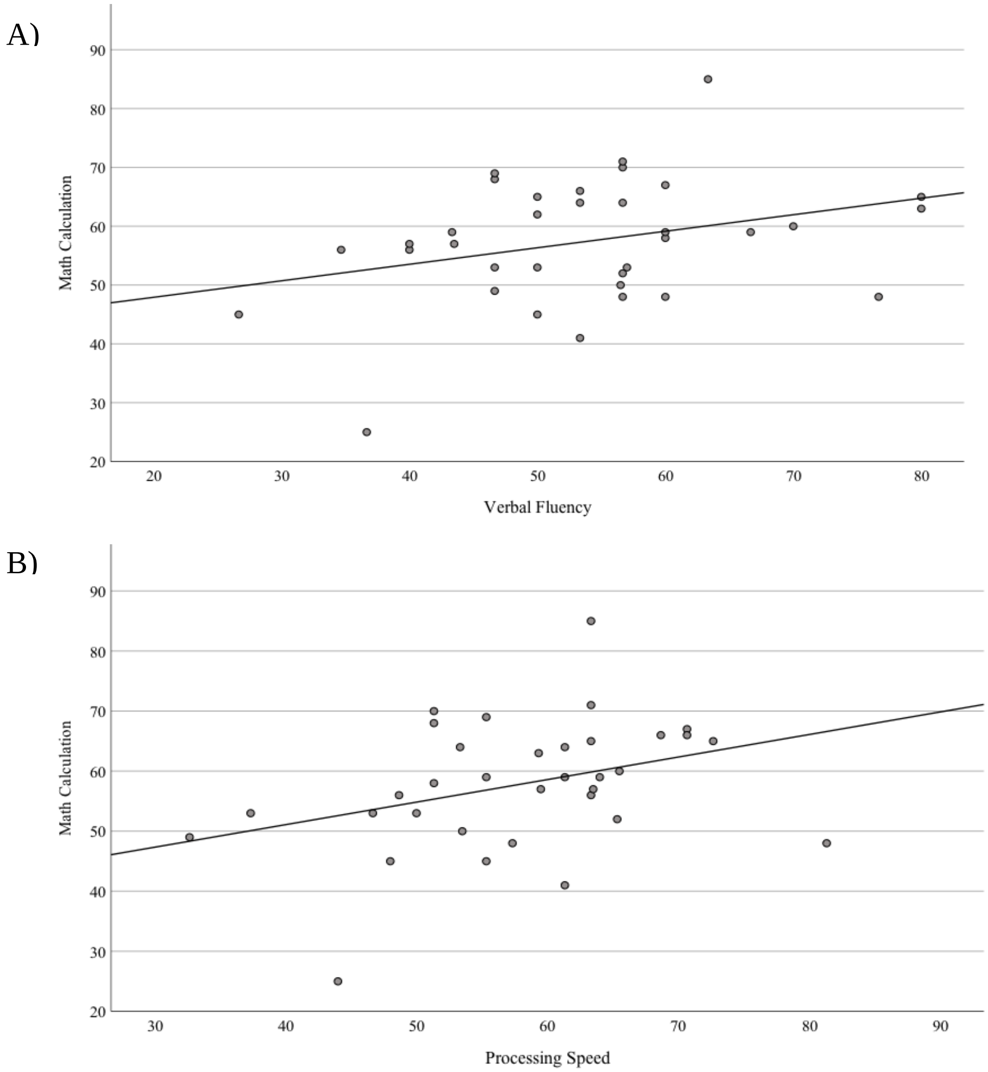
D)



Means and 95% confidence intervals of A) functional outcomes including adaptive functioning on the BASC and academic achievement, B) performance-based executive functioning T-scores, C) performance-based executive functioning deficit scores, and D) parent-rated executive functioning scores indicated on the BRIEF. Scores above red line indicate impairment.

Abbreviations: ADL, activities of daily living; FC, functional communication; GDS, global deficit score; SM, self-monitor; BRI, behavioral regulation index; EC, emotional control; ERI, emotional regulation index; WM, working memory; P/O, plan/organize; TM, task-monitor; OM, organization of materials; CRI, cognitive regulation index; GEC, global executive composite.

Figure 4. Math Calculation and Performance-Based Executive Functioning Correlations.



A) Math calculation was significantly correlated with verbal fluency, $r_{partial}$ (32) = 0.378, p<0.05, and B) processing speed, $r_{partial}$ (31) = 0.439, p < 0.05, when controlling for age at evaluation, age at diagnosis, sex, and VIQ.

APPENDIX: MEASURES USED

Performance-Based and Parent-Rated Measures.

Domain	Subdomain	Measure
Intelligence	Full-Scale	WISC-IV, WISC-V, WAIS-IV, SB-5, DAS-I DAS-II
	Verbal IQ	WISC-IV, WISC-V, WAIS-IV, SB-5, DAS-I DAS-II
Academic Achievement	Word Reading	WIAT-III Word Reading, WJ-IV Letter-Word Identification
	Math Calculation	WIAT-III Numerical Operations, WJ-IV Calculation
Performance-Based Executive Functioning	Cognitive Flexibility	D-KEFS Trail Making Test Condition 4: Number-Letter Switching
		Trails B
		TEA-Ch Opposite Worlds or TEA-Ch-II Red & Blues, Bags & Shoes
		NEPSY and NEPSY-II Animal Sorting
	Working Memory	WISC-IV, WISC-V, or WAIS-IV Working Memory Index
		DAS-II Recall of Sequential Order and Recall of Digits Backward Subtests
		SB-5 Working Memory Composite
		DAS-II Recall of Digits Forward
	Verbal Fluency	D-KEFS Verbal Fluency Test Condition 3: Category Switching
		NEPSY-II Word Generation Test Semantic
		COWAT Animals
	Processing Speed	WISC-IV, WISC-V, or WAIS-IV Processing Speed Index
Parent-Rated Executive Functioning		BRIEF-1 and BRIEF-2
Adaptive Functioning		BASC-2 and BASC-3 Adaptive Scale

Abbreviations: BASC, Behavior Assessment System for Children; BRIEF, Behavior Rating Inventory of Executive Function; COWAT, Controlled Oral Word Association Test; DAS, Differential Ability Scales; D-KEFS, Delis-Kaplan Executive Function Scale; NEPSY, Developmental Neuropsychological Assessment; SB-5, Stanford-Binet Intelligence Scales; TEA-Ch, Test of Everyday Attention in Children; WAIS, Wechsler Adult Intelligence Scale; WIAT-III, Wechsler Individual Achievement Test; WISC, Wechsler Intelligence Scale for Children; WJ-IV, Woodcock-Johnson IV Tests of Achievement.