1. STUDY TITLE: *Reliability and validity of a short neurocognitive rating scale in the Childhood Cancer Survivor Study*.

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Group: Neuropsychology

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3. BACKGROUND AND RATIONALE:

The Behavior Rating Inventory of Executive Function (BRIEF) is a widely employed questionnaire designed to assess real-world aspects of executive dysfunction.[1] The outcome of this questionnaire includes two overall indices: a Behavioral Regulation Index (BRI) and a Metacognition Index (MI). In the adult version of this measure (BRIEF-A) the BRI is comprised of three individual scales (Inhibit, Shift, and Emotional Control), while the MI is comprised of five individual scales (Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials). The BRIEF-A was standardized on a normative sample of 1,050 adults aged 18 to 90 years, and included both Self-Report and an Informant Report version of the test.[2] Reliability and validity indices were acceptable, though slightly better for the Informant Report version.

The Follow-Up 2 questionnaire of the Childhood Cancer Survivor Study included a shortened and non-validated version of the BRIEF-A, intended to assess only self-report of executive dysfunction. Whereas the standardized version of the BRIEF-A includes 75 items,[2] the shortened CCSS-BRIEF included 25 items. Ten of the 25 items from the CCSS-BRIEF were identical to items on the BRIEF-A, while five additional items were similar to BRIEF-A items though had minor modifications in wording. These 15 items were selected in order to sample relevant scales from the BRIEF-A. The remaining 10 items from the CCSS-BRIEF were unique and were intended to collect report on processing speed and academic functioning.

Since it's collection in 2002, the CCSS-BRIEF has not been properly validated in a clinical sample. No manuscripts or abstracts have been submitted that describe the factor structure, internal consistency, concurrent validity, or predictive validity of this questionnaire. In order to use the CCSS-BRIEF to describe and document executive dysfunction in the CCSS sample, validation must first be conducted and reported in a peer referenced journal. This concept proposal presents a plan to conduct such validation of the CCSS-BRIEF.

The neurocognitive constructs intended to be sampled by the CCSS-BRIEF overlap with constructs evaluated by other currently validated questionnaires. The Behavior Problem Index (BPI) is such a questionnaire. The BPI is a subset of the Child Behavior Checklist[3] and has been recently validated in a CCSS sample.[4] In this recent report, the following five factors were identified: Depression/Anxiety, Headstrong, Attention Deficit, Peer Conflict, and Antisocial behavior. In the development of the BRIEF-A, comparison to the Clinical Assessment of Depression (CAD)[5] was conducted. The results of this comparison indicted that the BRI and Emotional Control subscale from the BRIEF-A significantly correlated with the CAD Anxiety scale and the Depressed Mood scale.[2] However, the MI factor from the BRIEF-A did not correlate with these CAD measures. The BRIEF has also been found to be sensitive to deficits seen in individuals diagnosed with Attention-Deficit/Hyperactivity Disorder (AD/HD).[6] In particular, the MI scale has been reported to correspond to attention problems, as indicated on the Behavior Assessment Scale for Children,[7] and to distinguish between individuals with primary attention problems and those with hyperactivity and disinhibited behavior.[8] Based on this literature, it is reasonable to expect the BRI and MI components from the BRIEF to correspond with reports of depression/anxiety and attention deficits, respectively. Thus, Construct Validity for the CCSS-BRIEF could be obtained by comparing the resultant factors to the established factors of Depression/Anxiety and Attention Deficit from the BPI. Although the BPI was collected years before the CCSS-BRIEF, the BPI measures were obtained during adolescence when adult-like behavior and cognitive patterns are becoming engrained.

As emotional symptoms can wax and wane, comparing the CCSS-BRIEF to simultaneously collected measures of emotional functioning could provide Concurrent Validity. The Brief Symptom Inventory – 18 (BSI-18) is a screening questionnaire designed to assess symptoms of depression, anxiety, and somatic complaints.[9] This measure was collected in the CCSS Follow-Up 2 survey at the same time the CCSS-BRIEF was obtained. A recent report using the CCSS sample has demonstrated the consistency of the Depression, Anxiety, and Somatic Complaints factors in adult survivors of childhood cancer.[10] Thus, it would be reasonable to expect these BSI-18 factors to correlate more strongly with the concurrent BRI scale than the MI scale from the CCSS-BRIEF.

Further validation of the application of an instrument to a new population can be obtained by determining how well is distinguishes between clearly identified groups of individuals that do and do not have deficits in the assessed constructs. Deficits in executive functions have been repeated reported in samples of adults with epilepsy[11-15], stroke[16-18], and cerebrovascular abnormalities[19-21]. Such deficits have also been documented in survivors of childhood cancer treated with cranial radiation[22, 23]. Within the CCSS sample, subgroups at high risk for executive dysfunction can be compared to groups at relatively low risk. Group differences on indices from the CCSS-BRIEF would support predictive validity of the instrument.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

4.1.1. To validate the CCSS-BRIEF in a sample of siblings and cancer survivors from the CCSS database.

4.2. Objectives:

4.2.1. To determine the reliable factor structure of the CCSS-BRIEF.
4.2.2. To determine the internal consistency of the CCSS-BRIEF factor(s).
4.2.3. To determine the concurrent and construct validity of the CCSS-BRIEF.
4.2.4. To determine the predictive validity of the CCSS-BRIEF.

4.3. Hypotheses:

4.3.1. The CCSS-BRIEF will demonstrate a factor structure that includes at least a Behavioral Regulation Index (BRI) and a Metacognition Index (MI). A third factor related to processing speed is also expected.
4.3.2. The internal consistency of items loading on the BRI and MI factors will be acceptable.
4.3.3. The BRI factor will be significantly correlated with additional measures of emotional regulation (e.g. select factors from the Behavior Symptom Inventory and the Behavior Problem Index), while the MI factor will be significantly correlated with previous measures of attention problems (i.e. the Attention Deficit factor from the Behavioral Problem Index).
4.3.4. Performance on the CCSS-BRIEF will predict group membership when comparing subsets of individual with and without clear neurologic complications (e.g. cerebrovascular abnormalities, epilepsy, cranial radiation).

5. ANALYSIS FRAMEWORK:

5.1. Outcome(s) of interest: The primary outcomes of interest are reliability and validity indices of the CCSS-BRIEF scale. Specifically, we plan to conduct the following analyses:

5.1.1. An exploratory principal components factor analysis will be conducted using all CCSS-BRIEF reports collected from siblings. This analysis will provide a framework for the number and structure of factors. This analysis will then be re-run using a Least-Squares method of extraction to clarify factor loadings. The CCSS database includes roughly 390 siblings who have completed the CCSS-BRIEF. Although this number is much smaller than the survivor sample, it remains sufficient for factor analysis. Convention in behavioral sciences is the use of 5-10 subjects per variable of interest for this multivariate approach. As we are using 25 questions or variables, a conservative estimate of 250 subjects would be needed.
5.1.2. The Internal Consistency of the factors derived from the sibling sample will be analyzed using Cronbach's Alpha.
5.1.3. A confirmatory factor analysis will then be conducted using all reports from cancer survivors. Again a Least-Squares method of extraction will be used,

followed by Cronbach's Alpha. Chi-Square analyses for Goodness of Fit will be used to conclude comparability of factor structure within the survivor sample. In addition, a comparable pattern of loadings with be expected in the confirmation as was found in the exploratory phase. Although primary vs. secondary loading may shift, a loading weight of ≥ .30 will be expected for items on the original factors.

5.1.4. For all factor analyses, we plan to use an Oblique rotation method (e.g. Promax), rather than an Orthogonal method. Justification for this is the factors expected from the CCSS-BRIEF will be subsets of overall Executive Functioning and are thus not independent constructs.

5.1.5. Construct validity of the CCSS-BRIEF will be further explored by comparing factors to previously established measures. For this purpose, we have elected to use the factors from the BPI. We will correlate factor scores generated from the CCSS-BRIEF to those obtained from the BPI scales of Attention Deficit, Head Strong, Peer-Conflict, Depression/Anxiety, and Antisocial behavior. There currently exists in the CCSS sample 1,730 individuals who completed the BPI during Baseline and the CCSS-BRIEF during Follow-Up 2. Here, we should expect some specificity in the pattern of correlations. That is, the CCSS-BRIEF factor of Metacognition should correlation more strongly with the BPI Attention Deficit factor, while the CCSS-BRIEF Behavioral Regulation factor should correlate more strongly with the BPI Depression/Anxiety factor (although this latter correlation may be somewhat weaker given the fluctuating nature of emotional symptoms). We do not expect strong correlations between the CCSS-BRIEF and the BPI Head Strong or Peer Conflict factors. Such correlations would suggest the CCSS-BRIEF is assessing something more global than executive function.

5.1.6. Concurrent validity will be examined by comparing the BRI and MI CCSS-BRIEF factor scores to the Depression, Anxiety, and Somatization factors from the BSI, which was collected at the same time. All available reports from cancer survivors and siblings will be used. Here, again, we should expect some specificity in the pattern of correlations. That is, the CCSS-BRIEF factor of Behavioral Regulation factor should correlate more strongly with the BSI Depression and Anxiety factors. We do not expect strong correlations between the CCSS-BRIEF Metacognition factor and the BSI. Again, such correlations would suggest the CCSS-BRIEF is assessing something other than executive function.

5.1.7. Finally, predictive validity of the CCSS-BRIEF will be examined. For this purpose, we will compare CCSS-BRIEF performance in cancer survivors who are at high risk vs. low risk for executive dysfunction. Two high risk groups will be developed: one group will include all survivors with epilepsy and/or cerebrovascular abnormalities, while the other group will include survivors treated with high dose cranial radiation. These groups will be compared to a low risk group of healthy survivors with no history of CNS disease or CNS treatment. Multivariate analysis will be used to examine group differences and predict group membership. These analyses will be more preliminary and may be excluded from the initial manuscript. However, depending upon the outcome, it may provide pilot data for justification of an ancillary study to directly assess executive functions in these patients.

5.2. Subject population: Four data sets will be required for this project.

5.2.1. Data Set 1 (Factor Structure)

5.2.1.1. Inclusion criteria

- Cancer survivors and siblings who completed the CCSS-BRIEF in the Follow-Up 2 Questionnaire.

5.2.1.2. Exclusion criteria

- NA

5.2.2. Data Set 2 (Construct Validity)

5.2.2.1. Inclusion criteria

- Cancer survivors and siblings whose parents completed the Behavior Problems Index in the Baseline CCSS Questionnaire and who themselves completed CCSS-BRIEF in the Follow-Up 2 Questionnaire (n=1,730).

5.2.2.2. Exclusion criteria

- NA

5.2.3. Data Set 3 (Concurrent Validity)

5.2.3.1. Inclusion criteria

- Cancer survivors and siblings who completed both the CCSS-BRIEF and the Brief Symptom Inventory – 18 in the Follow-Up 2 Questionnaire.

5.2.3.2. Exclusion criteria

- NA

5.2.4. Data Set 4 (Predictive Validity)

5.2.4.1. Inclusion criteria

- Cancer survivors who completed the CCSS-BRIEF in the Follow-Up 2 Questionnaire.
- High Risk Group 1 = Survivors with Epilepsy and/or cerebrovascular abnormalities as reported at the time of the Baseline Questionnaire.
- High Risk Group 2 = Survivors treated with ≥ 50 Gy cranial radiation.
- Low Risk Group = Survivors without prior CNS disease and without CNS treatment

5.2.4.2. Exclusion criteria

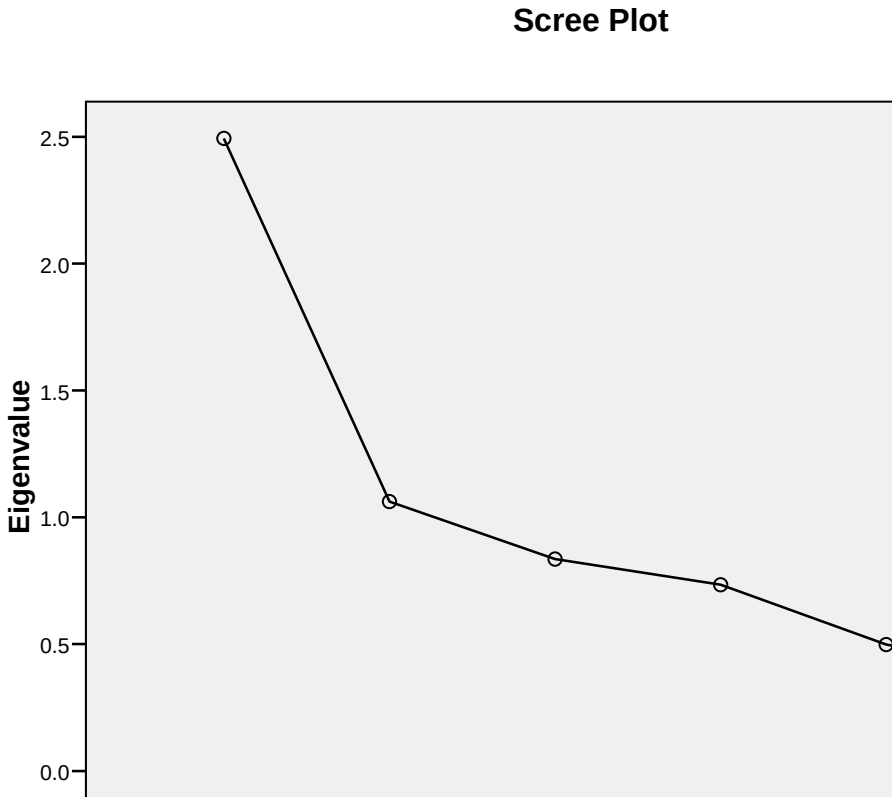
- Siblings
- Survivors without Epilepsy or CVA who had CNS disease.
- Survivors without Epilepsy or CVA who were treated with cranial or total body radiation.
- Survivors without Epilepsy or CVA who were treated with intrathecal chemotherapy or IV methotrexate.
- Survivors without Epilepsy or CVA who had positive reports on any of the following Baseline Questionnaire items:
  - F1-13, F16-17, G11-13, I7-10, I17, I20, I23-27, J1-5, J15, N7(6+ drinks)

5.3. Exploratory variables.

- Educational attainment. This is consistently correlated with intelligence, which itself it correlated with executive functioning.
- Current Living Arrangement. An individual living alone vs. with a parent or partner may have more demands placed on them for executive functioning and, thus, may experience more opportunities for success or failures.

5.4. Examples of specific tables and figures:

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1									
2									
3									
4									
5									
6									



	Component	
	1	2

Var1		
Var2		
Var3		
.		
.		
.		

Extraction Method: Principal Component Analysis

Rotated Component Matrix(a)

	Component	
	1	2
Var1		
Var2		
Var3		
.		
.		
.		

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
a Rotation converged in 3 iterations.

Correlation Matrix

		Var1	Var2	Var3	.	.	.	.
Correlation	Var1							
	Var2							
	Var3							
	.							
	.							
	.							
	.							
Sig. (1-tailed)	Var1							
	Var2							
	Var3							
	.							
	.							
	.							
	.							

Goodness-of-fit Test

Chi-Square	df	Sig.

Multivariate Test Results

	Value	F	Hypothesis df	Error df	Sig.
Pillai's trace					
Wilks' lambda					
Hotelling's trace					
Roy's largest root					

a The statistic is an upper bound on F that yields a lower bound on the significance level.

Univariate Test Results

Source	Dependent Variable	Sum of Squares	df	Mean Square	F	Sig.
Contrast	BRIEF behavioral regulation (BRI) T score					
	BRIEF metacognition (MI) T score					
	BRIEF global executive (GEC) T score					
Error	BRIEF behavioral regulation (BRI) T score					
	BRIEF metacognition (MI) T score					
	BRIEF global executive (GEC) T score					

group Difference Contrast			Dependent Variable		
			BRIEF behavioral regulation (BRI) T score	BRIEF metacognition (MI) T score	BRIEF global executive (GEC) T score
Level 2 vs. Level 1	Contrast Estimate				
	Hypothesized Value				
	Difference (Estimate - Hypothesized)				
	Std. Error				
	Sig.				
	95% Confidence Interval for Difference	Lower Bound			
		Upper Bound			

Contrast Results (K Matrix)

Multivariate Test Results

	Value	F	Hypothesis df	Error df	Sig.
Pillai's trace					
Wilks' lambda					
Hotelling's trace					
Roy's largest root					

a Exact statistic

6. SPECIAL CONSIDERATION:

6.1. Given the training and experience that Drs. Ness and Krull have with this type of data, and the relatively simple analyses planned, we believe that we can complete the

statistical procedures ourselves and, thus, not add to the list awaiting the Statistical Centers. However, we will have a member of the statistical coordinating center review the analyses and methods prior to sending the paper to the publications committee for review.

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