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Executive Function In Survivors Of Childhood Acute Lymphoblastic Leukemia

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Abstract

BACKGROUND Childhood acute lymphoblastic leukemia (ALL) survivors are at risk for impaired executive function, but it is unclear how to best screen for such impairment. We sought to determine 1) the reliability of neurocognitive assessment by performance-based testing versus parent report, and 2) how the measures relate to everyday function.

METHODS 256 survivors of standard risk childhood B-ALL (mean age 13.9 years at evaluation) were evaluated for executive function with three performance-based measures (Wechsler Intelligence Scale for Children-IV (WISC-IV), Controlled Oral Word Association Test, and Conners' Continuous Performance Test-II) and one parent-report measure (Behavior Rating Inventory of Executive Function (BRIEF)). The intra-class correlations between measures were assessed. The relation of the measures to the use of special education services and stimulants was analyzed with multivariate logistic regression.

RESULTS The reliability between performance-based and parent-reported measures was poor, with the highest agreement observed between the WISC-IV Working Memory Index and the BRIEF-Working Memory Scale (kappa=0.143). The use of special education services was significantly associated with impairment indicated by the BRIEF-WM Scale (odds ratio (OR) = 5.94, 95% confidence interval (CI): 2.97, 12.78) and the WISC-IV WM Index (OR = 3.56, 95% CI: 1.61, 7.85). Stimulant use was significantly associated with three BRIEF scales (WM, Inhibit, and Metacognition), but no performance-based measures.

CONCLUSIONS Performance-based and parent-reported measures identified different ALL survivors with executive function impairment. The association between the parent-reported BRIEF measures and the use of special education and stimulants suggests that this instrument has an important value for surveillance.

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BACKGROUND

Over 90% of children with acute lymphoblastic leukemia (ALL) will be long-term survivors, [1] but modern therapy consisting of frequent intrathecal chemotherapy, intensive systemic chemotherapy, and, occasionally, cranial radiation, can exert neurotoxic effects.[2] As a result, ALL survivors are at an increased risk for neurocognitive impairment as a late complication of their therapy. Affected cognitive domains include processing speed, attention, memory, fluency and cognitive organization.[3] Each of these specific domains contributes to overall executive function, "the cognitive abilities necessary for goal-directed behavior and adaptation to a range of environmental changes and demands".[4] Difficulty with executive function in childhood cancer survivors has been linked to reduced emotional regulation,[5] a decreased likelihood of living independently as adults, marrying, achieving higher education, and gaining employment.[6-10]

Neurocognitive surveillance is recommended by the Children's Oncology Group Long-Term Follow-Up Guidelines for all childhood ALL survivors because of past neurotoxic therapy.[11] The results of the assessment are used to determine the extent of neurocognitive evaluation necessary. Ultimately, results are used to determine the need for accommodations in school (e.g., extra time for work), special education services, and, when appropriate, other intervention strategies aimed at ameliorating cognitive function such as computer-based cognitive behavioral rehabilitation [12] or stimulants by prescription.[13] Both neuropsychological testing and patient report (or proxy report) are used to screen for executive function, but it is unclear which approach is optimal.

Historically, performance-based neuropsychological testing (usually by a psychologist) has been considered the "gold standard" measurement of executive function. Well-validated and

standardized measures of executive function are routinely administered to patients to assess functioning, and identify children with deficits.[14-19] However, performance-based testing requires significant professional resources and can be costly and time consuming. In addition, children may perform better in these test situations than "real world" settings.[20] Therefore, neuropsychological tests may be limited in the ability to identify children with meaningful impairment or those at risk for not meeting age- and developmentally appropriate goals.

Executive function assessed by patient/proxy report involves completing surveys regarding difficulty in real-world situations. The Behavior Rating Inventory of Executive Function, [21] a standardized parent-report measure, has been used to assess the executive function of pediatric patients with a variety of conditions.[22] Parent-report measures such as the BRIEF offer several benefits. Scales and questionnaires can be mailed to respondents, require a limited amount of training to administer and score, and capture the real-world manifestation of functions such as working memory and task initiation. However, there is concern that anxiety about their child's illness may alter parents' assessment of their child's executive function, as suggested by increased levels of reported impairment reported by parents compared with teachers.[23] Another concern regarding parent report is reduced expectations of child's performance and function, resulting in deflated reporting of impairment.[24]

Further research is needed to determine how to best screen for executive function in survivors of childhood ALL as it relates to meaningful impact on everyday life. We had a unique opportunity to address this question in a large patient sample from a multi-site long-term follow-up study of ALL patients treated without cranial radiation. In this study, we determined the reliability between performance-based and parent-reported measures of executive function, and evaluated how some dimensions of executive function, specifically working memory, fluency,

and impulse control measured by the two different approaches, relate to the use of special education services and stimulants.

METHODS

Study Population

Included in this study are 256 childhood ALL patients who were enrolled in the Children's Oncology Group clinical trial protocols 1922 and 1952, which were open March 1993 - August 1995 and May 1996 - February 2000, respectively. Patients were eligible for the current study if they were diagnosed at one of the 22 designated institutions, were in first remission, and were 6-16.99 years of age at the time of their executive function evaluation. Other inclusion criteria included no history of central nervous system leukemia, no history of cranial radiation, one year or longer since cessation of therapy, no history of pre-existing developmental disorders (e.g., Down Syndrome, developmental delay), and no history of very low birth weight (<1500 grams). This study methodology has been previously described.[25-27] The age restriction corresponds to the validated age ranges of the standardized neuropsychological instruments used in the executive functioning evaluation. Informed consent and assent were obtained for all study participants. The institutional review boards of all participating institutions approved the study procedures and documents.

Data Collection

Parents of the participating childhood ALL patients completed a questionnaire about the demographic characteristics and medical history of their children. Parents were asked about their marital status, education, and income. This questionnaire confirmed that the child was developing normally before the ALL diagnosis as an additional verification of eligibility for this

study. In addition, parents provided information on their child's neurologic events, use of special education services, and psychotropic drug use during and after ALL therapy.

The patients underwent a comprehensive, half-day, neurocognitive assessment supervised by a licensed psychologist. This evaluation was conducted at no cost to the patients. The evaluation included, among others, three performance-based tests: the Wechsler Intelligence Scale for Children (WISC-IV), the Controlled Oral Word Association Test (COWAT), and the Conners' Continuous Performance Test (CPT II). In addition, parents of patients completed the Behavior Rating Inventory of Executive Function (BRIEF), a standardized parent-report measure (Table 1).

Table 4 displays impairment categories based on validation studies of these instruments [16, 21, 28, 29]

The WISC-IV: Performance-Based

Patients were asked to perform two tasks from the WISC-IV, [28] Digit Span and Letter-Number Sequencing, which comprise the Working Memory Index. Digit span is a measure of attention and working memory and requires patients to listen to and then repeat series of numbers of increasing length forwards and then backwards.[28] Letter number sequencing measures attention and working memory. Children listen to a series of letters and numbers and have to reorganize the numbers in numerical order followed by the letters in alphabetical order.[28]

The COWAT: Performance-Based

This test is a measure of verbal fluency as measured by an individual's ability to generate words beginning with a specific letter. [29] COWAT performance is involves dimensions of

executive function such as cognitive flexibility, strategy utilization, suppression of interference and response inhibition, and it has also been proposed to involve the working memory processes as well. [29]

The CPT-II V.5: Performance-Based

The CPT-II [16] is administered on a computer. Patients are required to press a key as quickly as possible in response to target letters presented on the computer screen or to refrain from pressing the key when non-target letters are presented. It measures attention, impulse control and reaction time. The subscale "Total Commission Errors" measures impulse control, and "HIT Reaction Time" measures information processing efficiency. [16]

The BRIEF: Parent-Reported

The BRIEF, [21] contains 86 items comprising eight scales regarding inhibitory control, ability to shift from one task to another, emotional control, initiation of activity, working memory, planning/organizing, and work-checking habits. [21]

Three BRIEF subscales, and one composite scale were used to measure executive function in this study. These subscales included Working Memory, a 10-item scale; Initiate, an 8-item scale used as a measure of fluency; and Inhibit, a 10-item scale used as a measure of impulse control. The Metacognition Index reflects an individual's ability to initiate activity, to sustain working memory, and to organize one's materials and environment, among others. [21]

Statistical Analyses

Patient characteristics such as age, sex, and history of ALL therapy were summarized as appropriate.

Reliability of parent-reported as compared to performance-based measures of impaired functioning was examined using Cohen's kappa, a measure of inter-rater agreement.

Multivariate logistic regression models were used to examine the relationship between performance-based measures of executive function, parent-reported impairment, and patient's use of special education services and/or stimulants, adjusting for time since diagnosis, sex and race. Additionally, a backward stepwise logistic regression model was utilized to identify factors associated with a single outcome measure termed "everyday impairment," a combined measure of a positive history of special education services and/or stimulants.

All analyses were conducted using the software package SAS (version 9.3, Cary, North Carolina).

Results

Demographic and Clinical Characteristics

The 256 childhood ALL patients included in this study had a mean age of 12.5 years (SD = 2.4, median = 13) at the time of evaluation, and were on average about 9.19 years post diagnosis. There were slightly more females (53.0%, n = 136) than males (47.0%, n = 120). Of note, only one percent of the patients reported receiving special education services before treatment, as compared to 6.8% during treatment and 20.7% after treatment ($p < 0.001$) (Table 2).

Normative data from the general population for the WISC-IV, the COWAT, the CPT-II and the BRIEF were used to categorize impaired scores for each test or subscale. Statistically significant frequencies of impairment greater than the standard population were observed for the COWAT ($p = 0.001$), the BRIEF Working Memory subscale ($p = 0.005$), the BRIEF Initiate subscale ($p = 0.01$), and the BRIEF Metacognition Index ($p = 0.04$). Conversely, statistically

significantly lower frequencies of impairment were observed for the CPT-II Commissions and Omissions subscales ($p < 0.001$) (Table 3).

Impairment Classification According to Performance-Based Testing vs. Parent-Reported Measures

Reliability between impairment classified by performance-based testing versus parent-reported measures was assessed using Cohen's Kappa (Table 4). Of all the performance-based and the corresponding parent-reported pairs of executive function measures tested (n=7) only three pairs showed statistically significant agreement: the WISC-IV Working Memory Index and the BRIEF-Working Memory (kappa = 0.14), the WISC-IV Letter-Number Sequencing and the BRIEF-Working Memory (kappa = 0.12), and the Controlled Oral Word Association Test and the BRIEF Initiate (kappa=0.16). Even for these three pairs, the kappa values were close to 0, indicating poor reliability between the two different approaches.

Association between Impaired Cognition and Reported Use of Special Education Services

The relation between impaired cognition and reported use of special education services was assessed using multivariate logistic regression models, adjusting for age at evaluation (in years), gender, and race (white vs. non-white). Of the performance-based measures, impairment indicated by the WISC-IV Working Memory Index (odds ratio (OR) = 3.56; 95% confidence interval (CI): 1.61, 7.85; p=0.002) and Digit Span (OR = 3.99; 95%CI: 2.08, 7.65; $p < 0.001$) scales as well as the COWAT (OR = 3.70; 95%CI: 1.89, 7.26; $p < 0.001$) were found to be significantly associated with an increased likelihood of using special education services (Table 5). Impairment on three of the four BRIEF subscales was also significantly associated with the same outcome: Working Memory (OR = 5.94; 95%CI: 2.76, 12.78; $p < 0.001$), Inhibit (OR =

3.89; 95%CI: 1.59, 9.50; p = 0.003), and the Metacognition Index (OR = 3.80; 95%CI: 1.20, 8.57; p = 0.001).

Of the 60 patients receiving special education services after treatment, 21 (35.0%) were found to be clinically impaired based on the parent-report BRIEF, while only 15 (25.0%) were considered clinically impaired based on the performance-based WISC-IV Working Memory Index. Forty percent of these individuals (n = 24) were not identified as having impairment by either approach (i.e., performance-based or parent-reported measures) (Figure 1).

Association between Impaired Cognition and Reported Use of Stimulants

Impairment identified through performance-based measures was not associated with reported use of stimulants in this study population. In contrast, patients who were considered impaired based on one of the following three parent-reported scales from the BRIEF were significantly more likely to use stimulants: Working Memory (OR = 7.16; 95% CI 2.97, 20.28; p < 0.001), Inhibit (OR = 5.21; 95% CI 1.81, 14.98; p= 0.002), and the Metacognition Index (OR = 4.88; 95% CI 1.77, 13.40; p= 0.002) (Table 5).

Of the 23 patients who reported using stimulants, 12 (52.2%) were considered clinically impaired based on parent-reported BRIEF, and only 2 (8.7%) were identified as having clinically significant impairment based on the performance-based WISC-IV Working Memory Index (Figure 2).

Discussion

In this large cross-sectional study of childhood ALL survivors, we examined the utility of the BRIEF, a standardized parent-report instrument, as compared to performance-based measures to screen for executive function. Our analysis revealed that there is little concordance between

these two testing approaches as indicated by low kappa values. Both the performance-based and parent-reported measures were significantly associated with the use of special education services after adjusting for years since diagnosis, sex and race. However, the magnitude of association was larger for the parent-reported BRIEF Working Memory, Inhibit and Metacognition scales. For stimulant use, only parent-reported scales showed significant association. Our results suggest that parent report and performance based testing are complementary in identifying at risk patients. Parent-reported BRIEF scales identified more patients with executive function impairment who manifested as needing special education services and/or stimulants. If resources or psychological expertise is limited, the BRIEF is a useful and valuable instrument for surveillance in this population.

The current study not only examines concordance and discordance between two testing methodologies, but also considers the application of these tests in terms of ecological validity. Additionally, the study included a relatively large number of childhood ALL patients who were treated with contemporary regimens, and had availability of high quality data on both performance-based and parent-reported measures. Due to the size of the study population, there was also the ability to examine and control for multiple potential confounders in the analyses.

Consistent with studies in other populations,[20] scores on the parent-reported measures in this ALL population were significantly different from the standard normative population, reflecting more impairment in this group. Our results also indicate that parents rated their children as displaying more impairment than suggested by results of performance-based measures. Parents may be reporting higher levels of impairment, as their responses are based on continual observations of their child's behavior in a real life setting, as compared to performance-based measures, which occur in a structured environment, or "ideal" conditions.

Others have hypothesized that parental expectations of "normal behavior" may be altered as a result of their child's disease and the trauma associated with it; however, our study indicates that they may be even more sensitive to deficits in their children.

Current findings indicate that performance-based measures were only significantly associated with reported use of special education services only, while the parent-reported BRIEF was associated with the use of both special education services and stimulants. Our findings differed from previous reports. Krull et al. compared the parent-reported Childhood Symptom Inventory to a range of performance-based neuropsychological tests in 240 survivors of childhood cancer. [30] This report concluded that the parent-report assessment was inferior, but this instrument was primarily designed to measure emotion and behavior. Furthermore, the two assessment approaches were compared to achievement scores from the clinical testing environment, instead of everyday function. Howarth et al. studied the utility of the BRIEF in detecting working memory problems among 50 childhood brain tumor survivors. [20] The results of this study similarly showed only modest correlations between parent-reported impairment and performance-based impairment, but in this population, the BRIEF under-classified the number of patients with working memory impairment. This study was limited in that it only examined one aspect of executive function, working memory, which may be disproportionately affected in children who are treated with conformal radiation therapy, as compared to our study sample.

In a study of 199 children with NF1, functional impairment as defined by parent report on the BRIEF, detected different children than were detected as impaired by cognitive testing[31]. As in the current study, there is support that extrapolating real life impairment from performance-based tests may has its limitations.

Our results do not support a gold standard strategy for the measurement of executive function in childhood ALL survivors. The performance-based and parent-reported measures identified different patients as impaired, with minimal overlap. The value of the parent-reported BRIEF was confirmed, as it was significantly associated with the use of special education services and stimulants in survivors. Given the considerable cost (often not reimbursed by insurance), time, and professional expertise needed for traditional neuropsychological testing, one strategy could be to use the BRIEF for routine surveillance in patients with a history of neurotoxic treatment exposures who do not complain of acute difficulties. Children with evidence of impairment on the BRIEF could then undergo follow-up performance-based neuropsychological testing for a more complete evaluation. Conversely, in settings where performance-based measures are readily available, there is independent added benefit to additionally requesting completion of the BRIEF as it has been indicated as an important surveillance tool that may indicate the need for more comprehensive neuropsychological testing.

We acknowledge several limitations. First, this study employed a cross-sectional design, which made it infeasible to examine any changes in parent-reported executive function impairment over time. However, our primary focus was to compare two approaches for evaluation at a singular point in time, so for the purposes of this analysis, a measurement of change was not required. Additionally we recognize that stimulant use may alter the results of performance-based testing, as children who are impaired may fall into normal ranges due to the effects of the medications. However, the literature has suggested that stimulants are not as effective in cancer survivors, and thus performance-based testing should still indicate impairment for many of those taking stimulants.[32] Finally, the use of special education services and stimulants are only two measures of everyday function. Some have argued that factors such as

socioeconomic status or parental education may effect who gets referred for these specialized services, with children of parents with higher education or higher SES having a higher rate of referral. Our data did not show any significant associations between SES nor parental education with the reported use of special education services or use of stimulants. Other important ones that were not available in our study include attainment of goal target scores on state administered tests of achievement, eventual highest level of educational achievement, future income, and later ability to live independently. Finally, we acknowledge that special education and stimulant history are meant as proxies for clinically important impairment. However, though parental education and advocacy can also affect referral for these services/therapies, there was not a significant relationship between income or parental education level and the use of special education services or stimulants.

In a population at high risk for cognitive impairment, such as childhood ALL survivors, there is a strong need for a feasible and ecologically valid form of surveillance. The lack of concordance between the parent-reported and performance-based measures highlights the complexity of evaluating domains of executive function, and illustrates the value of comprehensive testing. When resources are more limited, our results suggest that the parent-reported BRIEF, could detect real life impairment, and should be used to supplement performance-based measures.

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Table 1: Summary of Standardized Tests Used to Measure Executive Function

Measure (with subscales as applicable)	**Method of Assessment**	**Construct Measured**
Wechsler Intelligence Scale for Children-IV		
Working Memory Index	Performance	Working Memory
Letter Number Sequencing	Performance	Working Memory
Digit Span	Performance	Working Memory
Controlled Oral Word Association Test	Performance	Initiation/Fluency
Conners' Continuous Performance Test-II		
Omissions	Performance	Inattention
Commissions	Performance	Inhibition/Impulsivity
HIT Reaction Time	Performance	Inattention/Impulsivity
Behavior Rating Inventory of Executive Function		
Working Memory	Parent Report	Working Memory
Initiate	Parent Report	Initiation
Inhibit	Parent Report	Inhibition
Metacognition Index	Parent Report	Working Memory/ Initiation

Table 2: Demographic Characteristics of Participants (n=256)

	Mean (SD) or N (%)
Age at Diagnosis (years)	3.90 (1.65)
Elapsed time between diagnosis and evaluation (years)	9.19 (1.37)
Age at Evaluation (years)	12.5 (2.44)
Sex (n, %)	
Female	136 (53%)
Male	120 (47%)
Race/ethnicity	
White, non-Hispanic	207 (82%)
Non-white	44 (18%)
Stimulant Use After Treatment	23 (9.0%)
Special Education Services	
Before Treatment	3 (1.2%)
During Treatment	17 (6.8%)
After Treatment	52 (20.7%)

Table 3: Overall Neuropsychological Performance on Performance-Based and Parent-Report Instruments

	Normative Standardized Population		**Study Sample**		**P-value**
	Definition of Impaired Scores	**Expected Frequency Clinically Impaired**	**T-score Mean (SD)**	**Clinically Impaired N (%)**	
Wechsler Intelligence Scale for Children-IV					
Working Memory Index	< 85 (1SD below mean)	98.2 (14.4)	16%	38 (14.8)	0.707
Letter Number Sequencing	< 7 (1SD below mean)	10.1 (2.8)	16%	32 (12.5)	0.26
Digit Span	< 7 (1SD below mean)	9.5 (2.8)	16%	58 (22.6)	0.06
Controlled Oral Word Association Test	< 7 (1SD below mean)	9.3 (2.7)	16%	72 (28.0)	0.001
Conners' Continuous Performance Test-II					
Omissions	>60 (1SD below mean)	46.4 (8.2)	15%	10 (3.9)	<0.001
Commissions	>60 (1SD below mean)	42.4 (15.3)	15%	10 (3.9)	<0.001
HIT Reaction Time	>60 or <40 (1SD above/ below mean)	42.9 (17.0)	15%	25 (9.8)	<0.001
Behavior Rating Inventory of Executive Function					
Working Memory	>65 (1.5SD above mean)	52.5(12.9)	8.8%	44 (17.2)	0.005
Initiate	>65 (1.5SD above mean)	51.7 (11.4)	8.9%	42 (16.4)	0.01
Inhibit	>65 (1.5SD above mean)	49.5 (12.2)	8.8%	26 (10.1)	0.65

Metacognition Index	>65 (1.5SD above mean)	50.8 (13.5)	9.5%	40 (15.6)	0.03

Table 4: Kappa Values for Reliability between Parent-Reported and Performance-Based Measures

	Behavior Rating Inventory of Executive Function Subscales (Parent-Reported)				
Performance Based Tests	Working Memory	Initiate	Inhibit	Metacognition Index	P-value
WISC-IV[a] Working Memory Index	0.15	na[b]	na	na	0.02
WISC-IV Letter-Number Sequencing	0.11	na	na	na	0.05
WISC-IV Digit Span	0.12	na	na	na	0.08
Controlled Oral Word Association	na	0.16	na	na	0.007
CPT-II[c] Commission	na	na	-0.005	na	0.47
CPT-II Hit Reaction Time	na	na	na	0.02	0.36
CPT-II Omission	na	na	na	0.002	0.49

[a]WISC-IV: Wechsler Intelligence Scale for Children IV

[b]na: not applicable

[c]CPT-II: Conners' Continuous Performance Test II

Table 5: Relation of Performance-Based and Parent-Reported Measures of Executive Function to Reported Use of Special Education Services and Stimulants*

		History of Special Education Services			History of Stimulant Use		
Measure	**Method of Assessment**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
WISC-IV[a] Working Memory Index	Performance	3.56	(1.61,7.85)	0.002	1.74	(0.38, 9.68)	0.47
WISC-IV[a] Digit Span	Performance	3.99	(2.08, 7.65)	<0.001	1.51	(0.59,3.96)	0.38
Controlled Oral Word Association Test	Performance	3.70	(1.89, 7.26)	<0.001	1.39	(0.55,3.48)	0.49
BRIEF[c] Working Memory	Parent	5.94	(2.76, 12.78)	<0.001	7.16	(2.97, 20.28)	<0.001
BRIEF[c] Inhibit	Parent	3.89	(1.59, 9.50)	0.003	5.21	(1.81, 14.98)	0.002
BRIEF[c] Metacognition Index	Parent	3.80	(1.20, 8.57)	0.0012	4.88	(1.77, 13.40)	0.002

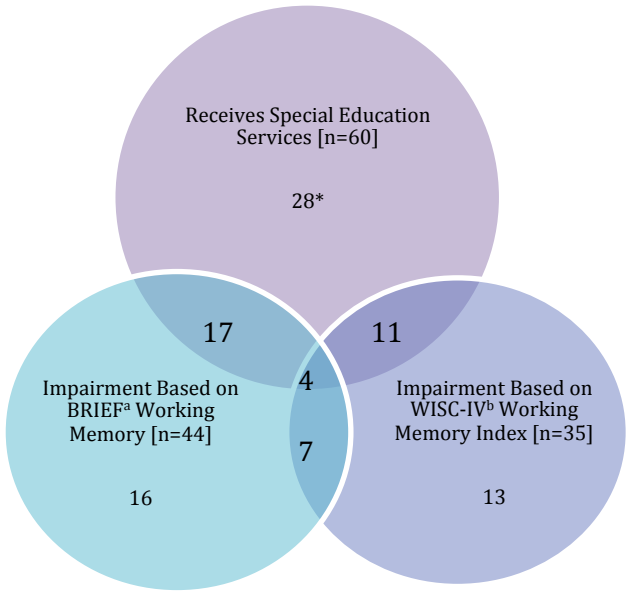
*Results based on multiple logistic regressions adjusted for time since diagnosis, gender and race

[a]WISC-IV: Wechsler Intelligence Scale for Children IV

[b] ns: not significant

[c]BRIEF: Behavior Rating Inventory of Executive Function

Figure 1: Impairment Detected by the BRIEF Working Memory Index and the WISC-IV Working Memory Index as Compared to Reported use of Special Education Services

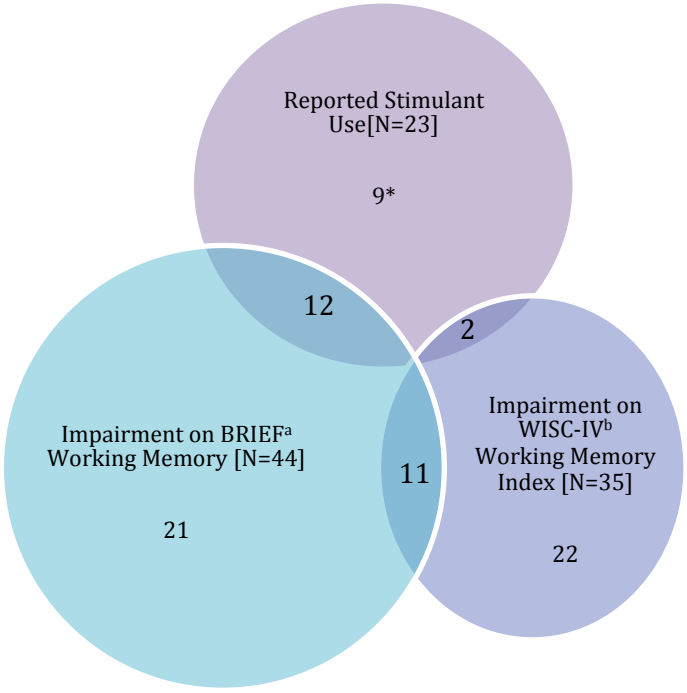


* Numbers indicated the number of children in each category (eg: "28" in the Receives Special Education Services indicates that 28 children receive special education services, but did not have impairment indicated on either instrument; "17" indicates that 17 children receive special education services, and also were considered impaired on the BRIEF working memory index)

[a]Behavior Rating Inventory of Executive Function (Parent-Report)

[b]Wechsler Intelligence Scale for Children

Figure 2: Impairment Detected by the BRIEF Working Memory Index and the WISC-IV Working Memory Index as Compared to Reported Stimulant Use



* Numbers indicated the number of children in each category (eg: "20" in Reported Stimulant Use indicates that 20 children use stimulants, but did not have impairment indicated on either instrument; "12" indicates that 12 children receive special education services, and also were considered impaired on the BRIEF working memory index)

[a]Behavior Rating Inventory of Executive Function (Parent-Report)

[b]Wechsler Intelligence Scale for Children