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Longitudinal Analysis of Risk Factors Affecting Reading Trajectories in Children Diagnosed with Pediatric Brain Tumors

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LONGITUDINAL ANALYSIS OF RISK FACTORS AFFECTING READING TRAJECTORIES IN CHILDREN DIAGNOSED WITH PEDIATRIC BRAIN TUMORS

By

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ABSTRACT

Prior research suggests aggressive cancer treatments contribute to cognitive impairments in children diagnosed with pediatric brain tumors. The literature also suggests that younger age at diagnosis (AAD) and treatment may result in disrupted cognitive trajectories due to limited brain plasticity. In line with this research, we hypothesized an interaction between radiation therapy (RT) and young AAD of brain tumors, where young AAD and RT results in lower standard scores on the WRAT-R Reading Comprehension Subtest. Analyses included archival data; the sample consists of 134 children diagnosed with pediatric brain tumors with multiple assessments resulting in 487 cases for analysis. Participants were diagnosed with mixed tumor types and locations. A two level multilevel model was used to analyze reading trajectories while taking into account AAD, time since diagnosis, socioeconomic status (SES), and RT. Results detected a positive interaction between AAD and RT (γ =2.08, p=.02). For participants with RT, younger AAD was associated with lower reading scores, whereas AAD had no effect for participants without RT. Results also detected a negative interaction between radiation and time (γ =-2.29, p=.00) indicating that children treated with RT have reading scores that decrease over time. These data suggested that children diagnosed with pediatric brain tumors treated with RT are at higher risk of reading impairment as reflected in their reading scores.

KEY WORDS: Cancer, brain tumor, childhood, reading, neuroplasticity, diffuse brain insult, longitudinal design

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Introduction

Medical advances have increased survival rate for individuals diagnosed with pediatric brain tumors, resulting in approximately 3 out of 4 children now surviving at least 5 years post tumor diagnosis (Kohler et al., 2011). Now that medical practitioners have the expertise to increase life expectancy in brain tumor patients, clinical researchers should study ways to improve quality of life for patients who are living with the long term outcomes of tumor diagnosis and treatment (Palmer, 2008). Specific demographic and treatment factors are hypothesized to effect cognitive outcomes (Micklewright, King, Morris, and Krawiecki, 2008); however, more research is necessary to understand how these specific factors effect performance changes over time. Empirical studies on pediatric brain tumor survivors remain limited due to the complex nature of tumor diagnosis, treatment, and costs associated with multiple waves of data collection. Research has suggested that surgery, complications, presence of radiation, and chemotherapy treatment may result in poorer cognitive performance (King et al, 2004; Micklewright, King, Morris, and Krawiecki, 2008).

Historically, a child's age at disruption in brain development has been thought to contribute to cognitive outcomes. Early researchers hypothesized that age at brain insult may be related to neuroplasticity and influence cognitive outcomes (Dennis, 2010). Animal research supported this theory and suggested that the young brain must reorganize in the event of injury, depleting a finite amount of neuroplasticity; diminished neuroplasticity is hypothesized to limit the brain's ability to change with age and learn new skills (Kolb, Gibb, & Robinson, 2003). There have been a number of studies on childhood traumatic brain injury which suggest that early brain insults result in worse cognitive outcomes (Anderson et al., 2010; Chapman, 2003; Dennis, 2000; Gragert and Ris, 2011; Greenham et al., 2010; Ponsford & Schönberger, 2010;

Senathi-Raja, Ponsford, and Schönberger, 2010; Spiegler et al., 2004; Taylor and Alden, 1997; Taylor, 1984).

Recent researchers have hypothesized that early vulnerability may be due to the nature of the brain insult. Studies on childhood traumatic brain injury and stroke populations suggest that early vulnerability exist with diffuse brain insults, but not for individuals with focal injuries (Anderson et al., 2009b, Ballantyne al., 2008; Chapman, 2003; Levin, 2003; Max, Bruce, Keatley, and Delis, 2010; Stiles, 1993). In line with these findings, researchers have suggested that early diffuse insults result in an abnormal developmental trajectory for new skill acquisition after the brain insult (Dennis, Yeates, Taylor and Fletcher, 2007; Taylor and Alden, 1997). Researchers have hypothesized that this is due to an underlying neurological process of consolidation, where individuals who have consolidated skills are able to maintain them after a brain insult, whereas children who have not learned basic skills will have more difficulty consolidating new information (Ewing-Cobb, Barns, and Fletcher 2003).

Given the substantial evidence from childhood traumatic brain injury and stroke populations it is important to see if the early vulnerability to diffuse brain insults exists in pediatric brain tumor populations. Studying age at diagnosis in pediatric brain tumor populations is also important because it is not always clear how childhood brain tumors span the definition of diffuse and focal brain injuries. Children diagnosed with pediatric brain tumors are unique in that they frequently have diffuse and focal factors contributing to cognitive deficits (i.e. brain surgery, cranial radiation, neurological complications).

One of the major factors that could be contributing to cognitive deficits is the neural damage cause by aggressive cancer treatments (Butler et al., 2008). In particular cranial radiation is generally thought to contribute to devastating cognitive outcomes, and numerous studies have been conducted which suggest that cranial radiation causes considerable deficits in intelligence, memory, and attention (Ellenberg, McComb, Siegel & Stowe, 1987; Gragert and Ris, 2011; Kirsch and Tarbell, 2004; Semnova, 2009). It has been generally accepted that radiation treatment has an effect on white matter pathways in the brain, which has been hypothesized to contribute to poor cognitive outcomes (Corn et al., 1994; Kirsch and Tarbell, 2004; Palmer et al., 2010). Radiation also has been hypothesized to have latent effects, where young children who receive cranial radiation during the development of white matter may have increasingly reduced white matter pathways as they age (Chong, 2002; Mulhern & Palmer, 2003). Thus, radiation treatment may disrupt the neurological process of myelination, and older children whose brains are more developed may be more resilient to the effects of cranial radiation (Palmer, 2008).

Some research also suggests that whole brain radiation causes more profound neurological problems than focal radiation, although there are limited experimental studies to support this claim (Lawerence, 2009); for the purposes of this study presence of radiation will be defined as having either type of cranial radiation. Studying effects of radiation treatment is important because it is considered a neurological risk factor, and some researchers suggest that treatment of pediatric brain tumors can have a larger influence on cognitive outcomes than more specific factors, such as tumor location (Gragert and Ris, 2011; Ris and Noll, 1994).

The effect of radiation therapy may be age dependent, and current physicians try to avoid cranial radiation for children diagnosed with brain tumors who are under the age of 3 years old (Semonva, 2009). Researchers have suggested that young individuals who receive radiation may have the worst outcomes due to early vulnerability to radiation therapy; however many of these were restricted by limited design and scope (small number of participants, assessments, and time spent following participants). For example, Silber et al. (1992) looked at one time point in a sample of 48 children with leukemia or brain tumors and found young age at diagnosis and cranial radiation treatment predicts poor performance on tasks of intelligence 2 years post diagnosis. Very few studies have looked at the longitudinal relationship between age at diagnosis and presence of radiation therapy in pediatric brain tumors.

It is generally accepted that children exposed to radiation treatment for pediatric brain tumors are at a significant risk for cognitive deficits which continues over time (Duffner, 2004; Mueller and Chang, 2009). However, it is important to study because researchers and physicians have yet to agree on an average age where an early vulnerability to radiation occurs. The literature suggests estimates ranging from 3 years old, which is used by physicians (Semonva, 2009), to 7 years old (Mulhernet al., 2005), which is frequently used by researchers. There are also researchers who suggest that young age at tumor development, independent from radiation treatment, is responsible for poor cognitive outcomes (Armstrong et al., 2004). While there are numerous studies on the effects of radiation on memory and intelligence, very little research exists on how cranial radiation effects reading ability in children diagnosed with brain tumors.

Historically studies with childhood brain tumors have investigated how specific diagnosis and treatment factors affect intelligence. These studies have laid a foundation for brain tumor research and the specific factors that may be associated with poor behavioral outcomes. However, intelligence encompasses a broad range of cognitive processes, such as memory, nonverbal reasoning, and attention. More research is needed to target specific problem areas for children diagnosed with brain tumors, which would help to develop effective intervention programs. Research suggests that academic achievement is an area where children diagnosed with brain tumors show particular weaknesses (Gragert and Ris, 2011).Difficulty in reading may impair the child’s ability to function in a traditional classroom environment, and furthermore, deficits in specific areas, such as language skills may substantially contribute to later academic and social problems (Brinton & Fujiki, 1989; Catts, 1993; Gragert and Ris, 2011; Greenham et al., 2010).

Given that many children are developing basic language skills at diagnosis and treatment, it is important to study the potential risk factors for young children who have not consolidated reading skills. Some research suggests young age at diagnosis and treatment is a strong factor influencing cognitive outcomes (Ellenberg, McComb, Siegel & Stowe, 1987). Language in particular is thought to be vulnerable to radiation treatment at a young age (Butler et. al., 2008; Palmer et al., 2010), and many studies have suggested that a young age at diagnosis may result in worse language outcomes (Mabbott et al., 2005; Mulhern et al., 2005; Spiegler et al., 2004; Riva and Giorgi, 2000; Robinson et al., 2010).

To date, only a few studies have used multilevel modeling to investigate reading skills in children diagnosed with brain tumors (Mabbott et al., 2005; Mulhern et al., 2005; Conklin, et al., 2008). These studies use longitudinal data to explore these relationships; however, more research is necessary over a longer period of time with more assessments to quantify the long term relationship between risk factors and reading outcomes. Additionally, the design of these studies does not include individuals who did not receive radiation treatment, limiting the generalizability of their results to only those individuals treated with radiation. Mabbott et al. (2005) limited their sample to only individuals with posterior fossa tumors, and their sample included 53 children and only investigated reading outcomes 2-3 years post diagnosis (13 of their participants only had a single assessment). Mulhern et al. (2005) also limited their sample to only individuals with radiation treatment and had 207 cases for their 90 participants.

To expand on these findings, the sample will include both children treated with and without radiation therapy, by including individuals without radiation we can look at how radiation affects children in comparison to individuals who were diagnosed with a brain tumor and did not receive radiation treatment. Mabbott et al. (2005), Mulhern et al. (2005) and Conklin et al. (2008) results did not include children who did not receive radiation therapy, so their results could be explained by either an early vulnerability to brain insult or an early vulnerability to radiation therapy. Additionally, Mulhern et al. (2005) divided age into a dichotomous age of old verses young (< 7 vs. ≥ 7 years of age). The current study analyzes age as a continuous variable and analyses included as many as 9 assessments over approximately 10 years in a heterogeneous group of brain tumors with 134 participants resulting in 487 cases for analyses.

The purpose of this study was to investigate the longitudinal relationship between risk factors and reading skills in children diagnosed with brain tumors. This study builds upon prior research by investigating the interaction between radiation and age at diagnosis in childhood brain tumors. Based on prior research, it was expected that individuals who were at a young age of diagnosis and received radiation treatment would have lower reading scores, consistent with our current understanding of early diffuse brain insults. In line with the early vulnerability hypothesis, and given the theoretical and empirical evidence for an early cognitive vulnerability to radiation treatment, it is hypothesized that younger age at diagnosis of brain tumor and presence of radiation is associated with lower reading standard scores (Ellenberg, McComb, Siegel & Stowe, 1987; Mabbott et al., 2005; Mulhern et al., 2005; Taylor and Alden, 1997).

Hypotheses 1: We hypothesized that young age at diagnosis of brain tumors would be associated with lower reading scores.

Hypotheses 2: We hypothesized an interaction between radiation therapy and young age at diagnosis of brain tumors, where young age at diagnosis and presence of radiation therapy results in poorer reading scores.

Methods

Procedure

Using archival data, the sample consisted of 134 children who participated in a longitudinal research study on functional outcomes associated with brain tumor diagnosis in children (Carlson-Green, Morris, & Krawiecki, 1995) who completed the WRAT-R as part of the study. The first assessments were as close to diagnosis of brain tumors as possible (Papazoglou, King, Morris & Krawiecki, 2009). The schedule for collecting data was an assessment at diagnosis, six months post diagnosis, and each year following diagnosis (Papazoglou, King, Morris & Krawiecki, 2009). This assessment schedule was not possible for every individual; therefore there is variation in the number and timing of individual assessments. All available data from assessments are included in analyses.

Measures

The Wide Range Achievement Test Revised (WRAT-R) reading subtest was used to assess reading skills in this longitudinal study on children diagnosed with pediatric brain tumors. The WRAT-R has been widely used to assess real world reading decoding skills in children with neurological impairments and pediatric cancer populations (Willis et al., 1997; Johnston et al., 1996; Prior et al., 1994; Stehbens and Kisker, 1984). Additionally, researchers report that the WRAT-R can be used to accurately assess individuals who fall in a low range of cognitive functioning (Johnstone et al., 1996).

All the children included in this study were at least 5 years old at the time of assessment, in accordance with WRAT-R administration protocol. The WRAT-R was divided into 2 forms, where level 1 is for participants from 5-11 years old and level 2 is for participants from 12-75 years old (Jastak and Wilkinson, 1984). Both forms of the WRAT-R reading subtest consisted of identifying letters and pronouncing words (Jastak and Wilkinson, 1984). For the level 1 form, raw scores were out of 100 points and composed of three sections which contain a total of 25 letters that the participant must correctly identify, and a forth section which consisted of pronouncing 75 words (Jastak and Wilkinson, 1984). The level two forms are out of 89 points, and have 15 letter identification questions and 74 pronunciation questions (Jastak and Wilkinson, 1984). The overall raw score was converted into a standard score by using the conversion chart in the WRAT-R manual, and on this chart WRAT-R age norms start in 6-month increments, and switched to 12-month increments at age 14 (Jastak and Wilkinson, 1984). Since norms were based in half age increments, half age at exam was chosen as the measure of time in the analyses.

Values described in the WRAT-R manual suggest that the Reading Subtest has good reliability and validity. The WRAT-R Reading Subtest test-retest reliability was .94, and had high convergent validity with PIAT Reading Recognition scores (r=.87) (Jastak and Wilkinson, 1984).

Participants

Ethnic backgrounds consisted of 102 Caucasian participants, 29 African-American participants, and three participants were of other ethnicities. Parental occupation and educational background were used to calculate socioeconomic status (SES; Hollingshead, 1957). Using the Hollingshead Two-Factor Index of Social Position, SES was on average 3.08 (*SD*=1.21; based on a 1-5 scale in which 5 is the lowest socioeconomic status) for the sample. Access to resources was an important factor to consider because educational and family resources have large impacts on children's' reading development, so SES was included in analyses as a potential confound. Medical history of the participants included 94 participants treated with radiation therapy, 59 had a hydrocephalous diagnosis, and 51 children had a prescription for seizure medication and 34 had chemotherapy at the time of evaluation. All of the participants included in this study had surgery to remove the tumor growth. The distribution of sex was approximately equal with 65 females and 69 male participants. Radiation was coded as a dichotomous variable (0= no treatment with radiation 1= exposure to radiation). Radiation treatment was clearly a much more complicated variable, but for the purpose of this study, presence of brain related radiation was considered a simple and reasonable proxy for its impact on reading outcomes.

The average age at diagnosis was 7.40 (*SD*=4.26) and ranged from prenatal to 16.72 years old. The average age at the first time point was 9.72 (*SD*=3.91) and the range was from 5 to 18.25 years old. See Table 1 for average time since diagnosis. Table 1 also displays percent impairment for the sample at each time point, however this is only a descriptive measure of impairment, and more detailed analyses would be necessary to reliably estimate the trend of impairment over time. See Table 2 and Table 3 for tumor locations and pathologies.

Table 1: Average Time Since Diagnosis and Percent Impaired for Each Time Point

Time Since Diagnosis	N	Mean Years (*SD*)	Percent Impaired* No RT (N)	Percent Impaired* Received RT (N)	Total Percent Impaired*
Time point 1	134	2.14 (3.01)	18.9% (40)	22% (94)	21.7%
Time point 2	101	3.06 (3.01)	12.9% (31)	22.9% (70)	20.4%
Time point 3	79	3.87 (2.79)	17.9% (28)	35.5% (51)	29.5%
Time point 4	64	4.75 (2.47)	13.6% (22)	53.4% (42)	39.7%
Time point 5	45	5.98 (2.79)	15.4% (13)	46.9% (32)	37.8%
Time point 6	29	6.55 (2.55)	0% (7)	45.5% (22)	34.5%
Time point 7	20	7.68 (2.75)	16.7% (6)	57.1% (14)	45%
Time point 8	11	8.45 (2.84)	0% (3)	62.5% (8)	45.5%
Time point 9	5	10.03 (3.53)	0% (2)	66.7% (3)	40%

*The threshold for impairment was a score greater than or equal to 1.5 standard deviations below the mean

Table 2: Tumor Location in Children Diagnosed with Brain Tumors (N=134)

Location	Number of participants
Cortical	61
Ventricle	18
Cerebellum	12
Pituitary Gland	12
Thalamus/Hypothalamus	11
Brainstem	8
Optic Nerve	3
Basal Ganglia	3
Corpus Callosum	2
Skull Base	2
Midline	1
Tectal Plate	1

Table 3: Tumor Pathologies in Children Diagnosed with Brain Tumors (N=134)

Pathology	Number of participants
Astrocytoma	60
Primitive Neuroectodermal (PNET)	39
Craniopharyngioma	14
Ganglioglioma	6
Germ Cell	5
Meningioma	4
Optic Nerve Glioma	3
Oligodendrogloma	2
Sarcoglioma	1

Results

Based on previous research, the hypothesis was that younger age at diagnosis and presence of radiation therapy would be predictive of lower reading ability over time. Standard score values on the WRAT-R Reading Subtest were used to access reading skills. Therefore, decline in standard score values represented participants falling behind in relation to their peers, rather than losing reading skills. We selected multilevel linear modeling to analyze the data because it allows for variability in individual slopes, dependent observations, unbalanced waves of data and missing data (Fields 2009). The data consisted of 134 participants with one to nine time points which resulted in 487 cases for analysis.

A two level model analyzed the long-term effects of age at diagnosis, socioeconomic status, and presence of radiation on reading skills in children diagnosed with brain tumors. The first level of this mixed model included participants' individual intercepts and trajectories of repeated WRAT-R reading standard scores over time. The intercept represented the average starting WRAT-R standard score at the most frequent age of testing. This model used unbalanced time points between testing. Slopes in level one represented the individuals change in reading scores over time. Level two predictors varied between participants and explained variance in level one slope and intercept values. The second level of the model consisted of multiple predictor variables: age at diagnosis, socioeconomic status, presence of radiation therapy, and time, measured by half age at exam, as well as interactions between these variables. The WRAT-R standard scores norms were based on half age at exam; therefore half age at exam was selected as the measure of time. We also hypothesized random slope variables (also known as slope as outcome variables) which were interactions between the predictor variables and the time variable. Socioeconomic status and age at diagnosis were grand mean centered to have a meaningful intercepts and to reduce multicollinearity. Time, measured by half age at exam, was mode centered to focus on an instance where the most data points exist and to have a meaningful intercept.

First, a null model determined if the individuals' trajectories varied significantly and this also created a comparison model for subsequent models. All results were given using Restricted Maximum Likelihood (REML) because prior research suggests that REML is more accurate with small sample sizes (Heck et al., 2010). Fields (2009) notes that autoregressive Heterogeneous is a common covariance structure used in repeated-measures data, and the Chi square model fit comparisons were significant indicating that autoregressive Heterogeneous was the best fitting covariance structure. This means that autoregressive Heterogeneous covariance structure significantly predicted the error structure of the data(see Table 4), AR Heterogeneous vs. Diagonal: $\chi^2(1) = 5.24$, $p = 0.02$; AR Heterogeneous vs. AR:$\chi^2(1) = 166.7$, $p <.001$.

Table 4.Estimates of covariance structure for the unconditional model

Covariance Structure of Unconditional Model	*AIC*	*-2LL*	*DF*
AR Heterogeneous	3721.58	3713.58	6
Autoregressive (AR)	3886.28	3880.28	5
Diagonal	3724.82	3718.82	5

Results of the unconditional model showed that there was significant variability in WRAT-R reading standard scores between participants and over time, which indicated that participant intercepts and slopes varied significantly (see Table 5; Wald $Z=3.74$ $p<.001$; Wald $Z= 5.84$, $p<.001$). In this model, the intraclass correlation, or amount of variability in reading scores that occurred between participants, was $78.9\% = 220.32 / 278.94 * 100$. Since there was significant variability, ("more than .05" see Heck, Thomas & Tabata, 2010, page 74) the intraclass correlation indicated that there was significant variance between participants. In other words, there were differences between individuals that could be explained by predictor variables.

Table 5.Estimates of covariance parameters for the unconditional model

Parameter	*Unstand. Estimate*	*SE*	Wald Z	*P one tailed*
Repeated Measures	54.25	4.59	11.83	.00
Intercept + Time [subject = idnum * half age at exam]	220.32	37.72	5.84	.00
Intercept [subject= idnum]	4.37	1.17	3.74	.00
ARH1 rho	.41	.16	2.53	.01

We used level two variables to explain individual variance in intercepts and slopes at level one of the model (see Table 6). Socioeconomic status, Radiation*Time, and an interaction between radiation and age at diagnosis were predictor variables that significantly improved the model. Interactions of socioeconomic status*time, age at diagnosis*time, and age at diagnosis*radiation*time as well as other interactions of predictors were not significant, so they were removed from the model to increase parsimony. Results suggested that lower socioeconomic status (SES was on a 1-5 scale where 5 is the lowest SES) had a significant negative impact on reading ability (γ =-6.77 p=.00), indicating lower socioeconomic status results in worse reading ability relative to peers.

Slopes as outcome variables allowed the slope of reading scores to vary based on predictor variables and results detected a negative interaction between radiation and time (γ =-2.29, p=.00; see Figure 1) indicating that children treated with radiation therapy have reading scores that decrease over time. A positive interaction between age at diagnosis and radiation was present, which meant that radiation therapy and younger age at diagnosis was associated with lower reading scores, whereas age at diagnosis had no effect for participants who were not treated with radiation therapy(γ =2.08, p=.02; see Figure 2).

In an effort to target a specific age range for optimal outcomes after radiation therapy, we looked at regions of significance of radiation therapy based on different ages at diagnosis. Regions of significance suggested that children younger than 5 years of age who receive radiation had significantly worse WRAT reading standard scores over time. In this model, there is no age where having radiation significantly improved reading scores (see Table 7).

Table 6.WRAT-R Reading Scores: Estimates of Fixed Effects

Parameter	*Estimate*	*Std Error*	*Degrees of Freedom*	*T*	*Sig.*
Intercept	94.60	2.64	141.06	35.89	.00
Time [half age at exam]	.43	.53	100.71	.80	.43
Radiation	-.32	3.16	141.25	-.10	.92
Age at Diagnosis	.75	.74	185.31	1.00	.32
SES	-6.77	1.08	105.56	-6.26	.00
Radiation * Time	-2.29	.63	100.98	-3.63	.00
Radiation * Age at Diagnosis	2.08	.88	182.08	2.36	.02

Table 7.Regions of Significance Based on Radiation at Different Ages of Diagnosis

Ages at diagnosis	*Estimate*	*SE*	*p one tailed*
1 year	-13.61	5.05	.008
4 years	-7.38	3.21	.024
5 years	-5.30	2.89	.071
6.8 years (Mean)	-.32	3.16	.92
16.72 years (Maximum)	19.03	10.06	.06

Figure 1. Interaction between Radiation and Time

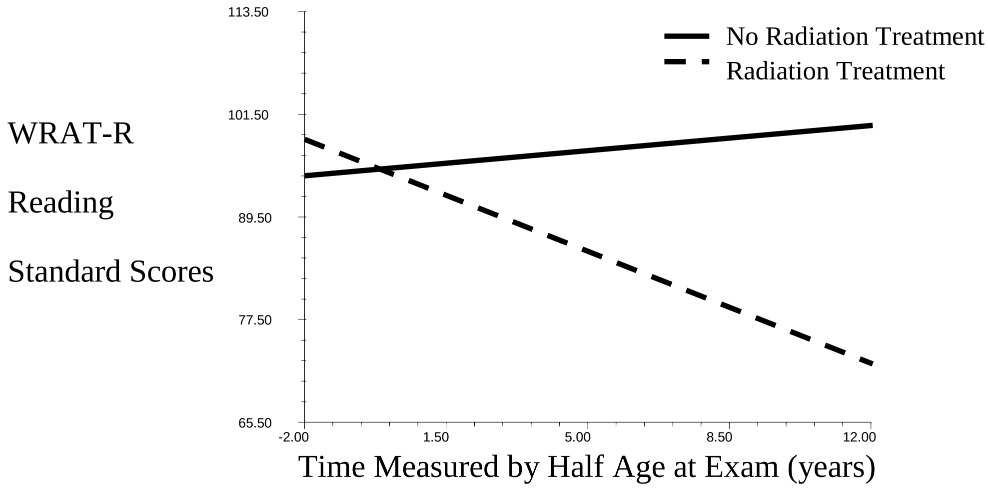
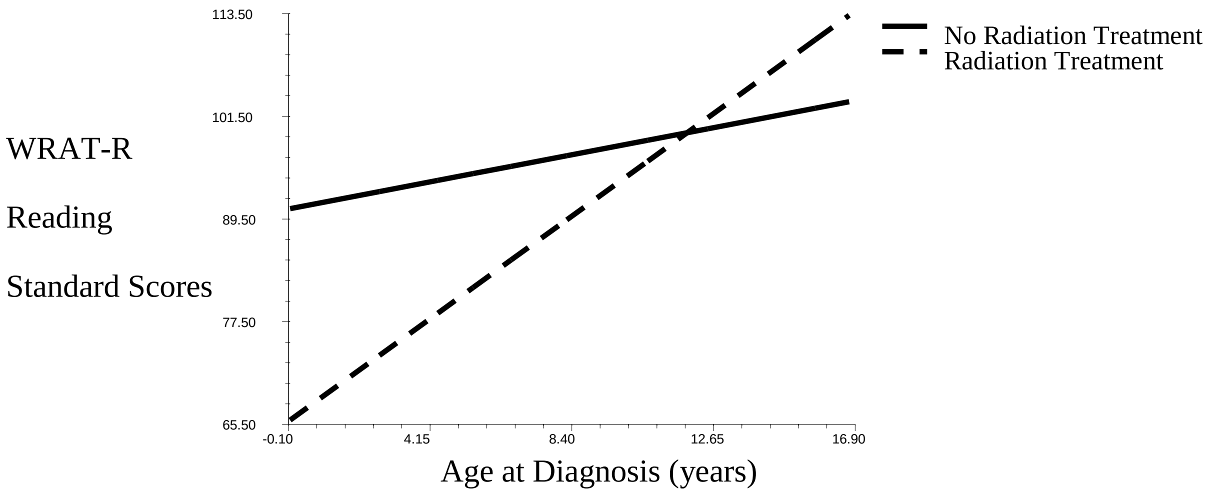


Figure 2. Interaction between Radiation and Age at Diagnosis



The Chi Square test assessed model fit, and the addition of predictor variables improved the fit of the model (unconditional growth -2LL = 3886.28 (df=6), full model -2LL = 3618.28 (df=11); $\chi^2(5) = 267.98$, p = <.001) While the added predictors improved the model, level two residuals (Wald Z = 3.40, p < .01) suggested that there was still significant variability between participants which could be explained by additional predictor variables (see Table 8). Future research should explore other predictor variables, such as tumor location or educational experience, to explain this variance.

Table 8.WRAT-R Reading Scores: Estimates of Random Effects

Parameter	*Unstand. estimate*	*SE*	Wald Z	*p one tailed*
Repeated Measures	53.87	4.47	12.05	.00
Intercept + Time [subject = idnum * half age at exam]	125.65	24.52	5.13	.00
Intercept [subject= idnum]	3.19	0.94	3.40	.001
ARH1 rho	.50	.18	2.69	.007

Discussion

Significant Risk Factors

Similar to the findings of Mabbott et al. (2005), Mulhern et al. (2005), and Ellenberg et al. (1987), the results supported a theory of early vulnerability for individuals treated with radiation therapy, where young age at diagnosis and treatment with cranial radiation resulted in children's' reading ability falling behind in relation to peers. Consistent with the current understanding of the latent effects of radiation treatment, our results suggested that longer time since radiation treatment was associated with lower reading scores (Mulhern & Palmer 2003). Additionally, lower socioeconomic status was uniquely associated with a persistent decline in reading ability. Given these results, time since radiation, early age at diagnosis when associated with radiation treatment and low socioeconomic status should be considered risk factors for poor reading achievement over time in children diagnosed with brain tumors.

These results suggested that for individuals who have radiation, the trend of lower reading performance at a young age is consistent with our current understanding of diffuse brain insults (Max, Bruce, Keatley, and Delis, 2010). Clinicians should consider risk factors such as presence of radiation treatment, age at diagnosis, time since radiation and socioeconomic status when developing language interventions for children diagnosed with brain tumors because the factors appear to have a significant impact on reading skills. The persistent decline in reading relative to peers over time suggests that long-term intervention programs are necessary to remediate reading difficulties in children diagnosed with brain tumors. Additionally, remediating problems in reading development could help to improve academic achievement, which is a common problem area for children diagnosed with brain tumors (Gragert and Ris, 2011). Reading difficulties impair children's ability to function in a traditional classroom environment, and could contribute to later academic and social problems (Brinton & Fujiki, 1989; Catts, 1993; Gragert and Ris, 2011; Greenham et al., 2010).

Future Directions

The hypothesis that younger age at diagnosis would be associated with poorer outcomes for children who did not receive radiation treatment was not supported by our analyses. However, given the substantial body of research which supports this theory (Anderson et al., 2009; Chapman, 2003; Senathi-Raja, Ponsford, and Schönberger, 2010; Spiegler et al., 2004; Taylor and Alden, 1997), results should be replicated with a larger sample over a longer period of time. Additionally, while our model was significant and parsimonious in comparison to previous models, there are still other factors which future researchers should explore that could be contributing to low reading scores such as tumor size and pathology, educational experience, and type and dosage of radiation which could be contributing to poor reading achievement in this population. Additionally, descriptive analyses suggested an increased trend of impairment for children treated with radiation; therefore future researchers should investigate which factors affect the rate of reading impairment overtime in children diagnosed with brain tumors.

This study looked at reading achievement over 10 years in a heterogeneous group of children diagnosed with brain tumors. Future studies should investigate long term outcomes through adulthood to determine if survivors reading scores stabilize or if they continue to fall further behind their peers. Long term survivor studies would help determine the persistence of language difficulties, and help pinpoint specific areas of difficulty for survivors. These factors are important for successful invention programs to improve these patients quality of life. Low reading ability is difficult in childhood, and could be debilitating in adulthood where reading is an essential component to educational and occupational success.

Research suggests that early cranial radiation disrupts white matter development and myelination, which may explain some of the underlying neurological mechanisms causing language difficulties in children diagnosed with brain tumors (Mulhern & Palmer 2003; Palmer et al., 2010, Palmer et al., 2008). However, future brain imaging studies need to further explore the relationship between the radiation at a young age and the resulting neurological changes. To have a complete understanding of this relationship, researchers should consider designing longitudinal brain imaging studies to explore the neurological changes responsible for the latent effects of cranial radiation. Longitudinal fMRI studies are essential for understanding the neurological changes caused by radiation, and how to best remediate neural disruption and damage.

Limitations

Attrition and missing data are inevitable limitations to longitudinal analysis. Due to the nature of pediatric brain tumors it is possible that attrition is related to diagnosis, prognosis, and treatment of pediatric brain tumors. Selective attrition can result in biased growth trajectories because high risk participants may be unable to return for follow up assessments. Future research should investigate attrition and survival analyses in pediatric brain tumor studies so researchers have a better understanding of the causes and extent of participant dropout.

Strengths

This study included a heterogeneous group of pediatric brain tumors to investigate global risk factors in uniquely vulnerable population. We also including individuals who have been treated with or without cranial radiation, in an effort to explore the unique vulnerability displayed in young children who experience cranial radiation. Few studies examine longitudinal relationship between neurological risk factors and reading skills over 10 years. We utilized up to 9 assessments in 134 pediatric brain tumor survivors resulting in almost 500 cases for analysis. Looking at the longitudinal relationship between age at diagnosis radiation and reading ability allows us gain more information about the trajectory of reading ability in children with brain tumors. This longitudinal model helps to quantify the persistence of reading deficits in this population. While current physicians try to avoid cranial radiation for children under the age of three years old (Semonva, 2009), future studies should investigate the cognitive outcomes of radiation treatment at young age (less than 5 years old). This information is a key component to targeting at risk population and developing specific and effective reading interventions for children who have brain tumors.

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