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QUANTIFICATION OF WHITE MATTER HYPERINTENSITIES IN LONG-TERM
SURVIVORS OF CHILDHOOD BRAIN TUMOR: RELATIONSHIPS WITH COGNITION

by

HOLLY A. ALEKSONIS

Under the Direction of Tricia Z. King, Ph.D.

ABSTRACT

This study investigated relationships among quantified white matter hyperintensity (WMH) volumes and core cognitive skills in long-term survivors of childhood posterior fossa tumor utilizing a novel automated neuroimaging approach. Thirty-five survivors and 56 healthy controls underwent MRI and neuropsychological testing. Results indicated that log transformed normalized total WMH volumes differentiated groups based on treatment type, where survivors treated with chemoradiation therapy had significantly higher volumes of total WMH compared to survivors with surgery only and healthy controls, and survivors with surgery only had higher WMH volumes than healthy controls. In the total sample, higher total WMH volumes were associated with poorer performance on all cognitive measures. Three types of analyses indicated varying results about relationships among WMH location and oral processing speed. The most robust analysis, multivariate regression, showed periventricular WMHs are related to oral processing speed performance.

INDEX WORDS: Childhood brain tumor, White matter hyperintensities, Leukoencephalopathy, Cognitive skills, Neurological Predictor Scale, Magnetic Resonance Imaging

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HOLLY A. ALEKSONIS

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

in the College of Arts and Sciences

Georgia State University

2020

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Holly Anne Aleksonis
2020

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by

HOLLY A. ALEKSONIS

Committee Chair: Tricia King

Committee: Vonetta Dotson

Lisa Krishnamurthy

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

August 2020

DEDICATION

This proposal is dedicated to my partner, friends, and family for their continuous support throughout my education. I am grateful for their love, encouragement, and patience as I pursue career opportunities and educational goals, even as they take me to different parts of the country.

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1 INTRODUCTION

Childhood central nervous system tumors are among the most common pediatric cancers in the United States, second to only leukemia, with incidence rates of approximately 5.65 cases per 100,000 (Ostrom et al., 2018). Moreover, posterior fossa tumors account for over half of all childhood brain tumor diagnoses (Rickert & Paulus, 2001). With advances in medical treatments, the five-year survival rates in children diagnosed with brain tumors is over 70% (Central Brain Tumor Registry of the United States, 2018). Improvements in survivor rates are in large part due to advances in treatments with the use of a combination of surgery, chemotherapy, and radiation therapy. Consequently, increasingly more children are becoming long-term survivors of childhood brain tumor and are living into adulthood and beyond (CBTRUS, 2018). However, these intense treatments do not come without consequences and may result in late effects that are apparent throughout adulthood (Briere, Scott, McNall-Knapp, & Adams, 2008; Brinkman et al., 2012). Well-documented late effects present in survivors of childhood brain tumor include deficits in core cognitive skills, specifically, processing speed, attention, and working memory, as well as secondary effects on academic achievement and intellectual outcome (King, Ailion, Fox, & Hufstetler, 2019). Treatments for some childhood brain tumors possess a double edge sword, in that they are both life-saving and linked to late effects in vital neurocognitive skills that are important for academic achievement and adaptive functioning (Kautiainen, Na, & King, 2019; King & Na, 2016).

Radiation and chemotherapy are detrimental to cerebral white matter integrity and are associated with deficits in cognitive outcomes in survivors of childhood brain tumor (Anderson & Kunin-Batson, 2009; King, Wang, & Mao, 2015; Mulhern et al., 1999). As a result of treatment, leukoencephalopathy, or the presence of white matter hyperintensities (WMHs), are

lesions commonly seen on T2-weighted MRI images in survivors of childhood brain tumor (Reddick et al., 2005). There is limited and mixed research on the effects of the presence of leukoencephalopathy in survivors of childhood brain tumor (Hyman et al., 2003; Sabin et al., 2018). However, research with other populations (i.e., older adults, Alzheimer's, dementia, stroke) has shown relationships among higher volumes of WMHs and deficits in cognitive and functional outcomes (Brickman, Muraskin, & Zimmerman, 2009; Gunning-Dixon & Raz, 2000). However, to our knowledge, no research has attempted to investigate links among quantified WMHs and performance on cognitive measures in a sample of adult survivors of childhood posterior fossa tumor. Elucidating relationships such as these may be able to aide physicians and families in determining risk for deficits in cognitive outcomes. Establishing an automated pipeline to quantify WMHs that utilizes routine imaging scan protocols collected throughout treatment and longitudinally at follow-ups could help with identifying those who may be most at risk for developing these deficits.

The aim of the proposed study is to quantify WMH volumes in a sample of long-term survivors of childhood posterior fossa tumor compared to a sample of healthy controls. Furthermore, we aim to investigate the relationship among WMH volumes and performance on cognitive measures of processing speed, attention, working memory and intelligence. Specifically, we aim to explore if WMH volumes serve as a mediation mechanism in the relationship among a measure of neurological risk and performance on the above-mentioned cognitive skills. Additionally, this study aims to explore differing relationships among periventricular and subcortical WMHs and performance on measures of these cognitive skills.

1.1 Cognitive Outcomes in Survivors of Childhood Brain Tumor

Survivors of childhood brain tumor are at increased risk for neurocognitive and psychosocial late effects (Anderson & Kunin-Batson, 2009; Turner, Rey-Casserly, Liptak, & Chordas, 2009). Even 10 years after diagnosis, survivors show deficits in multiple domains in comparison to peers (Briere et al., 2008; Brinkman et al., 2012). Quantitative meta-analyses indicate that survivors of childhood brain tumor experience clinically significant deficits in broad and specific domains of cognitive functioning (Robinson et al., 2010). Specific domains of neurocognitive dysfunction common in survivors include overall cognitive ability, executive function, working memory, processing speed and attention (Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013; Wolfe et al., 2013). Neurocognitive late effects have been given heightened attention in the literature because of their influence on academic and daily functioning (Wolfe, Madan-Swain, & Kana, 2012).

Processing speed, attention and working memory are considered the three core cognitive processing vulnerabilities after disease and treatment in short- and long-term survivors of childhood brain tumor (King et al., 2019; Palmer, 2008; Wolfe et al., 2012). Recently, King and colleagues (2019) utilized samples of both adult survivors of childhood brain tumor and healthy controls to test which conceptual models best fit their data – Palmer’s (2008), Wolfe’s (2012) or a combination of the two. Path model analyses indicated that a combined model best explained the data of both survivors and controls (King et al., 2019). The model shows that processing speed performance has direct influence on working memory, academic achievement, attention, and intelligence. Additionally, attention and working memory have cascading influences on academic achievement and intelligence performance. The strongest effect on processing speed in this model is presence of radiation therapy; age at diagnosis had an effect on working memory

performance. The combined model is a good representation of risk factors that may have an effect on cognitive performance outcomes, however, it does not help to explain the neurological mechanism by which these risk factors influence behavioral outcomes.

1.2 Neurological Risk is Predictive of Cognitive Skills and Brain Outcomes

While some factors such as radiation, age at diagnosis, and hydrocephalus contribute to poor outcomes seen in survivors of childhood brain tumor, there is no one risk factor that can inform which survivors are most likely to experience late effects in their lifetime (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Hardy, Bonner, Willard, Watral, & Gururangan, 2008). Rather, it is the culmination and interaction of many factors, including the tumor itself, treatment, hydrocephalus, seizures, etc., which contribute to the neurological risk and the increased likelihood of developing deficits in broad domains. A measure of neurological risk, the Neurological Predictor Scale (NPS), measures cumulative risk associated with factors common during brain tumor treatment such as radiation, chemotherapy, surgery, hydrocephalus, and others (Micklewright, King, Morris, & Krawiecki, 2008). The NPS is associated with a variety of cognitive skills and structural brain outcomes after childhood brain tumor.

The NPS has been shown to predict performance on core cognitive skills, such as processing speed, attention, working memory, intelligence, executive function, and academic performance (Kautiainen et al., 2019; McCurdy, Rane, Daly, & Jacobson, 2016; Taiwo, Na, & King, 2017). Additionally, the NPS is a better predictor of performance on processing speed, attention, working memory, and academic functioning measures than each individual risk factor from the measure (Kautiainen et al., 2019; Taiwo et al., 2017). Thus, it is clear that multiple treatments and complications contribute to risk for deficits in cognitive functioning many years after childhood brain tumor diagnosis and treatment. Many of these risk factors, especially

chemoradiation therapy, are known to be detrimental to cerebral white matter integrity (Anderson & Kunin-Batson, 2009; Reinhold, Calvo, Hopewell, & Van den Berg, 1990).

Therefore, it is not surprising that the NPS is also related to brain health outcomes.

Emerging evidence on relationships among NPS and brain white matter integrity suggests that these cumulative neurological risk factors and not just chemoradiation therapy, are potentially detrimental to white matter integrity. Smaller volumes in the hippocampus, putamen and corpus callosum are associated with higher scores on the NPS, signifying higher neurological risk, in childhood brain tumor survivors (Jayakar, King, Morris, & Na, 2015; K. M. Smith, 2016). In a study utilizing diffusion tensor imaging (DTI), lower mean fractional anisotropy values in the corpus callosum, frontal and temporal regions were robustly correlated with higher NPS scores in adult survivors of childhood brain tumor (King, Wang, et al., 2015). Additionally, in adult survivors of childhood cerebellar tumor, the percentage of atrophy in the cerebellum was positively associated with NPS scores, further exemplifying the links among the cumulative effects of neurological factors and compromised white matter integrity (Ailion et al., 2016). Finally, in a study utilizing DTI and deterministic tractography to explore white matter network properties, lower global efficiency or lower levels of global processing were associated with higher scores on the NPS (Na et al., 2018). Furthermore, global efficiency mediated the relationship among NPS score and cognitive flexibility in adult survivors of childhood brain tumor (Na et al., 2018). Collectively, research supports cumulative neurological risk factors, measured by the NPS, to be robustly associated with both cognitive skills and brain outcomes following treatment for childhood brain tumor.

1.3 Treatment Effects on Cerebral White Matter Integrity

Diagnosis and treatment for childhood brain tumor happens during childhood and adolescence, a period of significant change in white matter integrity and maturation, most predominantly in the frontal lobes (Barnea-Goraly et al., 2005; Nagy, Westerberg, & Klingberg, 2004). Survivors of childhood posterior fossa tumors consistently show reduced volumes of whole brain white matter when compared to controls, which appears to be related both to a loss of white matter volume from treatment and failure to show age expected growth (Ailion, Hortman, & King, 2017). Paralleling this change in cerebral white matter during adolescence and childhood are periods of widespread cognitive development in different areas, including executive function, working memory, and cognitive flexibility. Global white matter integrity volume loss is associated with global functioning such as intelligence and academic functioning in both short- and long-term survivors of childhood brain tumor, particularly in those who underwent chemoradiation therapy (King, Wang, et al., 2015; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Partanen et al., 2018). Decreased performance on core cognitive measures has been associated with decreased normal appearing white matter in specific subcortical brain regions (see (Ailion et al., 2017) for a review). Briefly, processing speed is positively associated with white matter in the corpus callosum and bilateral temporal lobes. Additionally, processing speed may mediate the relationship between white matter integrity in the inferior fronto-occipital fasciculus and parietotemporal-occipitotemporal pathway, measured by DTI, and word reading outcomes; suggesting the important relationships among white matter integrity and processing speed, which has cascading effects on other important cognitive skills (K. M. Smith, King, Jayakar, & Morris, 2014). Furthermore, other cognitive skills are linked to white matter integrity throughout the brain. For example, attention is positively associated with

white matter in the bilateral hippocampus and frontal lobes; working memory is positively associated with white matter in the bilateral parietal lobes and bilateral hippocampus (Ailion et al., 2017).

Radiation therapy, in particular, has a significant impact on demyelination and compromised white matter in long-term survivors of childhood posterior fossa tumor. In animal studies, radiation exposure induced cellular and vascular injury is associated with demyelination up to a year following initial exposure (Reinhold et al., 1990). White matter is more sensitive to radiation exposure because it is lower in density and has lower blood flow than grey matter (Reinhold et al., 1990). Additionally, the hippocampus is especially sensitive to ischemia and hypoxia caused by irradiation (Abayomi, 1996). WMHs, also referred to as leukoencephalopathy, are bright spots that appear on T2-weighted MRI images and are evidence of compromised white matter integrity; leukoencephalopathy is commonly seen in childhood cancer survivors after treatments utilizing chemotherapy and radiation therapy (Matsos et al., 2017). Associations among WMH volume and decreased performance on measures of cognitive skills have been identified in other populations (e.g., community samples, older adults, dementia; (Kloppenborg, Nederkoorn, Geerlings, & van den Berg, 2014). However, there is a dearth of knowledge about total WMH volume after childhood posterior fossa tumor and potential links to cognitive performance.

1.4 WMHs are Related to Cognitive Skills

There is limited and sometimes conflicting research on the relationships among cognitive outcomes and presence of WMHs after treatment for childhood brain tumor. In two samples of survivors of childhood ALL treated with chemotherapy, abnormal appearing white matter was not associated with decreased cognitive outcomes (Cheung et al., 2016; Sabin et al., 2018).

However, in one of these samples, leukoencephalopathy presence was associated with neurobehavioral problems indicated by scores on the Behavioral Rating Inventory of Executive Function parent report (Cheung et al., 2016). Additionally, in survivors of childhood ALL, dichotomized leukoencephalopathy presence was associated with decreased attention and working memory (Ashford et al., 2010). Furthermore, one study with survivors of childhood medulloblastoma treated with radiotherapy and chemotherapy found the presence of white matter lesions in visual review of T1- and T2-weighted scans, which were characterized by grade severity, to be associated with greater decline in intelligence and math (Fouladi et al., 2004). Another study was able to predict severity of leukoencephalopathy grade based on parent-reported cognitive function, suggesting that more severity of WMH presence is associated with worse cognitive outcome (Lai et al., 2017). In a study of long-term follow-up in adult survivors of low-grade glioma, presence of WMHs was significantly associated with cognitive performance, especially in those who were treated with radiotherapy (Douw et al., 2009). Of note, the research that is available on survivors of childhood cancer often only include either indication whether leukoencephalopathy is present or not, or the presence of WMHs is characterized based on a severity grade scale after review of MRI FLAIR and/or T2-weighted images by a trained radiologist or neurologist. These categorical methodologies lack specificity to the wide range of WMHs seen after treatment for childhood cancer. Methodology that objectively quantifies WMHs could provide a continuous measure that is more sensitive to differences in severity of WMHs.

To our knowledge, there is no current research that investigates relationships among WMH volumes and cognitive performance after treatment in long term survivors of childhood brain tumor. However, extensive research with other neurological populations (e.g., community

samples, older adults, traumatic brain injury, sickle cell) may provide some additional insight into the potential relationships among WMH volumes and cognitive outcomes. Extant literature on healthy aging adults provides evidence for small to moderate effect sizes of the relationships among presence of WMHs and cognitive skills, especially global cognitive functioning, attention, executive function, memory, and processing speed (Gunning-Dixon & Raz, 2000; Kloppenborg et al., 2014). Furthermore, in longitudinal studies, progression of WMHs was associated with worse cognitive outcomes overtime (Kloppenborg et al., 2014). In a large study utilizing young adults to older adults, total volumes of WMHs, traced by a single rater on MRI T2-weighted sequences, explained significant variance in working memory, processing speed, and fluency beyond demographic variables (Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). While the strongest effects were seen in adults over 60 years of age, it should be noted that volumes of WMHs in the younger sample were minimal to none and may not have had enough variance for significant effects to be detected (Vannorsdall et al., 2009). In other studies, quantified WMH volumes on MRI FLAIR sequences were predictive of functional outcomes after traumatic brain injury, where higher volumes were associated with poorer functional outcomes (Ding et al., 2008; Plata et al., 2007). Finally, in a sample of children with sickle cell disease, larger total volume of WMHs on MRI FLAIR sequences was associated with lower scores on full-scale intelligence, verbal intelligence, and processing speed tests (van der Land et al., 2015). In sum, increased volumes of WMHs are consistently associated with decreased performance in global cognition, working memory, processing speed, and executive functioning, especially on timed tasks, in samples of healthy older adults, community samples, and clinical populations. Increases in WMH volumes over time and more WMH burden are associated with declining cognitive performance in healthy and clinical older adults.

1.5 Periventricular and Subcortical WMHs May Relate to Different Cognitive Skills

Total WMH volume may tell us about total WMH burden and cognitive performance, however, investigating relationships among WMH location and specific cognitive skills may offer additional information. WMHs are commonly categorically separated into subcortical WMHs and periventricular WMHs as they may have varying function within the brain based on their differences in structure. Periventricular WMHs are those that are in contact with the wall of a ventricle, consist of longer fiber connections, and are thought to be more frequent than subcortical WMHs in older adults and individuals treated with radiation therapy (Bolanzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; Kanekar & Devgun, 2014; Vannorsdall et al., 2009). Subcortical WMHs are often more broadly defined as being located beneath the cortex and are not in contact with a ventricle wall (Vannorsdall et al., 2009). It is still not known how or if these groups have different relationships with cognition. To our knowledge, to date, no study has investigated relationships among WMH location and cognitive skills in survivors of childhood posterior fossa tumor. However, there is a growing body of research within older adult and community samples in which recent meta-analyses and systematic reviews reveal some trends about the potential connections among WMH location and performance on cognitive measures, especially within periventricular WMHs.

Periventricular WMHs are more consistently shown to be related to cognitive skills in healthy adult and older adult populations compared to subcortical WMHs (Bolanzadeh et al., 2012; Kloppenborg et al., 2014; E. Smith et al., 2011). When controlling for subcortical WMHs, increased periventricular WMHs were shown to be associated with decreased performance on memory and processing speed tasks in multiple studies included in a systematic review (Bolanzadeh et al., 2012). Another study with an adult community sample revealed

periventricular WMHs, defined as being in contact with a ventricle wall on T2-weighted images and traced by an individual, were significantly associated with performance of working memory and processing speed performance; subcortical WMHs were also associated with working memory (Vannorsdall et al., 2009). One study in older adults, utilizing a 0-9 severity lesion scale based on hyperintense T2-weighted and hypointense T1-weighted images, showed that periventricular WMHs were associated with psychomotor speed (i.e., processing speed), memory and a composite cognitive index when controlling for subcortical WMHs (de Groot et al., 2000). Significant subcortical WMH relationships with cognition that were initially found to be significant were no longer significant after controlling for periventricular WMHs (de Groot et al., 2000). In a longitudinal study with older adults, periventricular WMH volume, quantified from T2-weighted images with a semi-automated processing pipeline, was associated with lower processing speed (Van den Heuvel et al., 2006). Additionally, periventricular WMH progression paralleled declines in processing speed; subcortical WMHs did not show relationships with any cognitive tests in this study (Van den Heuvel et al., 2006). In contrast, one study with individuals with vascular dementia showed that subcortical WMHs as defined on T1-, T2-weighted and FLAIR images utilizing semi-automated thresholding methods, were associated with performance on measures of attention-executive-psychomotor functioning; Digit Symbol and Digit Span accounted for the most variance in statistical analyses (Cohen et al., 2002). Interestingly, whole brain volume was not associated with the same skills as subcortical WMHs and vice versa, showcasing a differential association with cognitive skills (Cohen et al., 2002). This finding suggests that whole brain volumes may facilitate different cognitive skills than specific white matter tracts that WMHs could disrupt.

Not all studies have revealed consistent independent associations among categorical WMHs and cognitive skills like the ones mentioned previously. It should be noted that one quantitative review showed that while total WMH burden was significantly associated with multiple cognitive domains, periventricular and subcortical WMH categorizations were not significantly associated with global functioning, speed, fluid intelligence or executive function (Gunning-Dixon & Raz, 2000). Periventricular WMHs, subcortical WMHs, and total WMHs are often shown to be highly correlated with each other and could explain why some studies do not find differing relationships among periventricular and subcortical WMHs and performance on cognitive measures (DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005). However, a more recent study with older adults, utilizing T2-weighted FLAIR images and lesion loading calculations, showed significant associations of processing speed and executive function with total, periventricular, and subcortical WMH volumes (Jiang et al., 2018). Overall, periventricular WMHs seem to be most consistently related to performance on measures of processing speed and memory, while subcortical WMHs have been shown to be related to performance on measures of attention span.

1.6 Aims of the Proposed Study

To our knowledge, no study has previously quantified the presence of WMHs, utilizing an automated imaging pipeline with T1- and T2-weighted images, in a sample of adult long-term survivors of childhood posterior fossa tumor. We will investigate differences in WMH volume of survivors compared to controls. Additionally, we will investigate differences in WMH volumes of survivors treated with and without radiation and/or chemotherapy. Next, we will determine potential relationships among WMH volume and measures of core cognitive skills- processing speed, attention span, working memory and intelligence- using correlation analysis. We will test

regression models to determine if the volume of WMHs mediates the relationship between scores on a measure of neurological risk and core cognitive skills. Finally, we will investigate relationships among periventricular WMHs and subcortical WMHs and performance on core cognitive skills.

1.6.1 Specific Aim 1: To quantify WMH volume in long-term survivors of childhood brain tumor and healthy controls.

Hypothesis 1a: Long-term survivors of childhood brain tumor will have significantly higher volumes of WMHs compared to healthy controls.

Hypothesis 1b: Additionally, survivors who were treated with radiation, chemotherapy, or a combination will have larger volumes of WMHs compared to those treated with surgery only and healthy controls.

1.6.2 Specific Aim 2: To investigate relationships among total volume of WMHs and outcomes on cognitive measures of processing speed, attention span, working memory, and intelligence.

Hypothesis 2a: Higher volumes of WMHs will be significantly associated with worse performance on measures of processing speed, attention span, working memory and intelligence.

Hypothesis 2b: Total volume of WMHs will mediate the relationship between the NPS and performance on core cognitive skills, processing speed, attention span, working memory, and intelligence.

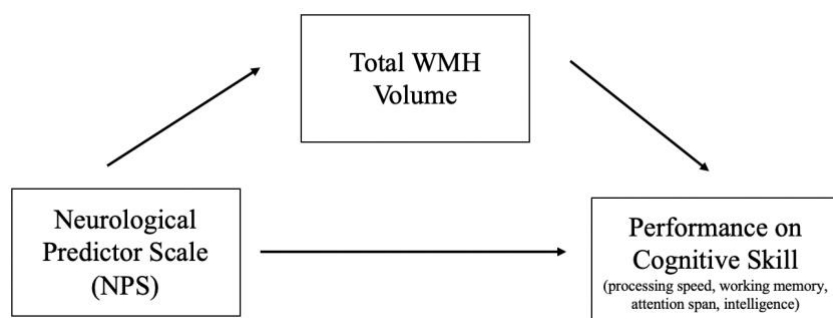


Figure 1. Hypothesis 2b: Proposed Mediation Model

1.6.3 Specific Aim 3: To investigate potential brain-behavior relationships among WMH categories and performance on measures of core cognitive skills (processing speed, attention span, and working memory).

Hypothesis 3: Periventricular WMHs will be related to performance on measures of processing speed and working memory and will not be related to attention span or intelligence, when controlling for subcortical WMHs and whole brain volume.

Subcortical WMH will be related to performance on a measure of attention span and will not be related to processing speed, working memory, or intelligence, when controlling for periventricular WMHs and whole brain volume.

2 METHODS

2.1 Procedures

2.1.1 Participant Screening and Recruitment

Participants were recruited as part of a parent study investigating long-term functional outcomes in childhood brain tumor survivors. The parent study protocol was reviewed and approved by the local institutional review board, and all participants provided written informed

consent. Survivors were recruited using mailings from three sources: (1) a previous longitudinal childhood brain tumor study, (2) a large hospital system database of survivors treated over 10 years ago, and (3) through the state Brain Tumor Foundation newsletter. Healthy controls were recruited through Georgia State University's undergraduate Psychology participation pool, the Center for Advanced Brain Imaging (CABI), friends of survivors, and community fliers. Participants were compensated for their time by psychological class credit, monetary compensation, or both.

Participants were considered ineligible or excluded from the current study if they indicated a diagnosis of Neurofibromatosis, met diagnostic criteria for pervasive developmental disorder, had experienced any significant neurological insult (e.g., traumatic brain injury, stroke), or if they did not indicate fluency in English. Participants were excluded if hearing loss was not corrected by a hearing aid or if they were unable to complete the full battery of testing due to insufficient hearing accommodations. Additionally, participants were excluded if they had impaired vision that was not corrected by corrective lenses or if they were unable to complete testing. Healthy control participants were also screened for past or current psychopathology with the Structured Clinical Interview for DSM-IV-TR Axis 1 and were excluded if they met criteria for a psychiatric disorder (First, Spitzer, Gibbon, & Williams, 2002).

The original sample of participants eligible to be used in the analyses for this study included 41 long-term survivors of childhood posterior fossa tumor and 58 healthy controls. During pre-processing, six survivors and two healthy controls were excluded because of motion artifacts in images. Those excluded from analyses did not significantly differ from the group averages in age at examination, years of education, gender, or performance on any of the cognitive measures. For variables specific to survivors, those excluded from analyses did not

significantly differ from those include on NPS score, age since diagnosis, tumor type, presence of hydrocephalus, presence of seizures, presence of chemotherapy or presence of radiation. The final sample of participants used in these analyses included 35 survivors of childhood cerebellar tumor and 56 healthy controls. Demographics of the sample can be found in Table 1. Survivors (42.9 % female) had a mean age of 21.29 (SD = 6.51; range: 8-35) and controls (51.8% female) had a mean age of 22.53 (SD = 4.41; range: 18-41) at the time of study participation. Survivors were on average 8.14 (SD = 4.72; range: 1-19) years old at diagnosis and an average of 13.13 (SD = 6.89) years since diagnosis, and an average of 12.01 (SD = 6.94) years since their last treatment. In this sample of survivors, 45.7% had a low-grade tumor and 54.3% had a high-grade tumor.

Table 1. Demographics of Controls, Survivors, and Group Comparisons

	Controls (n = 56)	All Survivors (n = 35)	<i>X²</i>
Gender	51.8% Female	42.9% Female	.407
Race	47.3% Caucasian 30.9% African-American 12.7% Asian 9.1% Other	64.7% Caucasian 20.6% African-American 2.9% Asian 11.8% Other	.254
Handedness (% Right)	90.4% Right	88.2% Right	.224
	M (SD)	M (SD)	<i>p</i>
Age (years)	22.53 (4.41)	21.29 (6.51)	.324
Education (years)	14.45 (1.72)	12.14 (3.53)	.001

This sample includes only those with tumors located in the posterior fossa region. Information about tumor types and treatment variables can be found in Table 2. 51.4% of the survivors received chemotherapy and 54.3% received radiation therapy with an average of 39.81

Gy. Of those who received either chemotherapy or radiation therapy treatments, 90.0% received both during the course of their treatment. All the survivors in this sample had surgical resection of their tumor. The average Neurological Predictor Scale (NPS) score was 6.21 (SD = 2.50; range = 2–9), with larger values signifying more cumulative neurological risk.

Table 2. Survivor Demographics and Treatment Characteristics

	All Survivors (n = 35)	Chemo/Radiation (n = 20)	Surgery Only (n = 15)	χ^2
Gender	42.9% Female	60.0% Female	20.0% Female	.018
Race	64.7% Caucasian 20.6% African-American 2.9% Asian 11.8% Other	73.7% Caucasian 10.5% African-American 15.8% Other	53.3% Caucasian 33.3% African-American 13.4% Other	.478
Handedness	88.2% Right	89.5% Right	86.7% Right	.884
	M (SD)	M (SD)	M (SD)	p
Age (years)	21.29 (6.51)	22.20 (6.14)	20.07 (7.00)	.345
Age at Diagnosis (years)	8.14 (4.72)	7.85 (4.98)	8.53 (4.50)	.674
Education (years)	12.14 (3.53)	12.26 (2.56)	12.00 (4.57)	.883
<i>Treatment Characteristics</i>	% (n)	% (n)	% (n)	χ^2
Tumor Type	51.4 (18) Medullo 31.4 (11) JPA 17.2 (6) Other	90.0 (18) Medullo 5.0 (1) JPA 5.0 (1) Other	66.7 (10) JPA 33.3 (5) Other	<.001
Chemotherapy	51.4 (18)	90.0 (18)	-	-
Radiation	54.3 (19)	95.0 (19)	-	-
Hydrocephalus	77.1 (27)	80.0 (16)	73.3 (11)	.642
Seizure Presence	4.8 (2)	5.0 (1)	6.7 (1)	.357

Note. medullo=medulloblastoma; JPA=juvenile pilocytic astrocytoma; other= fibillary astrocytoma, ependymoma, choroid plexus papilloma, anaplastic astrocytoma, pineoblastoma, and primitive neuroectodermal tumor (PNET)

2.1.2 Assessment of Processing Speed

Processing speed was measured using the Oral Symbol Digit Modality Test (OSDMT; (A. Smith, 1982). In this timed task, participants are given a key with symbols and their corresponding number. On this same page there are sequences of the same symbols and an empty box beneath each one. Participants are given 90 seconds to say the number that corresponds with the symbol in each box. The OSDMT has high test-retest reliability at .76 (A. Smith, 1982). Raw scores were converted into age-normed z-scores.

2.1.3 Assessment of Attention

Attention was measured using the Digit Span Forward subtest from the Wechsler Memory Scale-Third Edition (WMS; (Wechsler, 1997). During Digit Span Forward, participants are asked to immediately repeat a sequence of numbers at increasing difficulty until two consecutive failed sequences are obtained. The highest number of digits within a sequence repeated accurately will be used to represent attention span; Digit Span Forward and Digit Span Backward represent different constructs and should not be combined (Kieffer-Renaux et al., 2000; Rosenthal, Riccio, Gsanger, & Jarratt, 2006). A raw score covaried with age was used because the WMS only provides age-standardized normative data for the composite of Digit Span Forward and Backward. The test-retest reliability for the Digit Span Forward is high, .83 (Wechsler, 1997).

2.1.4 Assessment of Working Memory

Working memory was measured using the Auditory Consonant Trigram (ACT; (Stuss, Stethem, & Poirier, 1987). In this test, participants are asked to remember three consonants (e.g., B-D-T) that are first read by the examiner. Then, the participant is asked to count backwards from a given number, and after 18 seconds the participant is asked to recall the three consonants.

The ACT has a high test-retest reliability at .71 (Shura, Rowland, & Miskey, 2015). Scores were converted into z-scores for the version of the test given based on normative data (Stuss et al., 1987).

2.1.5 Assessment of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI) was used to obtain a measure of full-scale IQ (Wechsler, 1999). The measures include four subtests: Block Design, Vocabulary, Matrix Reasoning, and Similarities. The WASI has a very high test-retest reliability at .96 (Wechsler, 1999).

2.1.6 Measure of Cumulative Neurological Risk

The Neurological Predictor Scale (Micklewright et al., 2008) was used as a measure of cumulative neurological risk that includes treatment complications such as hydrocephalus, hormone deficiency, seizures, amount of brain surgery, presence and type of radiation, and chemotherapy. The values range from 0 (lowest level of risk) to 11 (highest level of risk) and were collected via retrospective medical chart review. The measure has documented reliability and validity in intellectual and adaptive functioning of adult long-term survivors of childhood brain tumor (King & Na, 2016).

2.1.7 MRI Data Acquisition

All participants were scanned using a 3 Tesla Siemens Tim Trio MRI scanner using the body coil for FR transmission and a 12 channel phased array head coil for RF receiving. Participants were outfitted with protective earplugs to reduce scanner noise. Two types of high-resolution (1.0 mm x 1.0 mm x 1.0 mm) structural MRI scans of the brain were acquired by collecting 176 contiguous sagittal slices for each subject: (1) a T1-weighted MPRAGE, and (2) a

T2-weighted SPACE. The T1 MPRAGE sequence was used with the following parameters: repetition time (TR) = 2,250 ms, echo time (TE) = 3.98 ms, inversion time (TI) = 850 ms, flip angle (FA) = 9°, isotropic resolution = 1x1x1 mm³, acquisition bandwidth = 160 Hz. The T2 SPACE had the following acquisition parameters: TR = 3,200 ms, TE = 402 ms, isotropic resolution = 1x1x1 mm³, acquisition bandwidth = 751 Hz.

2.1.8 Image Processing

Images were processed utilizing a modified version of the Tissue Integrity Gradation via T2w T1w Ratio (TIGR) method as developed and described by Krishnamurthy and colleagues (under review). As a brief overview of the methodology, T1- and T2-weighted MRI images are de-noised and co-registered together to remove gross head motion. In parallel, T1 weighted images are bias field corrected, followed by the estimation of an initial binary lesion mask in native space using LINDA (Pustina et al., 2016). Next, the images are skull stripped using a generated binary brain mask and applied to the bias field corrected T1-weighted image. Skull stripped images were touched up when needed using ITK-Snap to remove meninges and areas of calcification. Finally, a chimera spatial normalization is utilized to obtain a non-linear transform to MNI template space. Utilizing bias field corrected T1- and T2-weighted images, segmentation of WMHs was done using the Lesion Growth Algorithm in the Lesion Segmentation Tool toolbox for SPM12 with a threshold of .25 (Schmidt et al., 2012). Participants with total WMH volumes that were two standard deviations above or below the group mean were visually checked and false positives were manually fixed using ITK-Snap (as described above). Final segmentations were used to define the WMH mask in MNI space in group analysis. So that cerebellar resection lesions are not classified as WMH nor included in analyses, all cerebrospinal fluid space with a value of 1 will be removed from analyses.

Classification of periventricular and subcortical WMH volumes were identified through methods developed in-house. The right and left lateral ventricles of the MPRAGE image in MNI space were segmented for each participant using FSL FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011). These images were combined to create a mask that was dilated out by 2 voxels. Any voxels previously identified as WMHs that intersected or bordered with those that intersected with the dilated ventricle mask were identified as periventricular. All other voxels previously identified as WMHs and not included as periventricular were identified as subcortical.

Whole brain volumes were calculated using SPM12 by summing grey and white matter volumes. A ratio of WMH volume to whole brain volume was used to obtain normalized WMH volumes.

2.2 Data Analysis Plan

2.2.1 Confound Analyses

Confounding variables can negatively impact the validity of an experiment because they are related to both the independent and dependent variables. Consequently, if a confound variable is present, it is difficult to determine whether the effect of the independent variable is acting alone on the dependent variable or if it is influenced by a potential confounding variable. Conversely, a covariate is a variable that is related to only the dependent variable. While covariates do not influence the validity of the experiment, it is advantageous to control for covariates in order to increase specificity of the statistical model.

Demographic variables can act as potential confounds in analyses. Therefore, we chose to compare level of education, age at examination, gender and race across control and survivor groups. Additionally, the survivor groups were compared on age at diagnosis. Independent samples t-tests were used to compare groups on level of education and age at examination. Level

of education was significantly different between controls and total survivor sample ($p=.001$), but not between the two survivor groups ($p=.57$). The total survivor sample does include minors, so after the removal of minors, the control group and survivor group did not significantly differ on level of education ($p=.11$). Therefore, we did not control for level of education in these analyses. Groups did not differ in age at examination between controls and all survivors ($p=.19$), and between survivors with chemoradiation therapy and those without ($p=.37$). So, we did not control for age in our analyses, except in analyses with digit span forward because this score is not age corrected. Additionally, survivor groups did not differ in age at diagnosis ($p=.80$). Next, chi-square tests of independence were used to compare groups on gender and race. Survivors and controls did not differ in gender $\chi^2(1, n=99) = 0.49, p=.49$ or race $\chi^2(1, n=98) = 9.41, p=.09$. Similarly, survivor groups also did not differ in gender $\chi^2(1, n=41) = 3.35, p=.07$ or race $\chi^2(4, n=41) = 4.00, p=.41$. Results of these analyses can be found in Tables 1 and 2. Overall, we did not control for any of these variables in analyses, except for age when using digit span in analyses as described above.

Prior research has suggested that whole brain volume may be differentially associated with cognitive skills compared to subcortical WMHs (Cohen et al., 2002). If whole brain volume and either periventricular or subcortical WMHs are highly correlated, it is necessary to control for whole brain volumes in analyses to obtain an accurate representation of relationships between categorical WMH volumes and performance on measures of cognitive skills. Thus, to control for whole brain volumes, all WMH volumes were divided by whole brain volume to create a normalized WMH volume that can be directly compared across participants. The normalized WMH volume was used in analyses. Similarly, subcortical and periventricular volumes have also been shown to be highly correlated with each other in older adult populations (DeCarli et al.,

2005). Normalized subcortical and periventricular WMH volumes were significantly correlated with each other ($r=.409, p<.001$). In analyses, when examining relationships with subcortical WMH volumes, periventricular WMH volumes were controlled for, and vice versa when examining relationships with periventricular WMH volumes, subcortical WMH volumes were controlled for.

2.2.2 Tests of Assumptions

When appropriate and depending on the test, all assumptions of normality, heteroscedasticity, multicollinearity, homogeneity of variance, independence of residuals, and normality of residuals were conducted.

2.2.3 Analyses for Specific Aim 1

The first hypothesis of Aim 1 is that survivors of childhood posterior fossa tumor will have significantly higher total volumes of WMHs than healthy controls. We conducted an independent samples *t*-test to determine whether there are any significant differences in normalized WMH volume between survivors and healthy controls at the $p=.05$ level. We also calculated Cohen's *d* as a measure of effect size for these potential differences. An a priori sensitivity power analysis was conducted using *G*Power 3* (Faul, Erdfelder, Lang, & Buchner, 2007). Based on this power analysis, a medium effect size of 0.58 and critical *t* of 1.98 is needed in order to detect a significant difference among groups with an alpha level of .05 and 0.8 power. This suggests that our sample size of 91 has sufficient power to detect differences with a medium effect size.

The second hypothesis for Aim 1 is that survivors treated with radiation, chemotherapy or a combination (reference group) will have higher total WMH volume than survivors treated with surgery alone and healthy controls. We conducted a one-way ANOVA to determine if

differences at the $p=.05$ level are seen among the groups. To explore the significant ANOVA model, Gabriel's posthoc test was used to determine which groups are significantly different. To correct for multiple comparisons, we utilized a modified Bonerroni correction, called Holm's sequential Bonferroni procedure, which is slightly less conservative (Holm, 1979). This test is performed after analyses have been conducted in order to determine the alpha value. An a priori sensitivity power analysis using *G*Power 3* revealed that a significant difference among the groups will be detectable at a medium effect size of 0.32 and a critical F value of 3.09 based on an alpha value of .05 and .8 power.

2.2.4 Analyses for Specific Aim 2

The first hypothesis of Aim 2 is that there will be negative associations among total WMH volume and performance on cognitive skills in processing speed, attention span, working memory and intelligence in survivors of childhood brain tumor, such that, higher volumes of WMHs will be related to lower scores on cognitive skill measures. We conducted bivariate correlations for each cognitive skill to determine if there are any significant relationships among cognitive performance and total WMH volume. Similar to Aim 1, we utilized Holm's sequential Bonferroni procedure to correct for multiple comparisons. An a priori sensitivity power analysis was conducted using *G*Power 3* and revealed that an r critical value of $\pm .40$, a moderate relationship, will yield a significant correlation based on the survivor sample size of 41.

The second hypothesis of Aim 2 is that total WMH volumes will mediate the relationship between NPS score and performance on cognitive skills in the sample of survivors of childhood brain tumor. To investigate the potential mediating effect of total WMH volume on the relationship among NPS score and performance on each cognitive measure, a mediation analysis was conducted utilizing the PROCESS macro for SPSS (Hayes, 2017). The PROCESS macro

allows for bias-corrected mediation analyses using bootstrapping. We utilized 10,000 bootstrapped samples for our analysis. This method helped to increase power. In mediation analyses, in order to detect large significant effects when utilizing a bias correct method, a sample size around 50 is suggested for medium effect sizes and 34 for large effect sizes (Fritz & MacKinnon, 2007). While this analysis may be slightly underpowered, if a significant effect is found, it would suggest a particularly robust relationship among these variables. Again, we utilized Holm's sequential Bonferroni procedure to correct for multiple comparisons and determine the appropriate alpha value.

2.2.5 Analyses for Specific Aim 3

The first hypothesis of Aim 3 is that there will be a significant negative relationship among periventricular WMH volumes and performance on measures of processing speed and working memory. First, to control for total brain volume, a ratio of periventricular WMH volume over brain volume was calculated. The same procedure was conducted with subcortical WMH volumes to create a normalized subcortical WMH ratio. We conducted partial correlations controlling for subcortical WMH volume ratios to examine the relationships among normalized periventricular WMH volumes and cognitive skills. We utilized Holm's sequential Bonferroni procedure to correct for multiple comparisons. A Fisher r-to-z transformation was used to determine if the strength of relationships were significantly different from each other.

The second hypothesis of Aim 3 is that there will be a significant negative relationship among subcortical WMH volumes and performance on measures of attention span. Similar to the first hypothesis, we conducted a partial correlation controlling for periventricular WMH ratios, to determine if there is a significant relationship among subcortical WMH volumes and cognitive skills. We utilized Holm's sequential Bonferroni procedure to correct for multiple comparisons.

A Fisher r-to-z transformation was used to determine if the strength of relationships were significantly different from each other.

2.2.5.1 Supplementary Analyses for Specific Aim 3

2.2.5.1.1 Univariate Brain-Behavior Relationships

A univariate voxel-lesion symptom mapping regression was performed to identify brain-behavior relationships among cognitive skills and WMH lesions. This procedure was performed on relationships that were shown to be robust in significant analyses from Specific Aim 2. First, an overlap mask was created in which at least two subjects overlapped in the location of their WMHs. The data was fit to a model using Levenberg-Marquardt nonlinear least squares algorithm as implemented in Matlab (nlinfit). Once the model was fit to the data, the amount of variance accounted for by the model was estimated via the R^2 statistic. The statistical maps were thresholded at the R^2 value that corresponds to a $p=.05$ alpha value as determined by the number of subjects in the analysis.

2.2.5.1.2 Multivariate Brain-Behavior Relationships

Prior to multivariate analyses, new binary lesion images were created to exclude all lesions of the cerebellum. Brain-behavior relationships between significant cognitive skills identified in analyses of Specific Aim 2 and binary lesion imaging data were computed using LESYMAP's sparse canonical correlation analysis (sccan) threshold at a $p=0.05$ and FDR corrected (Pustina, Avants, Faseyitan, Medaglia, & Coslett, 2018).

3 RESULTS

3.1 Tests of Assumptions

Tests of normality, heteroscedasticity, and independence were not violated for the cognitive measures, and the sample was normally distributed. For the quantified measure of WMH volume, the whole sample and the individual group samples were highly skewed, kurtotic, and not normally distributed. To resolve this, the total, periventricular, and subcortical normalized WMH volumes were log transformed. The log transformed total WMH volume and subcortical WMH volumes passed all tests of assumptions including normality, heteroscedasticity, and independence. Even after the log transformation, the periventricular normalized WMH volumes of the healthy control group remained highly kurtotic and moderately skewed. This is because many of the healthy controls did not have any periventricular WMHs and many of the values clustered around zero. A square root transformation on the normalized periventricular WMH volumes decreased the kurtosis, from 31.24 to 12.74, but not enough to be in an acceptable range. Bivariate correlation analyses were performed with the log transformation, square root transformation, and rank-order transformations with no appreciable difference in results and interpretation. In order to help with ease of interpretation, results are all presented with the log transformed data. Based on studentized residuals, there were no outliers present in any of the variables to be included in analyses.

3.2 Descriptive Analyses of Cognitive Variables

To help characterize the sample and understand relationships of the cognitive variables among the groups, descriptive statistics and groups differences were assessed. Means and standard deviations of each cognitive measure based on group are reported in Table 3. An independent samples *t*-test revealed that survivors of childhood cerebellar tumor performed

significantly worse on the OSDMT, WASI FSIQ, and ACT compared to the healthy controls (p s=.002 - <.001), with medium to large effect sizes (d s=0.71-1.10). A univariate analysis of variance controlling for age showed that survivors performed worse on WMS digits forward when compared to healthy controls ($F(2,85)=4.15$, $p=.019$), with a moderate effect size ($d=0.63$).

Table 3. Group Comparisons of Cognitive Measures

	Survivors M (SD)	Healthy Controls M (SD)	<i>t</i>	<i>p</i>	<i>d</i>
OSDMT	-1.02 (1.64)	-0.03 (1.08)	3.19	.002	0.71
WASI FSIQ	-0.18 (0.90)	0.70 (0.69)	5.22	<.001	1.10
ACT 36s	-0.61 (1.17)	0.48 (1.13)	4.15	<.001	0.95
			F	p	d
WMS Digits Forward‡	6.20 (1.29)	7.04 (1.28)	4.15	.019	0.63

Note. OSDMT = Oral Symbol Digits Modality Test; WASI FSIQ = Weschler Abbreviated Scale of Intelligence Full-Scale Intelligence Quotient; ACT = Auditory Consonant Trigrams Test, 36 second delay; WMS = Weschler Memory Scale; ‡ Raw scores are reported and age was included in analysis as a covariate

A one-way analysis of variance analysis was run for each of the cognitive measures based on treatment group. Gabriel's post hoc analyses revealed a number of group differences between the groups based on treatment type. Table 4 shows the means, standard deviations, and statistics for each treatment group. Survivors who had undergone chemotherapy and/or radiation therapy performed significantly worse than healthy controls and survivors who underwent surgery only on the OSDMT (p s = .008 - <.001). Survivors who underwent chemotherapy and/or radiation therapy performed worse than healthy controls on the WASI FSIQ (p <.001) and ACT 36 second delay trials (p <.001). Survivors who had surgery only treatment performed significant worse than healthy controls on WASI FSIQ ($p=.014$). A univariate analysis of variance revealed that the groups significantly differed in their performance on WMS Digits Forward when age was included as a covariate ($F(3,85)=5.11$, $p=.003$). No other significant differences between groups were found.

Table 4. Group Comparisons of Cognitive Measures Based on Treatment Type

	Chemoradiation Therapy M (SD)	Surgery Only M (SD)	Healthy Controls M (SD)	F	p	d
OSDMT	-1.59 (1.55)*†	-0.26 (1.47)	-0.03 (1.08)	11.38	<.001	0.92
WASI FSIQ	-0.39 (0.83)*	0.08 (0.94)*	0.70 (0.69)	15.59	<.001	1.10
ACT 36s	-0.86 (1.09)*	-0.25 (1.21)	0.48 (1.13)	9.77	<.001	0.95
WMS Digits Forward‡	5.72 (1.08)	6.92 (1.08)	7.04 (1.28)	5.11	.003	0.87

Note. OSDMT = Oral Symbol Digits Modality Test; WASI FSIQ = Weschler Abbreviated Scale of Intelligence Full-Scale Intelligence Quotient; ACT = Auditory Consonant Trigrams Test, 36 second delay; WMS = Weschler Memory Scale; *Significantly different from healthy control group; † Significantly different from surgery only group; ‡ Raw scores are reported and age was included in analysis as a covariate

3.3 Results for Aim 1

The first hypothesis of Aim 1, that survivors would have larger normalized total WMH volumes than healthy controls, was supported. An independent samples *t*-test revealed that survivors of childhood cerebellar tumors had significantly larger log transformed normalized WMH volumes than healthy controls, $t(89) = -10.66$, $p < .001$, with a large effect size ($d = 2.29$). Normalized WMH volumes were .00544 (SD=.00603) mL and .00071 (SD=.00062) mL for survivors and healthy controls, respectively. Additionally, the second hypothesis of Aim 2, that survivors treated with chemotherapy and/or radiation therapy would have larger normalized total WMH brain volumes compared to survivors who were treated with surgery only and healthy controls, was supported. A one-way analysis of variance test revealed significant groups differences among survivors who received chemoradiation therapy treatment, those who received surgery only, and healthy controls, $F(2, 88) = 76.30$, $p < .001$, with a large effect size ($\eta^2 = 0.63$). A Gabriel's posthoc test showed that both the surgery only group (M=.00217 mL; SD=.00118) and the chemoradiation therapy group (M=.00789 mL; SD=.00702) had significantly larger

normalized WMH volumes, based on Holm's sequential Bonferroni procedure, compared to the healthy control group ($M=.00071$ mL; $SD=.00062$; $ps<.001$), with large effect sizes ($d=1.67$; $d=0.98$). Additionally, the chemoradiation therapy group had significantly larger normalized WMH volumes compared to the survivors with surgery only ($p<.001$), with a large effect size ($d=1.69$).

3.4 Results for Aim 2

The first hypothesis of Aim 2, that cognitive performance would be negatively correlated with normalized total WMH volumes, was partially supported in survivors of childhood posterior fossa tumor. Bivariate correlations revealed that lower scores on the OSDMT were significantly related to larger log transformed normalized total WMH volumes with a moderate effect size ($r=-.492$, $p=.003$). While there was a small relationship among lower scores on digits forward and larger log transformed normalized total WMH volumes ($r=-.220$), the relationship was not significant ($p=.252$). Additionally, there was no significant relationships among log transformed normalized total WMH volumes and scores on the ACT ($r=-.063$, $p=.744$) or the WASI FSIQ ($r=-.025$, $p=.887$).

The second hypothesis for Aim 2, that WMH volumes would mediate the relationship between NPS values and scores on cognitive measures, was not supported. The mediation analysis was only conducted with OSDMT scores because it showcased the strongest and only significant correlation in this group. Figure 3 depicts the direct and indirect relationships among the variables in the model. The indirect effect of the NPS score on processing speed through normalized total WMH volume was not significant, $b = -0.14$, 95% CI [-0.30, 0.016]. Higher NPS scores significantly predict larger log transformed normalized total WMH volumes in survivors of childhood brain tumor, $b = 0.087$, $p<.001$. Log transformed total normalized WMH

volumes did not predict performance on the processing speed measure when NPS is included in the model, $b = -1.56, p=.084$. The direct effect of the NPS on processing speed performance when the log transformed normalized total WMH volumes is in the model was not significant, $b = -0.097, p=.45$. While it would be informative to report on the overall effect of this non-significant model, Wen and Fan (2015) have cautioned against reporting effect sizes for mediations. As this mediation model was not significant, no other mediation analyses with the other cognitive measures were performed.

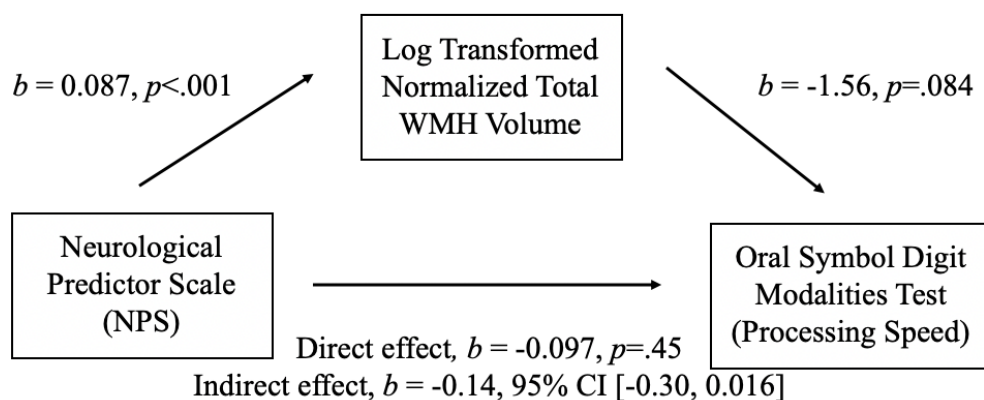


Figure 2. Results of Aim 2 Mediation Model with Survivor Participants

3.4.1 Supplementary Analyses for Aim 2

To explore potential differential relationships among the whole group, additional bivariate correlations were run. Significant and moderate negative relationships were shown, such that larger log transformed normalized total WMH volumes were related to lower scores on all cognitive measures, OSDMT ($r = -.414, p < .001$), WASI FSIQ ($r = -.370, p < .001$), ACT 36 second trial ($r = -.358, p = .001$), and WMS Digits Forward when controlling for age ($r = -.310, p = .004$). A scatter plot for the strongest correlation between log transformed normalized total WMH volume ratios and OSDMT z-scores is shown in Figure 4.

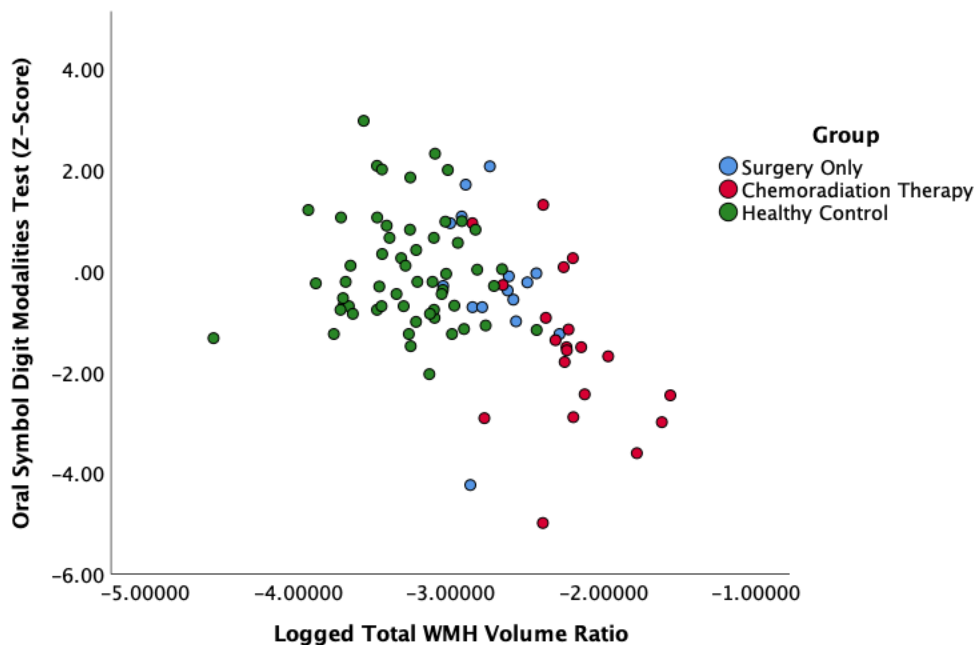


Figure 3. Scatter Plot of Relationship Among WMH Volume Ratio and Processing Speed

In an attempt to increase sample size and power of the mediation analysis, healthy control NPS scores were entered as zero and the mediation analysis was run again with them included. A mediation with OSDMT was run first because it showed the strongest relationship in the whole group correlations. Figure 5 depicts the direct and indirect relationships among the variables in the model. The indirect effect of the NPS score on processing speed through log transformed normalized total WMH volume was not significant, $b = -0.05$, 95% CI [-0.15, 0.04]. Higher NPS scores significantly predict larger log transformed normalized total WMH volumes in survivors of childhood brain tumor, $b = 0.125$, $p < .001$. Log transformed normalized total WMH volumes did not predict performance on OSDMT when NPS is included in the model, $b = -0.398$, $p = .304$. The direct effect of the NPS on processing speed performance when the log transformed normalized total WMH volume is in the model was not significant, $b = -0.116$, $p = .066$. As this

mediation model was not significant, no other mediation analyses with the other cognition measures were performed.

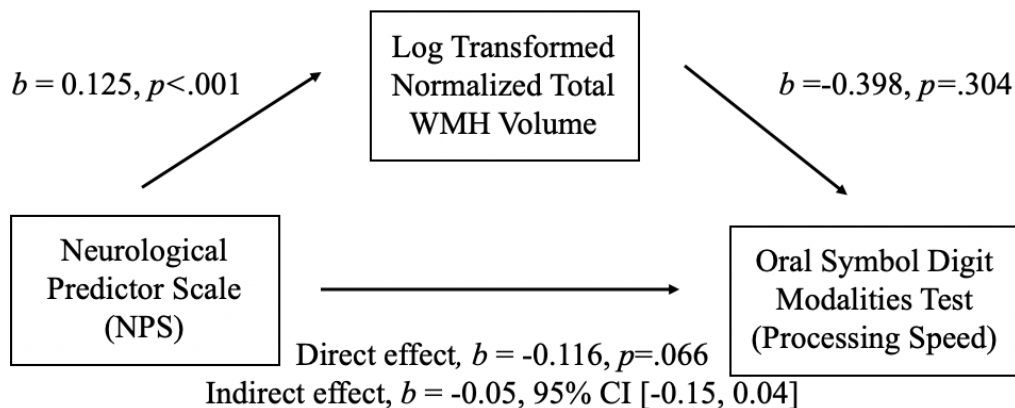


Figure 4. Mediation Model Results for Aim 2 with All Participants

3.5 Results for Aim 3

For Aim 3, it was hypothesized that there would be differential brain-behavior relationships in cognitive performance based on WMH location. The first analysis using normalized volumes depending on WMH location (i.e., periventricular or subcortical) was partially supported. Statistics for correlations are presented in Table 5. Partial correlations among log transformed normalized periventricular WMH volumes and performance on cognitive measures did not reveal any significant correlations when controlling for log transformed normalized subcortical WMH volumes. In contrast, partial correlations among log transformed normalized subcortical WMH volumes and performance on cognitive measures when controlling for log transformed normalized periventricular WMH volumes revealed a number of significant negative correlations. Consistently, higher log transformed normalized subcortical WMH volumes were associated with lower performance on cognitive measures with moderate relationships, $r = -.245$ to $r = -.314$. A scatter plot of the strongest relationships for each location are shown in Figures 6 and 7. Fisher r -to- z transformations did not reveal any significant

differences in the strength of relationships for the subcortical or periventricular WMH correlations.

Table 5. Partial Correlations Among Cognitive Measures and WMH Volumes Based on Location

	OSDMT	WASI FSIQ	ACT (36 s)	WMS Digits Forward \ddagger
Log Transformed Normalized Periventricular WMH Volume	-.200 $p=.071$	-.061 $p=.589$.032 $p=.778$	-.010 $p=.925$
Log Transformed Normalized Subcortical WMH Volume	-0.314 $p=.004$	-0.289 $p=.009$	-0.291 $p=.008$	-.245 $p=.025$

Note. OSDMT = Oral Symbol Digits Modality Test; WASI FSIQ = Weschler Abbreviated Scale of Intelligence Full-Scale Intelligence Quotient; ACT = Auditory Consonant Trigrams Test, 36 second delay; WMS = Weschler Memory Scale; \ddagger = Scores were covaried with age at time of examination

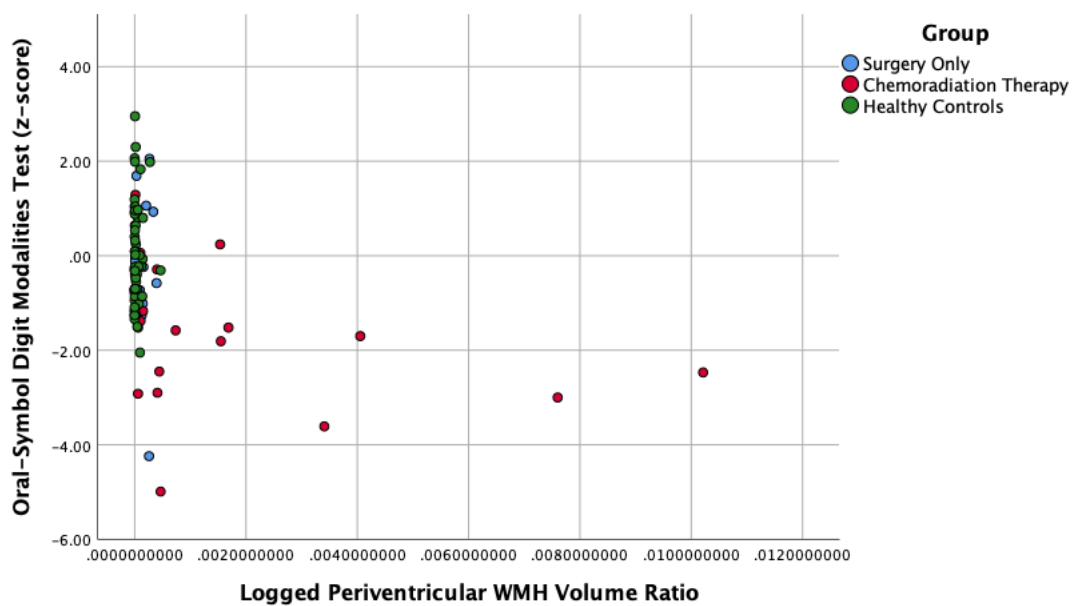


Figure 5. Scatter Plot of Relationship Between Processing Speed and Periventricular White Matter Hyperintensity Volume

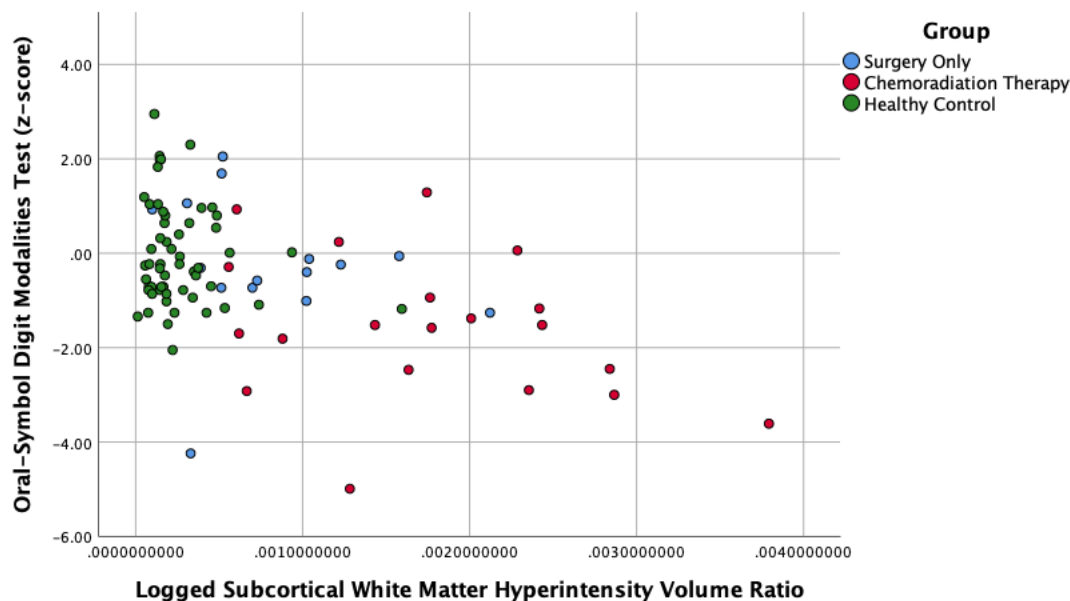


Figure 6. Scatter Plot of Relationship Between Processing Speed and Subcortical White Matter Hyperintensity Volume

3.5.1 Supplementary Analyses for Aim 3

3.5.1.1 Univariate Brain-Behavior Relationships

To further explore brain-behavior relationships among cognitive skills and WMHs, a univariate regression model was run with the cognitive measure that showed the strongest relationship with total WMH volumes, the OSDMT. Utilizing a lesion mask with an overlap of two subjects, maps were created to visualize voxels that had significant relationships with performance on the OSDMT. Figure 8 shows the locations of voxels that were related to processing speed at $p=.01$ and an R^2 threshold = .073. Clusters of voxels are primarily present in the posterior regions of the brain and periventricular WMHs appeared to be the majority. The largest significant cluster was 716 voxels, periventricular and was located next to the posterior and inferior portion of the left lateral ventricle. The second largest significant cluster was 574 voxels, subcortical, and located approximately in the right inferior parietal lobe.

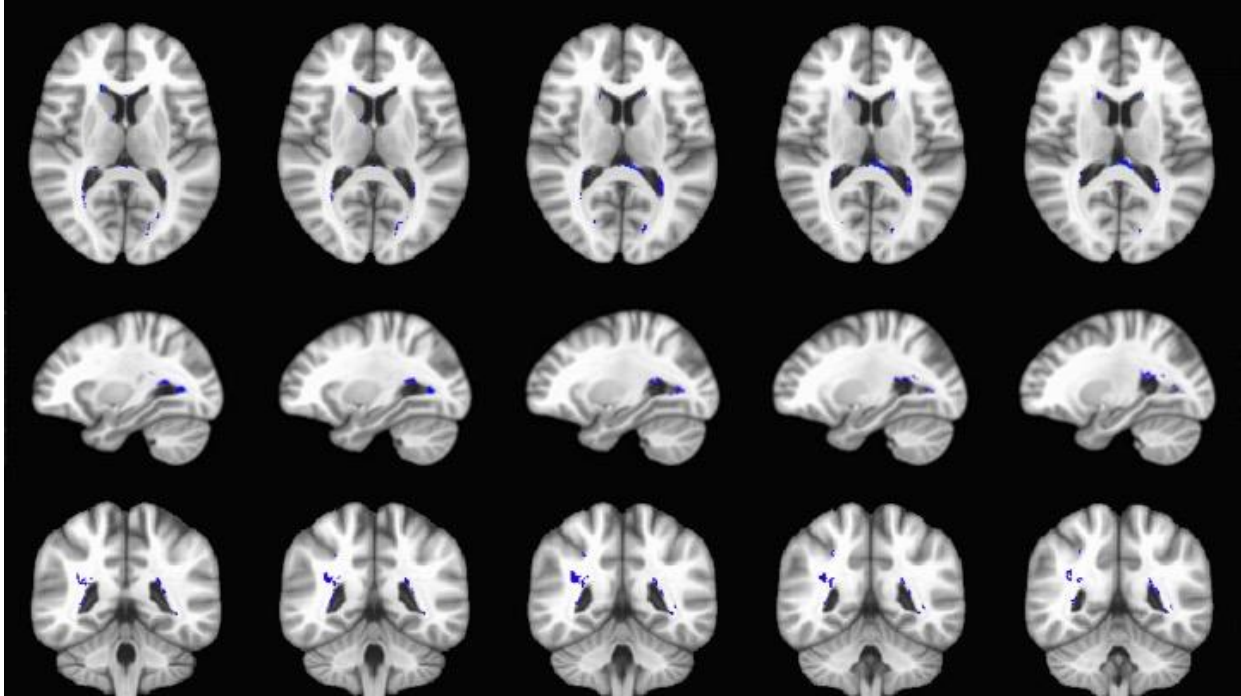


Figure 7. Significant Binary Lesion Voxels Related to Performance on Processing Speed Measure at $p=.01$, $R^2=.073$

Strength of these relationships was further explored at a more stringent cut-off. Figure 9 shows the locations of voxels that were related to processing speed at $p=.001$ and an R^2 threshold = .116. Surprisingly, and in contrast to the previously described threshold, subcortical WMH voxels were more robust and survived this increase in alpha value more than the periventricular WMHs. The largest significant cluster was 241 voxels, subcortical and located approximately in the right inferior parietal lobe. The second largest significant cluster was 186 voxels and periventricular. Considering the small R^2 values showing significant relationships in this population, univariate regression analyses were not performed with any of the other cognitive measures.

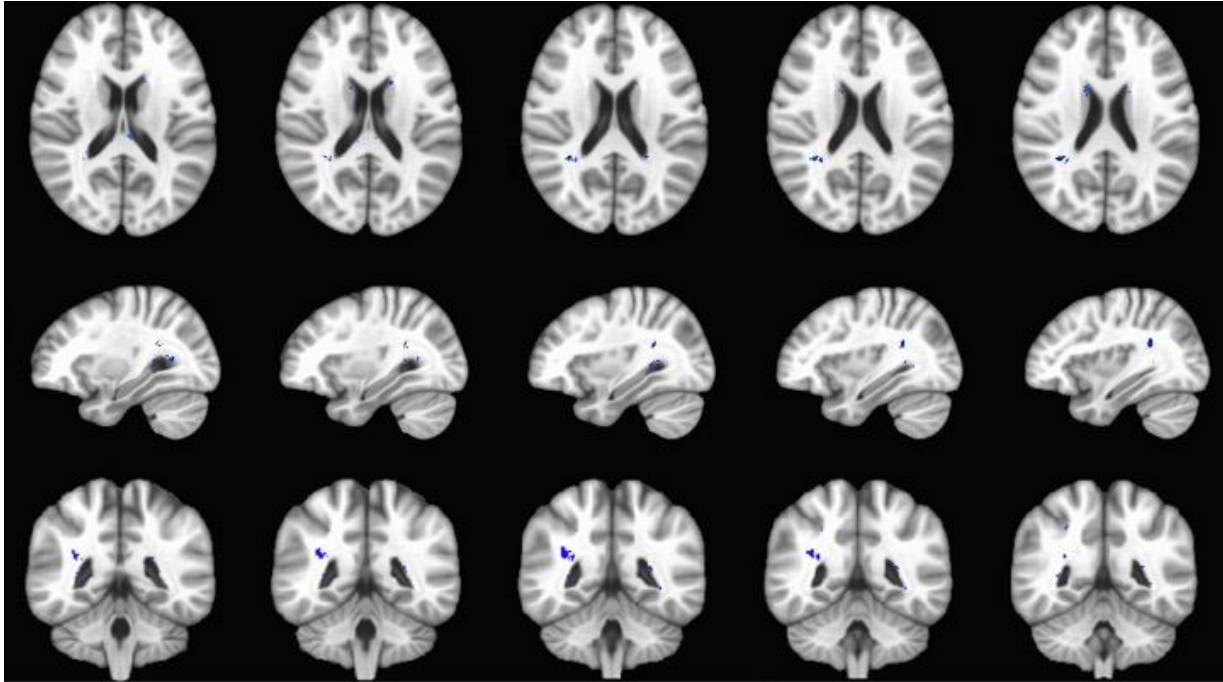


Figure 8. Significant Binary Lesion Voxels Related to Performance on Processing Speed Measure at $p=.001$, $R^2=.116$

3.5.1.2 *Multivariate Brain-Behavior Relationships*

To further explore potential significant brain-behavior relationships, a multivariate regression provided the advantage of testing voxels simultaneously in a model. Beginning with the most robust relationship, the multivariate regression brain-behavior analysis for OSDMT was significant ($p=.05$, FDR-corrected) when using a lesion overlap of 4 subjects. Based on binary lesion masks with the cerebellum excluded, significant brain-behavior relationships for processing speed are shown in Figure 10. Significant voxel clusters were almost exclusively periventricular WMHs and much larger than those found in the univariate analyses. For example, the two largest clusters were 2,115 voxels and 1,572 voxels, located in the posterior subcallosal region and next to the anterior portion of the right ventricle.

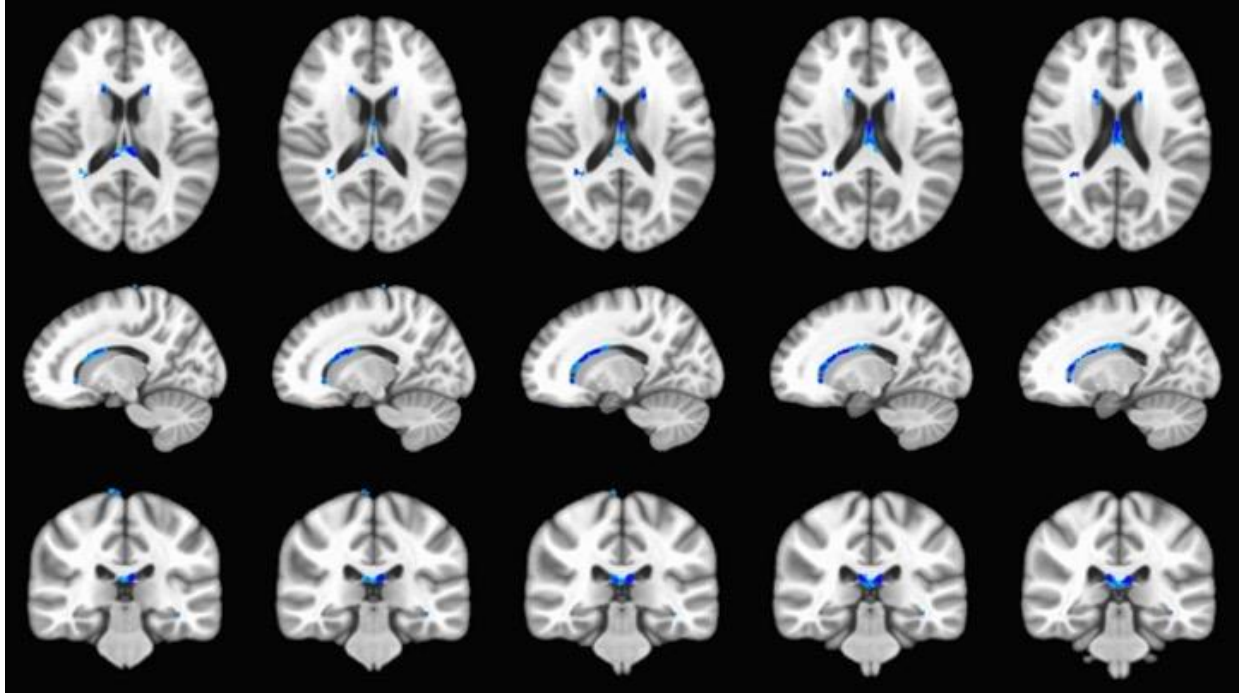


Figure 9. Multivariate Regression Results of Significant Voxels Related to Processing Speed Performance

With promising results shown with processing speed, the next strongest relationship, intelligence, was run in the multivariate regression analysis to explore potential brain-behavior relationships. The analysis for WASI FSIQ was significant ($p=.05$, FDR-corrected) when using a lesion overlap of 2 subjects. Based on binary lesion masks with the cerebellum excluded, significant brain-behavior relationships for intelligence can be seen in Figure 11. There were only two significant clusters of 280 voxels and 266 voxels, respectively. Both voxel clusters were periventricular. Considering the small nature of these significant findings, no other multivariate analyses were run with the other cognitive skills.

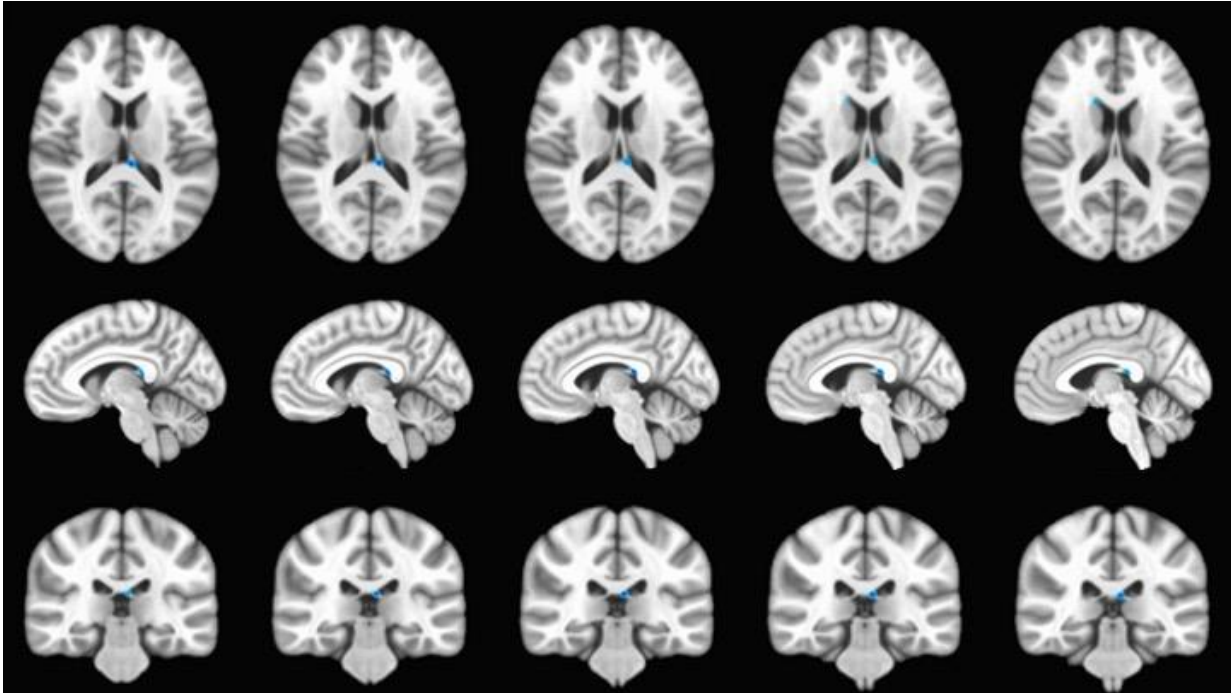


Figure 10. Multivariate Regression Results of Significant Voxels Related to Intelligence

4 DISCUSSION

4.1 White Matter Hyperintensity Volumes Based on Group

The purpose of Aim 1 was to investigate differences in total WMH volume ratios in survivors of childhood cerebellar tumor compared to healthy controls and based on type of treatment. We confirmed that survivors of childhood cerebellar tumor had significantly higher volumes of total WMHs compared to healthy controls with a large effect size. This is consistent with past literature showing that survivors of childhood brain tumor and other cancers are at increased risk of developing WMHs after treatment (Cheung et al., 2016; Reddick et al., 2005). Additionally, survivors who had undergone chemotherapy and/or radiation therapy treatments had significantly higher volumes of total WMHs compared to both healthy controls and survivors who underwent surgery only. This is also consistent with the literature that has shown neurotoxic treatments like chemoradiation therapy increase risk of development of WMHs and

result in increased compromised white matter in the brain (Sabin et al., 2018). Furthermore, there were a few survivors who had undergone chemoradiation who clustered at the high end of WMH volumes. Upon closer look at these participant demographics, it was clear that these survivors had higher severity of complications compared to other survivors, including hearing loss, endocrine dysfunction, and hydrocephalus. This suggests that it is the presence of chemoradiation therapy *plus* severity of complications that contributes to risk of developing WMHs.

Survivors who underwent surgery only had significantly higher total WMH volumes compared to healthy controls. To our knowledge, this is a novel finding that has not previously been reported. These results suggest that while survivors who undergo surgery alone, on average, do not have as high of volumes of WMHs as those who undergo chemoradiation treatment, they are still at increased risk of acquiring WMHs after treatment compared to healthy controls. It is likely that compromised white matter and increased volumes of WMHs can form in this population from tumor and treatment complications, as seen in the chemoradiation group. Further research investigating the relationship among treatment complications and WMH volumes could inform conclusions related to this hypothesis.

Survivors who are treated with surgery only are often reported as having better cognitive outcomes, sometimes similar to those of healthy controls, than survivors whose treatment includes chemoradiation therapy (King, Na, & Mao, 2015; Koustenis, Hernaiz Driever, de Sonnevile, & Rueckriegel, 2016). Consistent with previous literature, these results show that even though this group of survivors have better outcomes, they are still at higher risk of showing compromised white matter integrity, compared to their healthy peers, an average of 13 years after diagnosis (King, Wang, et al., 2015). Additionally, developing compromised white matter

early in life can place this vulnerable population at more risk for stroke, dementia, and impaired cognitive outcomes (Brickman et al., 2009; Debette & Markus, 2010; Kloppenborg et al., 2014). These results signify the importance of physicians and families fully understanding the risk of treatment on developing brains of survivors.

4.2 Relationships Among White Matter Hyperintensity Volumes and Performance on Cognitive Measures in Survivor Groups

The purpose of Aim 2 was to investigate relationships among total WMH volume ratios and performance on core cognitive measures. For the first hypothesis, this aim was partially supported in the sample of survivors of childhood cerebellar tumors. Lower scores on a measure of processing speed was significantly and moderately related to larger log transformed normalized total WMH volumes. These relationship among processing speed and WMH volumes in this population were similar or often stronger than shown in other populations, which ranged from an average of $r=-.15$ in older adults to $r=-.46$ in children with sickle cell disease (Gunning-Dixon & Raz, 2000; Kloppenborg et al., 2014; van der Land et al., 2015). It is not surprising that processing speed showed the strongest relationship with WMH volumes, as deficits in processing speed have been consistently linked to smaller white matter volumes in survivors of childhood brain tumor (Glass et al., 2017; Palmer et al., 2012; Scantlebury et al., 2016). As indicated in King and colleagues (2019) developmental model of long-term outcomes, processing speed appears to be the cognitive skill predominantly affected by various risk factors and has cascading effects on other core cognitive skills of attention and working memory.

A small non-significant negative relationship was shown among WMH volume and performance on a measure of attention span. Some evidence has linked white matter integrity and performance on attentional measures in survivors of childhood brain tumor (Ailion et al.,

2017; Ailion et al., 2020; Glass et al., 2017). In a sample of children with sickle cell disease, there was no significant relationships among WMH volume and the Digits Forward test (van der Land et al., 2015). In contrast, pooled fisher z effect sizes from multiple studies with older adults indicated a small relationship, similar to the one seen in our results (Kloppenborg et al., 2014). The measure used in these analyses was an attention span task; other attentional measures, such as the continuous performance test, which tap into vigilance and sustained attention behaviors, may be differentially related to brain involvement. While the relationship among WMH volumes and attention span was not significant, it is possible that there was not enough power in the analysis to detect a significant relationship in this sample. This result is promising, but more research with larger samples of survivors of childhood posterior fossa tumor is necessary.

There are some potential explanations for why the other cognitive measures did not relate to normalized total WMH volumes in this sample of survivors. It is possible that large WMH volumes impact processing speed directly and the relationships between white matter and the other cognitive measures is not as strong. Another possible explanation could be a restriction of range in this sample's WMH volumes. Most of the WMH volumes in this sample were quite large and grouped together. Exploring relationships with healthy controls included in the analyses was important to get a larger sample and increase the range of WMH volumes (See Section 4.2.1).

The second hypothesis of Aim 2, determining if there was an indirect effect of WMH volume on the NPS and processing speed, was not supported. Both the direct and indirect effect of the mediation model were not significant. This is surprising given current and past evidence that the NPS and processing speed performance are highly associated (Taiwo et al., 2017), and that total WMH volumes and processing speed are also highly correlated in this sample. From

this model, the NPS and total WMH volumes are shown to be highly related. It is possible that this relationship among the NPS and total WMH volumes took up a majority of the same variance in the relationship with processing speed. To help determine this, a hierarchical linear regression showed that total WMH volume ratios did not predict processing speed above and beyond NPS score (F change $p = .084$, R_2 change = $.081$). The NPS includes multiple questions about treatment and complications that could increase risk of developing WMHs (Micklewright et al., 2008), so it is not surprising that these two variables may share some of the same variance. This null indirect effect could also be the result of not enough power. As described in the analysis section, a large effect would need to be present to be able to detect a significant indirect effect with this sample size.

4.2.1 Further Relationships of WMHs and Cognitive Performance in Survivor and Healthy Control Groups

To explore further potential relationships among total WMH volumes and performance on cognitive measures, healthy control participants were included in Aim 2 analyses. With healthy controls included in the analyses, total WMH volumes were significantly related to performance on all cognitive measures assessed (i.e., processing speed, intelligence, working memory, and attention) with moderate strength. A scatter plot of the processing speed performance and total WMH volumes in Figure 4 shows clear distinctions between groups based on total WMH volumes. As proposed in Section 4.2, inclusion of healthy controls in analyses allowed for increased range in volume and cognitive performance scores to reveal stronger associations among brain structure and cognitive skills. Healthy controls are expected to have little to no WMHs, so it is not surprising the literature about relationships in young adults is limited. One study utilizing young and middle aged adults (20-59 years old) did not find

significant associations between WMH burden and cognitive performance (Vannorsdall et al., 2009). Similar to this sample of healthy controls, most young and middle-aged adults do not have high volumes of WMHs. The literature with healthy aging adults is much more prolific, with research providing evidence of relationships among WMH volumes and many cognitive areas (e.g., executive function, processing speed, attention, and memory) with small to medium effect sizes (Gunning-Dixon & Raz, 2000; Kloppenborg et al., 2014).

Unfortunately, the addition of healthy controls in the mediation model of Aim 2 did not appreciably change the results of the indirect effect of total WMH volumes on the NPS and processing speed performance. When comparing b coefficients between the two models (see Figures 3 and 5), the relationship among the NPS and total WMH volumes was stronger when healthy controls were included in the analysis ($b = 0.087$ vs. $b = 0.125$). Additionally, the direct effect was stronger, and the indirect effect was weaker when healthy controls were included in the analysis ($b = -0.097$ vs. $b = -0.116$; $b = -0.14$ vs. $b = -0.05$). This provides additional evidence that scores on the NPS and the total WMH volumes share overlapping variance in their relationships to performance on cognitive skills.

4.3 Relationships Among WMH Location and Cognitive Performance

The purpose of Aim 3 was to explore relationships among periventricular WMHs, subcortical WMHs, and performance on cognitive measures. The first hypothesis investigating relationships among periventricular WMH volumes and performance on cognitive measures when controlling for subcortical WMH volumes was not supported. The strongest brain-behavior relationship was among periventricular WMHs and processing speed; the relationship was small but not significant. There were no other relationships among periventricular WMH volumes and performance on cognitive skills. As shown in a scatter plot, there was a restriction of range issue

with these data. Almost all of the healthy controls and survivors with surgery only treatment had very small or no volumes of periventricular WMHs. Survivors who underwent chemoradiation therapy treatment had a lot more variability in volumes of periventricular WMHs. These results were surprising given literature has suggested that periventricular WMHs are often shown to be more common in the brain and related to cognitive outcomes (Bolanzadeh et al., 2012). It is possible that periventricular WMHs are commonly found in older adult populations, the population that a majority of literature has been published on, who have higher risk of cardiovascular complications. This sample, including the healthy controls, was primarily made up of young adults who are less likely to have the same cardiovascular risk factors than older adults. Additionally, our healthy control sample is rigorously screened for brain health and does not include individuals with significant medical or psychiatric histories (e.g., history of neurological condition, depression, bipolar, etc.), so we would expect little or no WMH volumes in these individuals.

The second hypothesis investigating relationships among subcortical WMH volumes and performance on cognitive measures when controlling for periventricular WMH volumes was largely supported. Significant and moderately strong relationships were present across all cognitive measures. The strongest relationship was seen between processing speed performance and subcortical WMH volumes. Subcortical regions may be disproportionately susceptible to radiation therapy treatments (Ailion et al., 2017), which could explain why there was larger variability shown in these areas in survivors.

While these results are interesting and promising, the relative importance of specifying location should be critically examined. DeCarli and colleagues (2005) have argued that differentiating between periventricular and subcortical WMHs is arbitrary because they are

highly related. The periventricular and subcortical WMH volumes in this study did significantly correlate ($r=.409$, $p<.001$); however, when controlling for the other, there were differing relationships indicated. To our knowledge, this is the first study to investigate cognitive performance with WMH location in this population, so additional research is needed before drawing further conclusions about these relationships in survivors of childhood brain tumor.

4.3.1 Differing Relationships Among WMH Location and Cognitive Performance Based on Analysis Method

The univariate linear regression analysis showed a number of significant voxels at both alpha levels of $p=.01$ and $p=.001$. Significant clusters of voxels were a mix of both subcortical and periventricular, with a majority of them being periventricular. This is a different result than was shown in the partial correlation analyses. However, this regression analysis had the advantage of testing each voxel individually as opposed to analyzing the volumes as a group. This likely allowed for increased specificity in identifying significant relationships among WMH locations and processing speed. While this is promising, it should be noted that the R^2 threshold value was small, ranging from 7.29% to 11.56% of the variance explained in the model. The ecological validity of these results should be critically considered to inform interpretation about brain-behavior relationships. In one study using univariate lesion symptom mapping with participants who had varying types of focal brain lesions, performance on a digit symbol coding task was related to lesions primarily in the left frontal and periventricular brain regions (Gläscher et al., 2009). The areas shown to be significant were much larger and widespread than the present study. Ultimately, this analysis is limited by where WMHs are found. Survivors of childhood brain tumor likely have smaller and less widespread WMHs compared to other populations, like lesions identified in stroke or multiple sclerosis.

Utilizing a multivariate lesion-symptom analysis revealed the most robust and potentially informative information about relationships among WMHs and performance on processing speed. Many of the largest clusters of voxels relating to processing speed were periventricular, primarily located in the subcallosal region. This finding was opposite from the correlation analyses that showed significant relationships with subcortical but not with periventricular WMHs. In addition to the restriction of range issue in the periventricular volumes, correlations analyses do not provide the same specificity that multivariate analyses do. Significant relationships with subcortical WMHs was likely seen because larger WMH volumes would be expected to relate to poorer performance on cognitive measures. However, in multivariate analyses, results are able to be more specific about the relationship down to the voxel level. This showcases the importance of utilizing sophisticated and specific analyses.

The large clusters of periventricular WMHs that are related to processing speed aligns well with established literature, which show strong relationships among periventricular WMHs and processing speed. In the older adult literature, periventricular WMHs are often most strongly and consistently associated with performance on processing speed measures (Bolandzadeh et al., 2012; Van den Heuvel et al., 2006; Vannorsdall et al., 2009). In one study with individuals with cerebral small vessel disease, WMH volumes in the anterior thalamic radiation, a similar location seen in this study's results, were predictive of performance on processing speed tests using voxel-based lesion-symptom mapping (Duering et al., 2011). Increased research on WMH presence and location in survivors of childhood brain tumor and cancer is needed to determine if similar conclusions are able to be drawn in this unique population.

White matter integrity and intelligence in survivors of childhood brain tumor have previously been shown to be highly related in analyses utilizing diffusion tensor imaging (King,

Wang, et al., 2015; Liu et al., 2015). However, the multivariate analysis used in these data showed only two smaller significant clusters that were related to poorer intelligence test performance. These two clusters were both located in periventricular areas. Intelligence is complex, made up of multiple domains, and involves the contribution of multiple brain networks. Additionally, it should be noted that our measure of intelligence did not include any timed measures and so, the relationships in this analysis are not related confounded by performance on measures of processing speed. More research looking at how compromised white matter impacts brain networks involved in intelligence test performance is needed in this population to draw stronger conclusions.

4.4 Strengths and Weaknesses

The proposed study has a number of strengths and weaknesses that should be discussed. To our knowledge, we are the first study to investigate brain-behavior relationships in long-term survivors of childhood brain tumor, utilizing multiple voxel-based lesion-symptom mapping techniques, that can inform the larger research community. This study was able to compare multiple methods to examine brain-behavior relationships and show the advantage of multivariate symptom-lesion mapping. Additionally, the methods outlined in this proposal are automated, utilize commonly acquired MRI scans, and do not require a radiologist or trained researcher to manually view and identify WMHs, thus reducing costs, time, valuable resources and potential user bias. Since the MRI sequences used are common in clinical practice, this method shows promise for utilization in routine clinical visits to identify those most at risk for experiencing impairments in cognitive functioning.

While this study has a number of strengths, there are some weaknesses to note. The sample only includes posterior fossa tumor survivors and so, the results may not be generalizable

to the wide range of tumor types and locations that are present in other survivors of childhood brain tumors. However, including only posterior fossa tumor survivors allowed us to mask the cerebellum and examine the entire cortex. Second, this study is cross-sectional in nature and longitudinal research is needed in order to fully understand how treatments affect cerebral white matter integrity over time. Furthermore, severity and presence of WMH volumes change over the course of an individual's treatment and lifetime (Kloppenborg et al., 2014; Reddick et al., 2005). Cross-sectional research such as this study is not able to quantify the dynamic nature of WMH progression and resolution. Next, most of the sample in this study were treated 9-30 years ago. The detrimental effects of chemoradiation therapy are well-documented and advancements in the use of proton radiotherapy, over photon radiotherapy, has allowed for increased precision for targeting the tumor and reduced irradiation of surrounding healthy tissue (Gondi, Yock, & Mehta, 2016; Greenberger & Yock, 2020). As such, treatment protocols are always changing, and this sample of survivors may not be representative of a younger group who received treatment more recently. The present study made steps towards filling a gap in the field investigating quantified WMH volume in survivors of childhood posterior fossa tumor and their relationships with cognitive skills.

4.5 Conclusions and Further Directions

Overall, this study showed that long-term survivors of childhood cerebellar tumor are at significant increased risk of developing WMHs following surgery and neurotoxic treatment. Additionally, WMH volumes were shown to be related to performance across core cognitive skills. Processing speed emerged as the cognitive skill most robustly related to WMH volumes. Results from multivariate analysis suggest that periventricular WMHs, and those located in the subcallosal region, may be highly influential to performance on measures of processing speed.

Cognitive processing speed is of particular interest and importance because of its contribution to other cognitive domains. To our knowledge, this is the first study to investigate potential relationships among WMH volumes and cognitive skills. While these preliminary results are compelling, replication and further exploration of potential brain-behavior relationships is necessary to draw stronger conclusions.

The highly varying results shown from the three different types of analyses exemplifies the importance of choosing the analysis most appropriate for the data. The multivariate analysis used in these analyses has an advantage over typical univariate symptom lesion mapping approaches because it is more accurate and specific (Pustina et al., 2018). The benefit of the multivariate regression analysis is that it tests all of the voxels with lesions simultaneously and creates a map that determines which groups of lesions together significantly relate to performance on cognitive skills. This methodology is still relatively new and has been used primarily in stroke populations. Utilizing similar methodology, WMHs in stroke patients have been shown to be related to performance on language measures and Montreal Cognitive Assessment (Thye & Mirman, 2018; Zhao et al., 2018). One study with childhood survivors of cerebellar tumor has used this methodology and results suggested relationships among lesions in the cerebellar outflow pathway and inferior vermis and presence of cerebellar cognitive affective syndrome (Albazron et al., 2019). To our knowledge, this level of analysis with WMHs and cognitive performance in long-term survivors of childhood posterior fossa tumors has not previously been conducted. These novel results are an important first look at robust relationships among WMHs and cognitive skills in this population.

This study was cross-sectional in nature, but WMH volumes dynamically change over time (Reddick et al., 2005). It would be interesting and informative to utilize longitudinal

research methods to show how WMH volumes evolve and change overtime in this population, including right after treatment and into older adulthood. This study was conducted with a sample of healthy controls and long-term survivors of childhood posterior fossa tumor who were primarily young adults at the time of evaluation. Research investigating WMH volumes is most frequently on older adult populations with higher volumes related to declines in cognitive domains (Kloppenborg et al., 2014). Furthermore, when controlling for performance on cognitive skills, older adults with higher cognitive reserve had higher WMH volumes (Brickman et al., 2011). Survivors of childhood brain tumor are developing WMHs earlier in life than the general population and likely already have decreased brain reserve compared to their peers, which could put them at greater risk of cognitive decline as they age (Dennis, Yeates, Taylor, & Fletcher, 2007). Additionally, survivors of childhood cancer are at higher risk than their peers for developing a variety of adverse health conditions, including cardiovascular disease, abnormal pulmonary function, and hearing loss (Heikens et al., 2000; Hudson et al., 2013). One study suggested that survivors of childhood medulloblastoma may show signs of early aging during young adulthood (Edelstein et al., 2011). Longitudinal research, utilizing novel neuroimaging methodology, as this population continues to age is imperative in order to get a better understanding about how early-life treatments impact cognition in older adulthood.

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