1. Study Title: Social adjustment in adolescent survivors of pediatric CNS tumors

2. Working Group and Investigators:

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3. Background and Rationale

Improved therapies for pediatric CNS tumor have increased survival rates, however, many survivors experience significant long-term functional limitations. CNS tumor survivors have been found to experience deficits in social adjustment (i.e., the ability to achieve personal goals in social interactions while maintaining positive relationships with others over time and across situations[1]) that worsen with time,[2] and negatively affect survivors' long-term quality of life.[3] Currently there are more than 115,000 survivors of pediatric central nervous system (CNS) tumor in North America.[4,5] As adults, these survivors are more likely than their siblings to require special education services, are less likely to attend college, less likely to live independently, and are at increased risk of unemployment[6]. In addition, survivors of pediatric CNS tumors are less likely to be married compared to their siblings[6]. However, over the past several decades research in the social adjustment of pediatric CNS tumor survivors has been limited, relying on small, single center cohort studies (average sample size = 66[2]) which has remained the primary criticism of research conducted in the field, to date[2,7]. Although there are a few notable studies that have been completed using large sample sizes, one in particular using the Childhood Cancer Survivor Study (CCSS) cohort[8], a detailed examination of risk and resilience factors specific to CNS tumor survivors and examination of specific social problems has not been completed.

There is a paucity of research directly investigating the type and severity of CNS insult and associations with social adjustment in pediatric CNS tumor survivors.[9] Where research has attempted to explore the impact of disease and treatment factors on social adjustment, little conclusive evidence has been obtained.[10–12] For example, cranial radiation therapy (CRT) and young age at diagnosis have been identified as risk factors for *cognitive deficits* among pediatric CNS tumor survivors,[13] however, there is less evidence to support the role of CRT in poor *social adjustment.*[8,14,15] The evidence related to age at diagnosis is mixed.[12,14] Further research is needed with a large diverse sample to better identify predictors of long-term social adjustment difficulties in this population.[11]

Demographic factors, such as sex and age have yielded contradictory results with respect to their role in social adjustment in pediatric brain tumor survivors.[16,17] In children with mild traumatic brain injury, male gender and younger age has been found to contribute to poorer social adjustment outcomes.[18]Socio-economic status (SES) plays an established role in social development for typically developing children[19] and children with other acquired brain injuries (i.e., traumatic brain injury[TBI])[20] whereby lower SES is linked to poorer social outcomes. There is no research that has directly examined the relationship of SES on social adjustment outcomes in pediatric CNS tumor survivors.

Poor physical mobility is often seen in survivors of pediatric CNS tumors, and may further compromise social adjustment outcomes.[6,21] Recent research has revealed that as adults, reduced physical function in survivors of pediatric CNS tumor has been linked to poor environmental access which was associated with reduced quality of life and social

function.[22] The proposed study will be the first to examine potential moderation effects of physical limitations on social adjustment in an adolescent sample of pediatric CNS tumor survivors.

We propose to examine social function in a large sample of CNS tumor survivors from the 1970-99 CCSS cohort. We will focus on those survivors whose parents (proxy) completed the Baseline surveys when the survivor was < 18 years of age. Social function in this group will be compared to a non-CNS solid tumor comparison group (i.e., neuroblastoma, Wilms tumor) as well as siblings whose parents (proxy) participated in the < 18 Baseline survey.

4. **Specific Aims**

Aim 1: To examine patterns of social adjustment (e.g., number of close friends, frequency of interactions, quality of interactions, social withdrawal, conflict) in adolescent survivors of pediatric CNS tumors in the combined cohort as compared to a non-CNS tumor comparison group (i.e., patients diagnosed with neuroblastoma, Wilms tumor) and to the sibling cohort.

Hypothesis 1: We hypothesize that pediatric brain tumor survivors will have fewer friends, fewer interactions, poorer quality of social interactions and greater social withdrawal and conflict compared to non-CNS tumor survivors and siblings.

Aim 2: To identify demographic (e.g., sex, age), socioeconomic (e.g., household income), disease (e.g., tumor diagnosis), and treatment (e.g., radiation dose and site, age at diagnosis) factors that are related to social function in adolescent survivors of pediatric CNS tumor.

Hypothesis 2: Male gender, lower household income, diagnosis of Medulloblastoma and/or PNET, higher dose of cranial radiation, and younger age at diagnosis will be associated with poorer social adjustment outcomes.

Aim 3: To examine the association between and moderation effect of physical, cognitive and sensory limitations (e.g., weakness/paralysis, poor endurance, special education services and vision and/or hearing loss) and social adjustment in adolescent survivors of pediatric CNS tumor.

Hypothesis 3: Physical, cognitive and sensory limitations will moderate the effects of personal demographic, socioeconomic, disease and treatment factors on social adjustment outcomes.

5. Analysis Framework

Population

Participants will be adolescent survivors of pediatric CNS tumors in the original and expansion cohort for whom the baseline survey was completed by their parent (proxy) when they were between the ages of 12 to 17 years, and siblings for whom the baseline survey was completed by their parent (proxy) when they were 12 to 17 years of age. There are 663 survivors of CNS tumors in the combined cohort, 1374 non-CNS solid tumor survivors in the combined cohort, and 649 siblings in the original cohort who meet these inclusion criteria.

Note: we will also include siblings < 18 years at Baseline from the expansion cohort, if the data is available at the time of analyses.

Variables

Variables for Aim 1

- Social Adjustment: measured with the social withdrawal scale from the Behavior Problems Index (BPI)[23] and individual questions in the Baseline < 18 survey (Original; Expansion): Number of Close Friends (J.16; K.1), Frequency of Interactions (J.17; K.2), Quality of Interactions (J.18 a,b,c,d; K.3 a,b,c,d), Social Withdrawal/Peer Conflict (J.19 m,q,w; K.4 m.q.w), Antisocial behavior (J.19 d,i,l,j,n; K.4 d,i.l,j,n).

The BPI[23] is a 28-item scale that is completed by proxy reporters for adolescents 12-17 years of age with responses recorded on a three-point Likert scale ranging from "not true" to "often true." The items that comprise the BPI are a subset of items from the Child Behavior Checklist (CBCL).[24] Internal reliability estimates for the BPI have been reported as $\alpha = 0.86$ for peer conflict/social withdrawal.[8]

Variables for Aim 2

Outcome Variables

- Social Adjustment (Original; Expansion): Number of Close Friends (J.16; K.1), Frequency of Interactions (J.17; K.2), Quality of Interactions (J.18 a,b,c,d; K.3 a,b,c,d), Social Withdrawal/Peer Conflict (J.19 m,q,w; K.4 m.q.w), Antisocial behavior (J.19 d,i,l,j,n; K.4 d,i.l,j,n).

Predictors

- Personal Demographic
    - Sex (A.2; male or female).
    - Current age (Original; Expansion).
- Socioeconomic Status
    - Household Income (Q.8; T.1; Original, Expansion). Income will be categorized as: 1) <$20,000; 2) $20,000-$39,999; 3) $40,000-$59,999; and 4) ≥$60,000.
    - Family size (A.7; Baseline; Expansion).
- Disease
    - Tumor Diagnosis will be operationalized using four diagnosis categories: 1) Astrocytoma; 2) Medulloblastoma; PNET; 3) Ependymoma and 4) Other CNS tumor.
- Treatment
    - Radiation dosimetry will be operationalized consistent with research that has previously examined the effect of radiation on psychological/neuropsychological outcomes[25]. Specifically, we will use four segments of brain including: 1) posterior fossa ; 2) temporal lobe; 3) frontal cortex; and 4) parietal or occipital lobe. Using data abstracted from the radiation therapy records, average and maximum radiation dose to each segment of the brain was previously calculated. For each case, each of the four brain segments will be assigned to one of the following dose categories based on average dose to the segment 1) none; 2) 0.1-29 Gy; 2) 30-49 Gy; and 3) >50 Gy.
    - Age at diagnosis.

Variables for Aim 3

- Social Adjustment (Baseline; Expansion): Number of Close Friends (J.16; K.1), Frequency of Interactions (J.17; K.2), Quality of Interactions (J.18 a,b,c,d; K.3 a,b,c,d), Social Withdrawal/Peer Problems (J.19 m,q,w; K.4 m.q.w), Conflict/antisocial (J.19 d,i,l,j,n; K.4 d,i.l,j,n).
- Physical limitations: as measured by the SF-36, Role-Limitations - Physical (N. 10 a,b,c,d,e,f; O. 6 a,b,c,d,e,f; Original; Expansion).
- Cognitive Limitations: as measured by 'School History' (Baseline; Expansion): O3; R3.
- Sensory impairments as measured by 'Hearing/Vision/Speech' (Baseline; Expansion): (C.1, C.2, C.3, C.8; C.1, C.2, C.3, C.8, C.9)

Statistical Analyses

Descriptive Characteristics of the Sample

Demographic characteristics of the sample (e.g., age, gender of child, gender of parent, socioeconomic variables) will be calculated and comparisons between survivors and siblings will be made using t-tests or chi-square where appropriate. Potential impact of the proxy-reporter (i.e., mother, father, guardian) will also be considered and if differences exist, controlled for in subsequent analyses.

Statistical Analysis for Aim 1

Social adjustment will be operationalized using the five items specified above (i.e., number of close friends (categorical, based on 4 responses), frequency of Interactions (categorical based on 3 responses), quality of interactions (categorical based on 4 responses), social withdrawal/peer problems (continuous based on 3 items), conflict/antisocial behavior) (continuous based on 4 items). Distributions will be examined to identify categories of sufficient size for each variable that represent poor outcomes (e.g. <1 or <2 close friends).

Latent profile analysis (LPA) will be used to identify clusters of siblings based on item level responses of social adjustment variables. Latent clusters will first be identified in the sibling cohort (discovery) and validated in the survivor cohort to verify the same general cluster pattern. For the discovery set, the number of potential classes will not be pre-specified. A minimum of 5% of the sample will be required in each cluster to be included. The centers of the cluster model in the sibling cohort will then be used to derive the latent clusters in the survivor cohort using nearest centroid method. Frequencies and percentages of cluster membership will be compared between survivors and siblings using Chi-square tests adjusting for those variables for which they differ (e.g., gender, household income, family size).

Statistical Analysis for Aim 2

Utilizing the same latent clusters(s) for social adjustment derived in Aim 1, multivariable logistic regression analyses will be conducted for each cluster as a dichotomized variable (determined based on class membership yes/no). That is, membership in a given cluster will be predicted using the following variables: tumor diagnosis; radiation dosimetry; age at diagnosis; sex; age; household income. Separate models will be run for disease and treatment variables to avoid confounding.

Statistical Analysis for Aim 3

Multivariable logistic regression will also be used to examine associations between physical limitations/cognitive limitations/sensory impairments and clusters of social adjustment outcomes. To examine the potential moderation effect of physical limitations/cognitive limitations/sensory impairments on social adjustment we will: 1) identify the significant relations between the independent variables (i.e., tumor diagnosis; radiation dosimetry; age at diagnosis; gender; age; household income; and family size) and social adjustment as the dependent variable(s) assessed in Aim 2; 2) complete three separate multivariable regression analyses that examine whether the independent variables (i.e., tumor diagnosis; radiation dosimetry; age at diagnosis; gender; age; household income; and family size) significantly predict: 1) physical limitations; 2) cognitive limitations; 3)sensory impairments; and finally 3) complete three separate hierarchical regressions to examine whether: 1) physical limitations; 2) cognitive limitations; and 3) sensory impairments are significant predictors of social adjustment, while controlling for the independent variables. We will evaluate moderation using the methods described by Baron and Kenny[26]

6. Tables

Table 1. Participant Characteristics

	CNS Survivor (n =)		Non-CNS Solid Tumor Survivor (n =)	Sibling (n =)		*p*
	N (%)	M (SD)		N (%)	M (SD)	
Age						
Sex						
Male						
Female						
Family Income						
<$20,000						
$20,000 - $39,999						
$40,000 - $59,999						
≥$60,000						
Ethnicity						
Hispanic						
Non-Hispanic						
Race						
White						
Black						
Other						
Age at Diagnosis						
Time Since Diagnosis						
Diagnosis						
Astrocytoma						
Medulloblastoma, PNET						
Other CNS Tumor						
Cranial Radiation						
None						
Whole Brain						
Partial Brain						
Cranial Radiation Dose						
None						
0.1-29 Gy						
30-59 Gy						
>50Gy						

Table 2. Model fit indices for two to six social cluster solutions from the datasets of siblings and survivors

	Siblings					Survivors				
Class	**2**	**3**	**4**	**5**	**6**	**2**	**3**	**4**	**5**	**6**
AIC										
BIC										
aBIC										
Entropy										
LMR test										
Class %										

Table 3. Comparison of Social Adjustment Among Survivors and Siblings

	CNS Survivors				Non-CNS Solid Tumor Survivors (n/%)	Siblings (n / %)	*P* (CNS vs. Siblings)	*p*
	Total (n / %)	Astrocytoma (n / %)	Medulloblastoma, PNET (n / %)	Other (n / %)				
Number of Close Friends								
0								
1								
2 or 3								
4 or more								
Frequency of Interactions								
Less than 1								
1 or 2								
3 or more								
Quality of Interactions								
Get along with his/her brothers and sisters								
Get along with other children								
Behave with his/her parents								
Play and work by himself/herself								
Social Withdrawal/Peer Problems								
Has trouble getting along with other children								
Is not liked by other children								
Is withdrawn, does not get involved with others								
Conflict/Antisocial								
Cheats or tells lies								
Bullies, or is cruel or mean to others								
Does not seem to feel sorry after he/she misbehaves								
Is disobedient at home								
Has trouble getting along with teachers								

Table 4a. Multivariable Logistic Regression Analysis of Factors Predicting Social Adjustment

Variables	Social Class 1		Social Class 2	
	OR	CI 95%	OR	CI95%
Personal Demographic				
Age (per year)				
Sex				
Female	1.0		1.0	
Male				
Sociodemographic				
Household Income*				
<$60,000				
≥$60,000	1.0		1.0	
Diagnosis				
Astrocytoma				
Medulloblastoma, PNET				
Other CNS Tumor	1.0		1.0	
Treatment				
Age at Diagnosis (per year)				

*Adjusted to Expansion cohort values.

Table 4ba. Multivariable Logistic Regression Analysis of Factors Predicting Social Adjustment

Variables	Social Class 1		Social Class 2	
	OR	CI 95%	OR	CI95%
Personal Demographic				
Age (per year)				
Sex				
Female	1.0		1.0	
Male				
Sociodemographic				
Household Income*				
<$60,000				
≥$60,000	1.0		1.0	
Treatment				
Age at Diagnosis (per year)				
Cranial Radiation Dose				
None	1.0		1.0	
0.1-29 Gy				
30-49 Gy				
>50Gy				

*Adjusted to Expansion cohort values.

Figure 1. Examination of the moderation effect of physical limitations on social adjustment

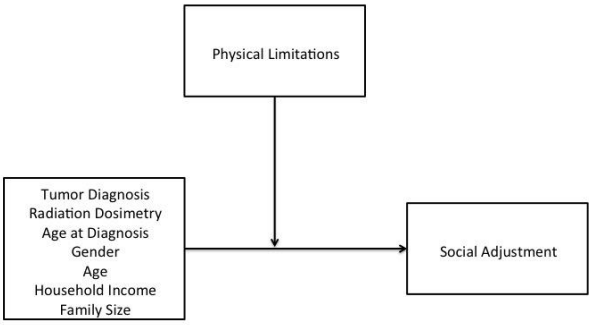

Figure 2. Examination of the moderation effect of cognitive limitations on social adjustment

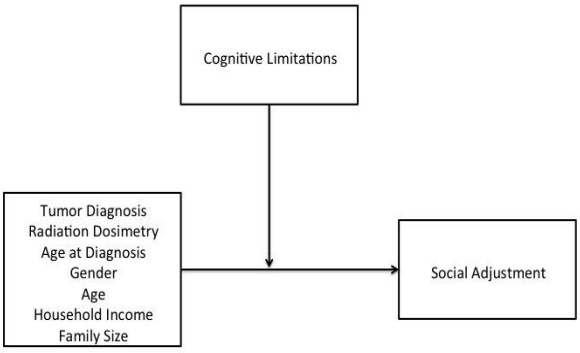

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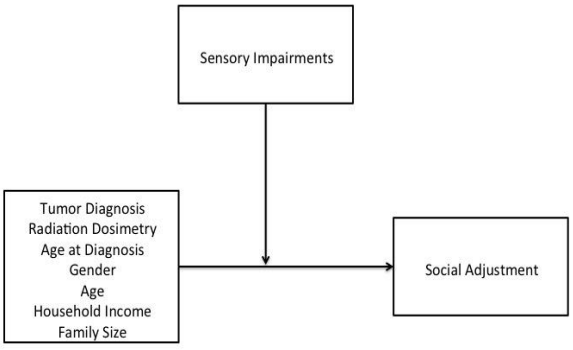
Figure 3. Examination of the moderation effect of sensory impairments on social adjustment.



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