

survivors [6]. Global psychological distress is associated with a CNS tumor diagnosis, more intensive treatment, female sex, diagnosis during adolescence, and unmarried status [4-6]. Interestingly, while survivors as a whole have increased global distress compared with siblings, mean scores for the group are below (i.e. better than) those of the general population [4]. HRQOL outcomes mirror those of emotional distress as lower educational attainment, female sex, low household income, unemployment, unmarried status, uninsured status, major medical problems, and treatment with surgery or cranial radiation are associated with survivor report of poor HRQOL [4, 10].

In a more recent CCSS study by Liu *et al.*, non-Hispanic black (NHB) and Hispanic survivors reported lower educational attainment when compared to non-Hispanic white (NHW) survivors. A larger proportion of minority survivors did not complete or attain education beyond high school, had annual household incomes <\$20,000 or were uninsured. This study found that while there were differences in mortality and cardiovascular events for populations based on race/ethnicity, these differences were no longer observed when adjusting for socioeconomic status and/or cardiovascular risk factors. This suggested that the observed differences by race/ethnicity were driven by racial/ethnic differences in SES and traditional cardiovascular risk factors [11]. This study did not include neurocognitive, emotional or HRQOL outcomes.

With the expansion of the CCSS cohort, new investigations into associations between race/ethnicity and neurocognitive, emotional and HRQOL outcomes are possible. There is an increase in available survivor and sibling data from racial and ethnic minority groups including a total of 1536 non-Hispanic black survivors and 151 siblings, and 1806 Hispanic survivors and 214 siblings. This is more than twice the number of both non-Hispanic black and Hispanic survivors included in the original cohort. Additionally, the CCSS-NCQ, BSI-18 and SF-36 used to evaluate neurocognitive, emotional and HRQOL domains respectively are now available from this cohort using follow-up 5 at a similar time from diagnosis and treatment as those surveys from follow-up 2 in the original cohort. Given the complex interplay of socioeconomic, educational attainment, health insurance and demographic factors on neurocognitive and emotional outcomes, our primary comparison for this analysis of the impact of race/ethnicity will be between survivors and siblings of the same race/ethnicity group, which will allow for a comparison of differences between survivors and siblings across three race/ethnicity populations.

Given the historically demonstrated influence of CNS-directed therapy on neurocognitive, emotional and HRQOL outcomes, and to determine whether there are treatment-specific associations between race/ethnicity and these outcomes, we will specifically look at differences in outcomes stratified by CNS radiation exposure. We will include methotrexate exposure, both systemic and intrathecal, in our analysis given the previously observed negative effects on neurocognitive and emotional outcomes in patients receiving this chemotherapy as part of their treatment regimen [2, 4-6, 12]. We will also include corticosteroid exposure in our analysis, differentiating between patients who received dexamethasone and those who did not, given previously observed negative effects on neurocognitive and emotional outcomes in patients received corticosteroids who did not receive CNS radiation therapy [6-9].

2. Specific Aims
 - 2.1. Evaluate differences in neurocognitive outcomes between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the NCQ.
 - 2.2. Evaluate differences in emotional outcomes between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the BSI-18.
 - 2.3. Evaluate differences in health related quality of life (HRQOL) between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the SF-36.

3. Hypotheses
 - 3.1. While we hypothesize we will observe differences in neurocognitive outcomes between survivors and siblings within each racial/ethnic group, we expect no difference (i.e., test the difference but expect not rejecting the null hypothesis of no difference) when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will display a similar difference in neurocognitive outcome when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.
 - 3.2. While we hypothesize we will observe differences in emotional distress between survivors and siblings within each racial/ethnic group, we expect no difference when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will have a similar difference in emotional distress when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.
 - 3.3. While we hypothesize we will observe differences in HRQOL outcomes between survivors and siblings within each racial/ethnic group, we expect no difference when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will have a similar difference in HRQOL outcomes when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.

4. Methods
 - 4.1. Study Population: The study population will include survivors and siblings in both the original and expansion CCSS cohorts who had complete information for race/ethnicity in the baseline questionnaire. We will use neurocognitive, emotional and HRQOL data from follow-up 2 for participants from the original cohort and follow-up 5 for participants from the expansion cohort. Analyses regarding treatment variables will be restricted to survivors who have signed medical record releases and have treatment exposure data abstracted by CCSS institutions.
 - 4.2. Outcome Variables
 - 4.2.1. CCSS-NCQ (J1-25 on FU2 and Q1-33 on FU5): Neurocognitive impairment in survivors will be assessed using the self-reported CCSS-NCQ which was developed for use and validated within the CCSS cohort using 4 factors; Task Efficiency, Emotional Regulation, Organization, and Memory. Scores will be reported as a continuous variable for the primary analysis.
 - 4.2.2. BSI-18 (G1-18 on FU2 and L1-18 on FU5): Emotional distress will be assessed using the self-reported Brief Symptom Inventory-18 (BSI-18) which has been validated in cancer patients and with the CCSS cohort [13, 14]. The BSI-18 includes the global distress index as

well as 3 subscales for anxiety, depression and somatization assessed based on symptoms within the past 7 days. Scores will be reported as a continuous variable.

4.2.3. SF-36 (E1-22 & F1-14 on FU2 and O1-8 & P1-3 on FU5): Health Related Quality of Life (HRQOL) will be assessed using the self-reported Medical Outcomes Short Form-36 (SF-36) which includes questions regarding general health, well-being, and quality of life over the previous 4 weeks. This tool has been used in population studies and survivor samples, including within the CCSS [10, 15, 16]. The SF-36 includes eight subscales of various aspects of well-being where higher scores represent “better” quality of life. Scores will be reported as a continuous variable.

4.3. Covariates:

4.3.1. Sex

4.3.2. Age at diagnosis

4.3.3. Age at follow-up

4.3.4. Chemotherapy (CNS exposure including systemic MTX (none, $<4.3 \text{ g/m}^2$, $\geq 4.3 \text{ g/m}^2$), IT MTX (none, $<230 \text{ mg/m}^2$, $\geq 230 \text{ mg/m}^2$), Corticosteroids (none, dexamethasone, non-dexamethasone)) [7, 8, 17].

4.3.5. CNS radiation exposure (None, >0 and $<20 \text{ Gy}$, $\geq 20 \text{ Gy}$ and $<30 \text{ Gy}$, $\geq 30 \text{ Gy}$ to $<50 \text{ Gy}$, $\geq 50 \text{ Gy}$) [6, 12]

4.3.6. Major Medical Condition

4.4. Statistical Analysis Framework:

Rationale: We initially intended to follow the model utilized in the most recent CCSS Race/Ethnicity paper by Liu *et al.* where outcomes were analyzed adjusting for clinical/demographic variables, then with the incremental addition of treatment and finally SES into the model [11]. However, socioeconomic status is likely a result of neurocognitive function (i.e. education, employment and income, as currently collected by CCSS surveys, are all downstream to neurocognitive outcome in the causal pathway). Additionally, CCSS does not have parental education status at the time of diagnosis or treatment which would be ideal for adjustment. For these reasons, we are proposing a comparison of each survivor group to their racial/ethnically specific sibling group, leveraging the assumption that siblings shared a similar SES environment to survivors.

4.4.1. Frequency distributions will be used to categorize relevant covariates according to reasonable groupings consistent with prior CCSS manuscripts. (Table 1) Descriptive statistics including means and standard deviations will be calculated for the primary outcome of interest (NCQ, BSI-18 and SF-36). (Tables 2-4)

4.4.2. Comparisons of the primary outcome variables (CCSS-NCQ, BSI-18 and SF-36) will be made between racial/ethnic groups and their siblings using general linear models (Tables 2-4) with a modification by Generalized Estimating Equations to account for possible within-family correlation between survivors and siblings from the same family. Outcomes will be reported as means, differences in means and associated standard deviations based on a continuous variable from the raw scores. For each outcome, we will initially compare sibling and survivor outcomes within race/ethnic groups and will then examine the role of clinical/demographic factors such as diagnosis, sex, age and treatment that may explain survivor-sibling differences. Further analyses will compare the intra racial/ethnic survivor-sibling differences across racial/ethnic stratum. For example, we will test whether the

difference between NHB survivors and siblings is different from the difference between NHW survivors and siblings.

- 4.4.3. We will then modify the model to assess survivor-sibling differences in each racial/ethnic group stratified by CNS radiation exposures. This will be accomplished by adding an interaction between the CNS radiation indicator and the survivor/sibling status indicator (this will stratify survivors by CRT but not siblings), but adjusting for the same covariates as in 4.4.2. Within the structure of that model, we will assess the differences between CRT treated survivors and non-CRT treated survivors and siblings within each racial/ethnic group and compare those differences with one another. Further analyses will compare within CRT stratum survivor-sibling differences across racial/ethnic groups.

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<p>80-99999 ≥100,000 Educational attainment < HS graduate or GED High school graduate Any college or post-HS training College graduate or post-graduate degree Social/Financial Independence, n (%) Marital Status Never married Ever married Lives independently Yes No Employment Unable to work Unemployed Employed/Student Medications, n (%) Antidepressants Yes No Anxiolytics Yes No Major Medical Condition, n (%) Yes No</p>	
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*Only direct CNS radiation doses were included, this does not include low doses from body site scatter.

**Income values adjusted to 2016 dollar values.

Table 2. Neurocognitive Outcomes Across Racial/Ethnic Groups of Childhood Cancer Survivors												
Task Efficiency												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Emotional Regulation												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Organization												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Working Memory												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.

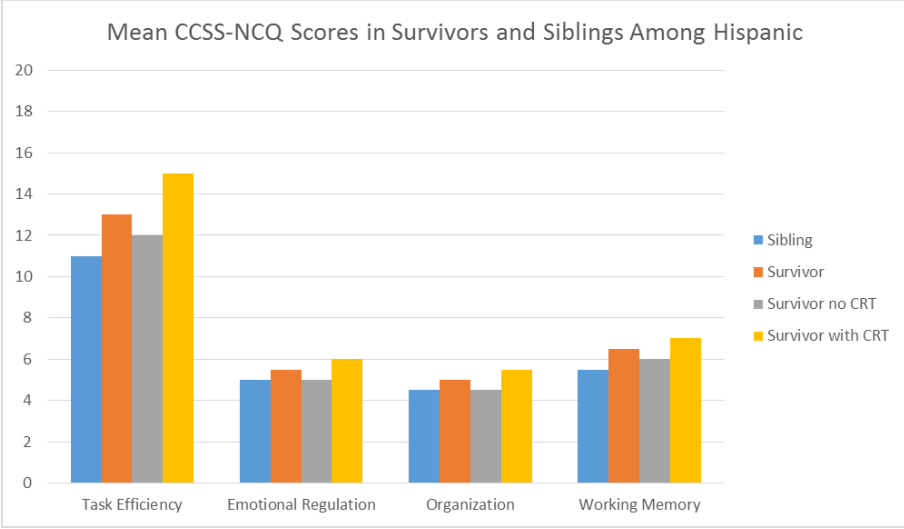
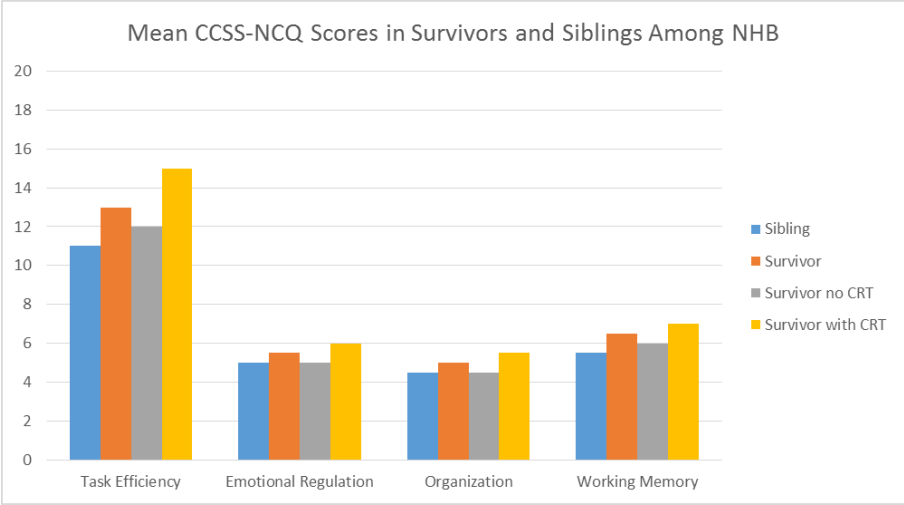
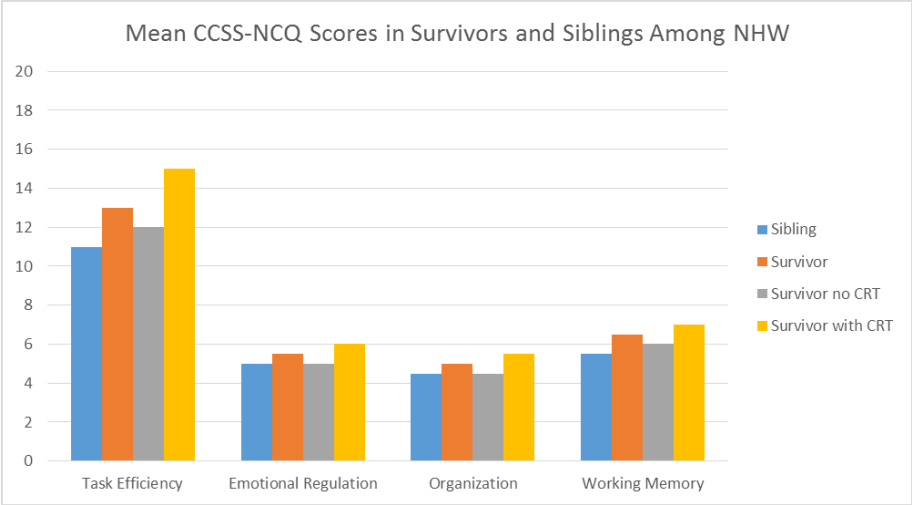


Table 3. Psychological Outcomes Across Racial/Ethnic Groups of Childhood Cancer Survivors												
Depression												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Anxiety												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Somatization												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Global Status Index												
NHW				NHB				Hispanic				
	Mean	SD	P	Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.

Table 4. Health-Related Quality of Life Outcomes Across Racial/Ethnic Groups of Childhood Cancer Survivors

Role Emotional												
NHW				NHB				Hispanic				
Mean	SD	P		Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Social Function												
NHW				NHB				Hispanic				
Mean	SD	P		Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Mental Health												
NHW				NHB				Hispanic				
Mean	SD	P		Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Physical Component Summary												
NHW				NHB				Hispanic				
Mean	SD	P		Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	
Mental Component Summary												
NHW				NHB				Hispanic				
Mean	SD	P		Mean	SD	P	P*	Mean	SD	P	P*	
Sibling			-			-	-			-	-	
Survivor			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor no CRT			0.xx			0.xx	-			0.xx	-	
Difference from sibling			-			-	0.xx			-	0.xx	
Survivor with CRT			0.xx			0.xx	-			0.xx	-	
Difference from Sibling			-			-	0.xx			-	0.xx	

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.