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SURVIVORS OF CHILDHOOD CEREBELLAR TUMORS: ATROPHY, LACK OF LESION SPECIFICITY, AND THE IMPACT ON BEHAVIORAL PERFORMANCE

by

ALYSSA AILION

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

ABSTRACT

Research suggests that the cerebellum is involved in cognition, but its exact role is unclear. The efficiency theory posits that the cerebellum supports processing speed. Other researchers argue that the cerebellum is functionally heterogeneous, and damage to lobes of the cerebellum causes selective loss of cognitive functions. This study sought to determine whether selective impairment in motor, verbal fluency, or processing speed occurred depending on the lobe of the cerebellum that was lesioned. Lesion mapping was used to measure lesion size and volumetric methods were used to measure atrophy in 25 adult survivors of cerebellar tumors. Participants had too a high degree of heterogeneous cerebellar lesions and accompanying atrophy to explore specialization. However, total cerebellar atrophy negatively impacted written and oral processing speed to a greater degree than total cerebellar lesion size. Younger ages at diagnosis and radiation therapy were associated with greater cerebellar atrophy.

INDEX WORDS: Cerebellum, Brain tumor, Atrophy, Structural MRI, Cerebellar-cortical loops, Age at diagnosis

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ALYSSA AILION

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

Master of Arts

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Georgia State University

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ALYSSA AILION

Committee Chair: Tricia Z. King, Ph.D.

Committee: Robin Morris, Ph.D.

Bruce Crosson, Ph.D.

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Office of Graduate Studies

College of Arts and Sciences

Georgia State University

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1 Introduction

Historically, researchers thought the cerebellum was only involved in motor functioning (Flourens, 1824; Rolando, 1809); however, recent behavioral research suggests that the cerebellum also is involved in cognitive tasks (Stoodley, 2012; Stoodley and Schmahmann, 2009; Schmahmann and Sherman, 1998). For example, patients with cerebellar damage experience changes in a wide range of domains, such as difficulties with language, executive functioning, and changes in personality (Schmahmann and Sherman, 1998). There are a number of theories regarding the role of the cerebellum in cognition. One theory is that the cerebellum's function is to increase brain efficiency. The efficiency theory posits that whole cerebellum works to support the efficiency of other brain regions, and individual regions within the cerebellum are not responsible for any specific functions (Bower, 1997). In support of a functionally homogeneous cerebellum, researchers have found that the volume of the whole cerebellum in healthy adults is related to working memory performance, measured by the WAIS-III Working Memory Index (Posthuma et al., 2003). Further supporting the functionally homogeneous cerebellum, the amount of cerebellar damage is associated with poorer semantic and phonemic verbal fluency (Vaquero et al., 2008). Nevertheless, the evidence for globalized function is mixed; for example, single pulse synchronized transcranial magnetic stimulation (sTMS, 1 pulse, 120% MT Intensity, double cone, 110 mm/ handle up) of lobes VI and crus I (For visual depiction of lobes, see Figure 1) in the cerebellum results in slowed processing speed on verbal working memory tasks, but does not change processing speed on motor tasks (Desmond, Chen, and Shieh, 2005).

Researchers have found that the brain has interconnected networks, which are responsible for motor or cognitive functions (D'Angelo and Casali, 2013; Koziol and Budding, 2009), and any disruption in the neural network can affect motor or cognitive performance. Specific hemispheres of the cerebellum have been implicated in these loops in primates (Kelly and Strick, 2003). Cortical brain regions are connected to the cerebellar hemispheres via the pontine nuclei and the cerebellar vermis. From the cerebellar hemispheres, the information is then projected to the dentate nucleus which then travels through the thalamus before returning to the cortex. Different lobes of the cerebellum are thought to be functionally heterogeneous because they connect to different cortical brain regions associated with either motor or cognitive processing (D'Angelo and Casali, 2013; Berl et al., 2012; Kelly and Strick, 2003). Further supporting a functionally heterogeneous cerebellum, damage to specific lobes of the cerebellum causes selective loss of cognitive functions (Schweizer et al., 2010; Stoodley and Schmahmann, 2008; Leggio et al., 2000).

Desmond et al. (1997) proposed a theoretical loop between the frontal lobes and lobe VI and crus I of the cerebellum (see Figure 2) that supports verbal working memory (Desmond, Chen, and Shieh, 2005; Chen and Desmond, 2005). In support of this theory, disruptions to the white matter pathway connecting the cerebellum to the frontal lobes (i.e., DTI and fMRI) results in poorer working memory performance (Law et al., 2011; Ziemus et al., 2007). Recent studies investigating both healthy and neurological injury populations have converged on three specific regions of right hemisphere of the cerebellum associated with phonemic fluency: lobe VI, crus I, and crus II (See Figure 1; Mariën et al., 2013; Schweizer et al., 2010, Stoodley and Schmahmann, 2009, Richter

et al., 2007). Furthermore, animal tracer injection research provides evidence that a distinct non-motor loop exists and includes crus I and crus II of the cerebellum (Kelly and Strick, 2003; see Figure 3). Therefore, human and animal models converge to suggest that there is a closed loop between the cerebellar hemispheres and frontal cortex, which supports verbal working memory performance and specifically implicates phonemic fluency ability (Mariën et al., 2013; Law et al., 2011; Stoodley and Schmahmann, 2009, Richter et al., 2007; Kelly and Strick, 2003; Middleton and Strick, 2001; Desmond et al., 1997).

Motor performance is frequently negatively impacted following cerebellar damage. In addition to the verbal working memory loop, there is a distinct motor loop that connects the cerebellum to the motor cortex (Dum and Strick, 2003), and it appears that the motor and verbal working memory loops are dissociated in the cerebellum (Kelly and Strick, 2003; see Figure 3). Similarly, specific regions of the cerebellum, lobes V and VIII, are activated during motor tasks (Stoodley and Schmahmann, 2009), and damage to these regions results is poorer motor performance (Kuper et al., 2013).

The question remains: Does poorer phonemic fluency performance result from damage to the functionally distinct cerebellar lobes, which are implicated in the cerebellar-frontal loop, or from damage to the functionally homogeneous cerebellum? By exploring the amount of damage to the lobes of the cerebellum, the current study sought to determine whether selective impairment in motor or verbal fluency (phonemic and semantic) performance occurred based on the lobe of the cerebellum that was damaged. The dentate nucleus and vermis also were included as a region of interest because they are involved in both loops. Based on behavioral evidence, processing

speed was explored as a potential marker that may underlie the difficulties seen on verbal fluency and motor tasks. Given the finding of selective disruption of processing speed for verbal working memory (Desmond, Chen, and Shieh, 2005), the current study also explored whether selective impairment in written and/or oral processing speed occurred based on the lobe of the cerebellum that was damaged. If selective impairment did not occur, then one explanation could be that the regions of the cerebellum were not functionally distinct. Therefore, the current study also explored relationship between the amount of damage to the entire cerebellum and performance across measures.

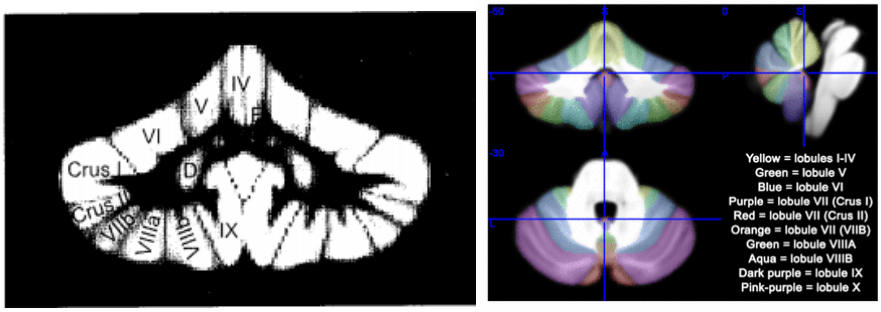


Figure 1 Atlas of the cerebellar hemispheres (Diedrichsen et al., 2009)

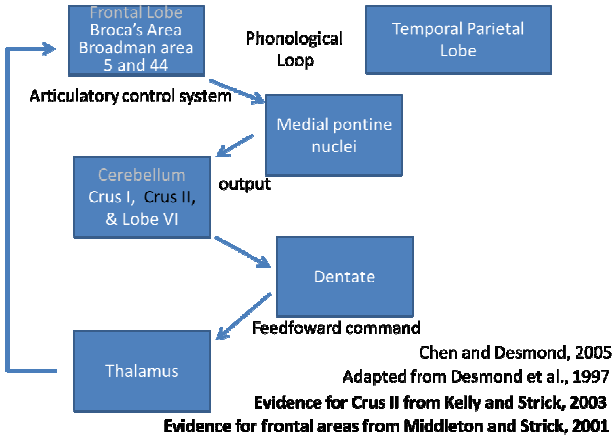
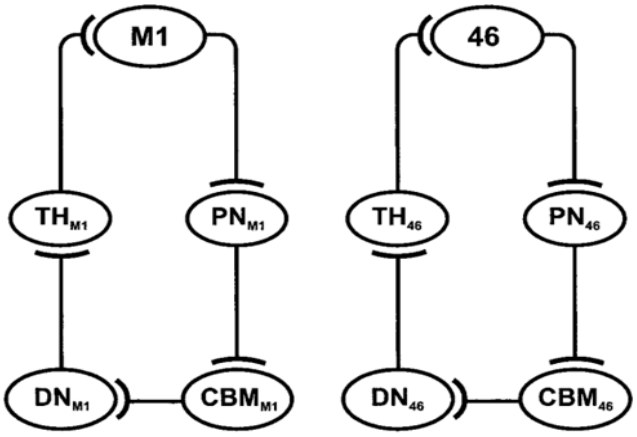


Figure 2 Proposed model for the verbal working memory cerebellar-cortical loop



M1: Primary Motor Cortex

46: Dorsolateral Prefrontal Cortex

PN: Pontine Nuclei

CBM$_{M1}$: HIV-HVI (mostly V) & HVIIB–HVIII (mostly VIII)

CBM$_{46}$: Crus I - crus II (mostly crus II)

DN: Dentate nucleus (anatomically distinct channels)

TH: Thalamus

Figure 3 Distinct motor and cognitive cerebellar-cortical loops (Kelly and Strick, 2003)

1.1 Childhood Brain Tumors

Individuals diagnosed with childhood brain tumors are a complex population who commonly experience cerebellar damage. Cerebellar brain tumors are the most common brain tumor in childhood (Gurney, Smith, and Bunin, 1999). From 1993 to 1995, tumors in the cerebellum accounted for 43% of brain tumors in children younger than 15 years old (Legler et al., 1999). The high proportion of cerebellar tumors in childhood and an increasing survival rate make it particularly important to determine the role of the cerebellum in cognitive processing. Until recently, researchers and clinicians thought that the cerebellum only contributed to motor functioning; therefore, neurosurgeons would often remove cerebellar tumors without consideration for the cerebellum's role in cognitive functioning (de Ribaupierre et al., 2008). Both the functional roles of the cerebellum in general and the specific roles of particular regions of the cerebellum are important to consider for the surgical planning of cerebellar tumor

resections. Typically, after tumor diagnosis a neurosurgeon will conduct a tumor biopsy and resection, which, depending on the type and location of the tumor, may be followed by radiation and chemotherapy treatment. Shortly following tumor resection, up to 24% of children develop cerebellar mutism syndrome, also known as posterior fossa syndrome, which is characterized by a temporary inability to speak, emotional lability, changes in personality, and motor abnormalities (Robertson et al., 2006; Pollack, 1997). Posterior fossa syndrome can last from weeks to months (Pollack, 1997). High risk factors for posterior fossa syndrome include medulloblastoma pathology, brain stem invasion, and damage to the cerebellar vermis (Robertson et al., 2006; Pollack, 1997).

A large body of literature has explored outcomes following brain tumor treatment and complications. Understanding how treatment factors have impacted verbal fluency and motor performance was important for the current study. Survivors treated with cranial radiation show significant declines relative to peers in the following domains: intelligence, visual-motor integration, problem solving, and verbal fluency (Spiegler et al., 2004). Other factors, such as the size of tumor, amount of resection, intracranial pressure, seizures (etiology, frequency, and type), treatment with anticonvulsants, age at diagnosis, and complications, also have been associated with neurocognitive sequelae (For reviews see Butler and Haser, 2006; Ris and Noll, 1994). Additionally, while some research indicates that chemotherapy and quickly treated acute hydrocephalus do not significantly impact cognitive outcomes (Ellenberg et al., 1987; Ris and Noll, 1994), other researchers have found that chemotherapy (Anderson and Kunin-Batson, 2009) and hydrocephalus (Hardy, Bonner, Willard, Watral, and Gururangan, 2008) do affect neurocognitive functioning. Younger age at diagnosis and

radiation treatment also has been related to poorer global functioning (Palmer et al., 2003). While some researchers suggest that verbal fluency difficulties could be due to cancer treatment, other studies have found that verbal fluency difficulties (semantic/phonemic not specified) are present after surgical resection, but before additional treatment (Riva and Giorgi, 2000).

Very few studies look at how the damage and removal of specific areas in the cerebellum due to tumor resection are associated with outcomes. One study has investigated how lesions in the cerebellum are associated with motor performance recovery in survivors of childhood brain tumors (Küper et al., 2013). To date, only one study has looked at how tumor resection in specific areas of the cerebellum is related to semantic and phonemic verbal fluency performance in brain tumor populations (Kirschen et al., 2008). Kirschen and colleagues (2008) found no verbal fluency differences between 12 children diagnosed with brain tumors and matched controls, and did not report an analysis between the lobes of the cerebellum and phonemic fluency. The small number of studies on this topic is likely due to the complexity of brain tumor diagnosis and treatment as well as the relatively rare occurrence of brain tumors. Other studies on phonemic fluency have included heterogeneous cerebellar injury samples, typically including only 1-3 participants with brain tumors, as well as more commonly occurring neurological damage, such as strokes (i.e. Justus, Ravizza, Fiez, and Ivry, 2005; Ravizza et al., 2006). It is important to note that the majority of prior research is on neurological injuries that occurred in adulthood, whereas the current study investigated tumors that were diagnosed and treated in childhood.

Studies on cognitive outcomes of childhood brain tumors suggest that verbal fluency ability declines following tumor diagnosis and treatment. Spiegler et al. (2004) found that verbal fluency scores (semantic/phonemic not specified) decline about 1 standard deviation every 5 years post diagnosis in a population of 17 children diagnosed with malignant posterior fossa brain tumors treated with cranial radiation. In a study including 8 children with posterior fossa tumors, researchers found that children performed significantly lower than a control population on semantic fluency measures (De Smet et al., 2009). Riva and Giorgi (2000) found that verbal fluency (semantic/phonemic not specified) performance in childhood was on average 2.9 standard deviations below the normative mean for right lateralized cerebellar tumors, and 1.7 standard deviations below the normative mean for left sided cerebellar tumors (n=26). Therefore, it appears that verbal fluency ability declines following childhood tumor diagnosis and treatment. Nonetheless, more research is necessary on the differences in the types of verbal fluency, especially phonemic and semantic fluency, and the underlying mechanisms explaining these difficulties.

Individuals diagnosed with pediatric brain tumors commonly experience damage to their cerebellum, and exhibit motor and verbal fluency performance difficulties. However, based on prior literature on brain tumor populations it remains unclear whether performance difficulties are due to damage to specific areas of the cerebellum or due to cerebellar damage in general. Determining the functional specification of the lobes of the cerebellum is of particular importance for surgical planning of cerebellar tumor resections. To differentiate each potential explanation, this study explored

specific neuroanatomical regions and their association with phonemic verbal fluency and motor performance following tumor diagnosis and treatment.

1.2 The Cerebellum

Childhood cerebellar brain tumors typically develop in the vermis or cerebellar hemispheres, with the highest occurrence in the posterior lobe (Zuzak et al., 2008). Vermis resection is associated with lower IQ (Steinlin et al., 2003), posterior fossa syndrome in children (Robertson et al., 2006; Pollack, 1997), and cerebellar cognitive affective syndrome in adults, which results in a number of cognitive, personality, and motor changes (Schmahmann and Sherman, 1998). Specifically, evidence suggests that the vermis is involved in verbal working memory (Kirschen et al., 2008), and damage to the paravermis and vermis negatively impacts speech rate (Richter et al., 2007). Moreover, animal virus tracing studies suggest that the cerebral cortex projects to the vermis of the cerebellum via the pontine nuclei (Coffman, Dum, and Strick, 2011; Thielert and Their, 1993). Taken together, the vermis appears to be critical to both the motor and verbal working memory loops, as well as performance on both tasks.

The dentate nucleus is another critical region of connection; information from all of the lobes of the cerebellum is transported to various areas in the brain through the dentate nucleus (Sultan, Hamodeh, Baizer, 2010). The dentate nucleus is divided into ventral and dorsal halves. Researchers have found that the frontal lobes project to the ventral half of the dentate nucleus, whereas the motor loop connects to the dorsal half of the dentate nucleus (Middleton and Strick, 2001). Furthermore, damage to the dentate nucleus also is associated with posterior fossa syndrome, presumably because this results in a disconnection between the cerebellum and both cortical and subcortical

regions (Küper and Timmann, 2013). Further supporting the importance of the dentate, researchers have found that poorer verbal fluency (semantic and phonemic) is associated with damage to the dentate nucleus (Vaquero et al., 2008). Thus, like the vermis, the dentate nucleus is crucial to both the motor and verbal working memory loops.

In conclusion, there is evidence to suggest that the vermis and dentate nucleus are essential components of cerebellar-cortical loops (Coffman, Dum, and Strick, 2011). Thus, the current study explored the dentate nucleus and the vermis as essential regions common to both phonemic fluency and motor pathways. The current study expected to find that the lesion size in the vermis and dentate would be related to motor and verbal fluency (regardless of phonemic or semantic) performance as well as written and oral processing speed. The current study did not expect damage to the dentate nucleus to discriminate among semantic or verbal fluency tasks due to each regions involvement in verbal fluency.

1.3 Behavioral Performance

1.3.1 Verbal Fluency

Verbal fluency is the ability to generate words quickly based on certain criteria. The ability to name words requires a number of cognitive processes. These processes include a semantic and phonological word representation, access to word knowledge from memory, the manipulation of words in short term memory, and speech production (Cantwell and Rubin, 1992). Verbal fluency requires a component of executive functioning and verbal skills. Performance on verbal fluency measures also requires components of initiation, simultaneous processing, and processing speed.

There are different types of verbal fluency measures. Phonemic fluency is the ability to generate words that start with a specific letter, and neuroanatomically is associated with the right cerebellum and the frontal lobes (Baldo, Schwartz, Wilkins, and Dronkers, 2006). Semantic fluency is the ability to generate words that belong to a specific category, and is associated with the temporal lobes (Baldo et al., 2006; Troyer et al., 1998). The current study focused on phonemic fluency because of the interest in the role of the cerebellum in verbal fluency. Semantic fluency was used as a comparison task to ensure that fluency difficulties are not due to difficulties with the word generation component of verbal fluency tasks. While generally considered a good comparison measure, the semantic fluency measure is a clinical measure that may not be sensitive enough to determine subtle semantic fluency difficulties. Also of note, the semantic fluency measure is generally considered an easier task, as opposed to the phonemic fluency task, which is slightly more challenging.

Researchers suggest that phonemic fluency is more affected by cerebellar lesions than semantic fluency (Mariën et al., 2013), and there is evidence that semantic and phonemic fluency are neuroanatomically distinct. However, there is mixed behavioral evidence on the laterality of damage to the cerebellum. For example, damage to either side of the cerebellum is associated with difficulty with phonemic fluency, but not semantic fluency (Leggio et al., 2000). However, fMRI and PET studies on healthy individuals suggest that the right cerebellum and left prefrontal regions are activated during phonemic fluency tasks (Schlosser et al., 1998; Hubrich-Ungureanu et al. 2002). In general, researchers have suggested that language and motor tasks are right lateralized in the cerebellum and spatial tasks are left lateralized (Stoodley, Valera,

and Schmahmann, 2012; Stoodley and Schmahmann, 2009). Additionally, in stroke patients, voxel based lesion symptom mapping shows that damage to crus II of the right cerebellum is associated with poorer phonemic fluency (Richter et al., 2007). Thus, right cerebellar lesions typically result in worse phonemic fluency outcomes; however, questions still remain about how damage to the left cerebellum relates to phonemic fluency performance (for review see Mariën et al., 2013). Considering that the left cerebellum is connected to the right dorsolateral prefrontal area, which is associated with attention (e.g., Lau et al., 2004), it is possible that the left cerebellum may also be involved in attention. Based on behavioral evidence, the current study planned to add an exploratory component to investigate phonemic fluency outcomes following damage to left cerebellar regions.

Within the cerebellum, there is reliable evidence to suggest that phonemic fluency is localized in lobes VI, crus I, and crus II (Mariën et al., 2013; Stoodley, 2012; Stoodley and Schmahmann, 2009). A meta-analysis of 25 fMRI studies found that activation in the right crus I and II and bilateral lobe VI were most associated with language (Stoodley and Schmahmann, 2009). When compared to executive functioning measures (e.g. go-no-go task, risk taking tasks, Tower of London, decision making tasks), language (e.g. verbal fluency- phonological and semantic, word stem completion, word generation, semantic decisions, reading words) had greater activation in right lobe VI, and right crus I. Thus, Stoodley and Schmahmann (2009) identified activation peaks for language and verbal working memory in lobes VI and crus I. Using voxel based lesion symptom mapping, research from cerebellar strokes also suggests that damage to the right crus II of the cerebellum is associated with poorer phonemic

fluency (Richter et al., 2007). Furthermore, lobes VI, crus I, and crus II correspond with both virus tracing in animals and human single pulse synchronized transcranial magnetic stimulation studies (Desmond, Chen, and Shieh, 2005; Kelly and Strick, 2003). Taken together, there is substantial theoretical and empirical evidence that lobe VI, crus I, and crus II are implicated in phonemic fluency performance.

The temporal component to verbal fluency tasks was an important consideration for the current study. Difficulty during the first 15 seconds of phonemic fluency tasks can be attributed to impaired initiation or inflexible search strategies, as the first 15 seconds typically results in the most words generated (Troyer et al., 1998). Difficulty exclusively with phonemic fluency tasks (as opposed to both semantic and phonemic) is likely due to an inflexible search strategy, considering the phonemic fluency task requires the individual to generate a novel organizational strategy based on letters; whereas, the semantic task requires less effort because the individual is simply retrieving previously organized words from semantic memory (Koziol and Budding, 2009). Schweizer et al. (2010) found that individuals with right cerebellar lesions produced significantly fewer words in the first 15 seconds of phonemic fluency tasks when compared to both controls and individuals with left cerebellar lesions. Furthermore, Schweizer et al. (2010) found no differences in the last 45 seconds of the phonemic fluency task among groups. However, during the semantic fluency task the individuals with right cerebellar lesions produced significantly fewer words than the control group, with no differences in the beginning or end of the task (Schweizer et al., 2010).

Another factor that may explain differences in the amount of words generated on phonemic verses semantic fluency is task difficulty. Hickok and Poeppel (2007) suggest

that unfamiliar words and phonemic aspects of speech require more sensory motor integration. Therefore, the phonemic fluency measure may engage the phonemic aspects of speech and/or may be more likely to produce low frequency words, which would require additional sensory motor integration and implicate the cerebellum. In contrast, semantic categories, such as animals or boy's names, prime high frequency automated words that rely less on sensory motor coding, and thus less engagement with the cerebellum. If differences are due to task demands, one would expect global task differences and different trajectories of verbal fluency performance over time. The current study conducted analyses on the first and last 15-second blocks of verbal fluency performance to determine whether timing explains any differences in verbal fluency performance.

Despite the large body of research on the cerebellum, questions remain regarding the cerebellum's specific role during phonemic fluency performance. Prior lesion studies have not included a control region in the cerebellum, so it is unclear whether results are due to damage to the hypothesized lobes involved in verbal fluency or damage to the cerebellum in general. The current study used lesion–symptom mapping to determine whether lesion size in specific lobes of cerebellum was related to phonemic fluency performance and the specificity of this relationship by including control regions and control tasks.

1.3.2 Fine Motor Performance

Fine motor performance was chosen as the control task for the current study because animal tracer injection studies suggest that there is a distinct motor loop that connects the cerebellum to the motor cortex (Dum and Strick, 2003). Due to the neuroanatomical dissociation between the motor and verbal working memory loops, fine motor performance measures were ideal for the current study. Prior literature suggests that motor ability is localized in the right lobes V, VIIIA, and VIIIB (7 studies included in meta-analysis; see Stoodley and Schmahmann, 2009), and these regions are indeed part of the motor loop (Kelly and Strick, 2003). Thus, motor performance allowed an ideal comparison task to determine if selective impairment occurs based on which lobe of the cerebellum was damaged.

Some researchers argue that the relationship between the cerebellum and verbal fluency is due to the motor speech involved with language production. However, other researchers have demonstrated that the relationship between cerebellar lesions and verbal fluency is not due to motor difficulties associated with speech (Molinari et al., 1997). Furthermore, researchers have reported that the right cerebellum is activated during a silent phonemic fluency fMRI task (Hubrich-Ungureanu et al. 2002). Taken together, there is evidence to suggest that that the difficulties seen in phonemic fluency extend beyond any motor difficulties that affect speech abilities.

1.3.3 Processing Speed

Processing speed is a central component of verbal fluency and motor performance. While some researchers suggest that the cerebellum is functionally homogeneous and responsible for task efficiency (Bower, 1997), there is evidence that

specific lobes of the cerebellum are functionally heterogeneous with regard to processing speed. For example, single pulse synchronized transcranial magnetic disruption of crus I and lobe VI results in slower verbal working memory processing speed, whereas motor processing speed remains unaffected (Desmond, Chen, and Shieh, 2005). Morton and Patterson (1980) argue that phonological output and orthographic output are distinct, but connected through an underlying semantic system. Similarly there is some evidence that phonology does not mediate orthographic output, and may be independently activated (e.g., Miceli et al., 1997). Taken together, there is some behavioral evidence to suggest that written and oral modalities of processing speed should be explored separately. Additionally, processing speed is of particular interest in the current study because cranial radiation is associated with poorer processing speed in childhood brain tumor populations (Mabbott et al., 2008). In order to gain a greater understanding of how processing speed underlies the difficulties seen in verbal fluency and motor performance, written and oral processing speed were included in the current study. To address the notion that the cerebellum is functional homogeneous the current study also explored the relationship between damage to the entire cerebellum and a composite measure that included the average of processing speed (oral and written), verbal fluency (semantic and phonemic), and motor performance.

The current study explored which lobes of the cerebellum are involved in either motor and/or phonemic fluency performance. Phonemic fluency and motor performance were chosen due to their association with specific lobes of the cerebellum and their involvement in cerebellar-cortical loops. In addition to exploring overall phonemic

fluency performance, the current study investigated the number of words generated during the first and last 15 seconds of the both phonemic and semantic fluency in order to understand any underlying factors (i.e. initiation or strategy generation) which may have contributed to the results. Because motor and verbal fluency tasks were timed, the current study included oral processing speed and written processing speed as potential underlying factors that affected performance on each task.

1.4 Lesion Symptom Mapping

Lesion symptom mapping is a neuroimaging technique that helps to determine the function of brain regions by evaluating the relationship between the lesion location and performance on behavioral measures (Rorden, Karnath, and Bonilha, 2007). Furthermore, lesion symptom mapping has been used with a heterogeneous population of brain tumor patients to determine how brain lesions influence behavioral measures (Kuper et al., 2013). Kuper et al. (2013) found that the grooved pegboard was associated with lesions in lobe V (intermediate cerebellum), the cerebellar nuclei (dentate), and lobe VIII (lateral cerebellum). Additionally, percent of lesions in lobes of the cerebellum has been used in brain tumor populations (Kirschen et al., 2008; Ravizza et al., 2006). The current study looked at the percent of lesions in lobes of the cerebellum, similar to the technique used by Ravizza et al. (2006) and Kirschen et al. (2008) with brain tumor populations.

2 Specific Aims

The primary aim of this study was to investigate how damage to regions of the cerebellum related to phonemic fluency performance in adult survivors of childhood

brain tumors and the specificity of this relationship. Prior studies have suggested that damage to lobe VI, crus I, and crus II is related to phonemic fluency. Therefore, the current study expected to replicate this association and expand on it by testing it with a new population (brain tumor survivors) and determining the specificity of this relationship with other regions and measures. To examine the specificity of this relationship, the current study examined comparison brain regions and comparison tasks. Prior research has suggested that damage to lobes V, VIIIA, and VIIIB corresponds with poorer motor performance, and the current study expected to replicate and expand on this finding by testing it with a new population (brain tumor survivors) and determining the specificity of this relationship with other regions and measures. Furthermore, the current study expected that damage to lobe VI, crus I, and crus II would be dissociated from both motor performance and semantic fluency performance. Additionally, the current study expected to find dissociations between lobes V, VIIIA, and VIIIB and phonemic and semantic fluency performance. Since there has been evidence that the dentate and vermis are involved in connecting these regions to their respective cerebellar-cortical loops and speech production, the current study also expected to find that cumulative percent damage to the dentate nucleus and the vermis would be associated with poorer phonemic fluency, motor, and semantic fluency performance.

The second aim of the study was to explore possible underlying factors that contributed to performance on verbal fluency and motor tasks in adult survivors of childhood brain tumors. Prior research provides empirical evidence that processing speed for verbal information is selectively disrupted following single pulse synchronized

transcranial magnetic stimulation of crus I and lobe IV. Thus, the current study explored the relationship between the regions of interest and both oral processing speed and written processing speed. The current study expected these results to be consistent with the findings for phonemic fluency and motor ability described above. Finally, because prior research has reported that damage to the entire cerebellum relates to global processing difficulties, the current study expected to find a relationship between the lesion size in the cerebellum and composite impairment across measures.

2.1 Specific Aim 1

Tested a double dissociation between phonemic fluency and motor performance and their respective regions of interest in the cerebellum, and explored each ROI's relationship with semantic fluency in adult survivors of childhood brain tumors and the specificity of these relationships. Then further investigated how lesion size in the dentate/vermis ROI related to each task.

2.1.1 Hypothesis 1

Cumulative percent lesion of right lobe VI, crus I, and crus II would be associated with phonemic fluency, and dissociated from motor performance and semantic fluency performance.

2.1.2 Hypothesis 2

Cumulative percent lesion of right lobes V, VIIIA, and VIIIB would be associated with motor performance, and dissociated from phonemic fluency performance.

2.1.3 Hypothesis 3

Cumulative percent lesion of the dentate nucleus and the vermis would be associated with phonemic fluency, motor, and semantic fluency performance.

2.2 Specific Aim 2

Tested a double dissociation between oral processing speed and written processing speed performance and regions of interest in the cerebellum to explore how damage to specific regions of the cerebellum related to oral processing speed and written processing speed in adult survivors of childhood brain tumors and the specificity of these relationships.

2.2.1 Hypothesis 1

Cumulative percent lesion of right lobe VI, crus I, and crus II would be associated with oral processing speed, and dissociated from written processing speed.

2.2.2 Hypothesis 2

Cumulative percent lesion of the right lobes V, VIIIA, and VIIIB would be associated with written processing speed, and dissociated from oral processing speed.

2.2.3 Hypothesis 3

Cumulative percent lesion of the dentate nucleus and the vermis would be associated with both written and oral processing speed.

2.3 Specific Aim 3

Examined how percent lesion in the whole cerebellum related to composite impairment across measures.

2.3.1 Hypothesis 1

Cumulative percent lesion in the entire cerebellum would be related poorer composite performance (average of phonemic fluency, semantic fluency, motor performance, oral processing speed, and written processing speed).

3 Methods

3.1 Survivor Recruitment

Data for this study was obtained from a larger study on the long-term outcomes following pediatric brain tumor diagnosis. In the larger study, survivors of childhood brain tumors were recruited from two sources. Survivors were either part of a long-term follow-up to a prior longitudinal study on childhood brain tumors, or survivors were recruited from a database of brain tumor survivors obtained from Children's Healthcare of Atlanta (CHOA). Each participant was mailed a letter that described the study and asked them to call the research laboratory if they were interested in participating. Once they called the laboratory, participants were informed of the study description, risks, benefits, and compensation. Survivors of childhood brain tumors completed a screening form and were excluded if they had any of the following conditions: neurofibromatosis, MRI incompatible medical implants, or serious health complications (that would make an MRI scan impossible). Survivors also were excluded if they had an impairment in hearing or vision that would make them unable to complete the study. It was common

for survivors with a diagnosis of hydrocephalus to have a metal shunt placed in their skull to drain excess fluid. The participants with shunts were asked to provide the serial number for their implant, which was provided to the MRI technician to ensure that the participant would be safe in the 3 Tesla MRI scanner.

Control participants were recruited from the Georgia State University community through the psychology participant pool, fliers posted around the community, and the Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging (CABI). Inclusion criteria included fluency in English, adequate hearing and vision to complete the study. Controls were excluded if they endorsed substance use, medical illnesses, or psychiatric problems. All procedures were reviewed and approved by the Georgia State University (IRB# H03177) and Georgia Institute of Technology (IRB# H14088) Institutional Review Boards.

3.2 Procedure

Participants were asked to come to 2 separate study visits. Informed consent was obtained at both visits. At the first visit, all participants completed a structured clinical interview (SCID-II; First, Spitzer, Gibbon, and Williams, 2002) and a battery of cognitive testing with a trained graduate student. A MRI safety screener and a medical history questionnaire were completed with the participant. Participants were then administered a battery of neuropsychological tests. This testing session took approximately 4 hours. Participants who preferred not to complete an MRI (e.g. due to claustrophobia, safety concerns, or scheduling conflicts) did not continue to the second visit and were compensated for their time. Survivors received $50 for the first visit, and controls received research credit.

Of the 108 survivors recruited, 61 continued to the second visit of the study. Survivors indicated a number of reasons for not participating including most often the presence of a metallic medical implant and occasionally a lack of interest. The second visit of the study took place at the Georgia State University/Georgia Institute of Technology Shared Center for Advanced Brain Imaging. Upon arriving, each participant completed an additional MRI safety screening, which was then approved by an MRI technician for the scan. Once cleared for the MRI scan, a graduate student explained the MRI study procedures and completed an informed consent form with the participant. Participants were informed that they could discontinue the study at any time. Following the scan, a member of the research team debriefed and compensated each participant. Survivors and controls received $50 for the second visit.

3.3 Participants

Of the 61 participants who participated in the second part of the study**,** 29 had tumors in the cerebellum. Of these participants, four had poor quality imaging data. One participant had poor image quality due to movement, two had issues with registration, and one other participant had poor image quality due to an artifact. The remaining 25 participants were selected for inclusion in the current study. The participants were on average 9 years old (*SD*=5) at diagnosis, and their average age at exam was 24 (*SD*=5). The average Full Scale IQ (WASI) was 96.92 (*SD*=17.45). Thirteen individuals were diagnosed with medulloblastoma tumors, 10 with astrocytomas, and the remaining two individuals were diagnosed with an ependymoma and a pineoblastoma. In the current sample, 52% of the participants were female. Ethnicity in the sample was 80% Caucasian, 12% African American, 4% Hispanic, and 4% Asian. With regard to

treatment, 76% of the sample had a history of hydrocephalus, 56% had a history of radiation treatment, 60% had a history of chemotherapy (only 1 participant had chemotherapy without radiation therapy), 52% had a hormone deficiency, and 4% had a history of taking seizure medication. Of the participants who had radiation treatment (n=14), 100% had whole brain radiation therapy and almost all participants (93%), except for one individual, had an additional focal boost of radiation to the posterior fossa. Treatment protocol numbers included: CCG 9961 Arm A (n=3), POG 8695 (n=2), ACNS 0331 (n= 1), ACNS 0332 (n= 1), CCG 9961 and CHP 691 (n=1), CCG 9961 Reg B (n=1), POG 9331 Arm B (n=1), POG 9961 Arm A (n=1), and three participants did not have protocol numbers listed in their medical records (n=3). Four individuals had cerebellar mutism in childhood. Treatment factors, lesion location, and performance in adult survivors of childhood brain tumors may be related. The current study explored treatment variables (e.g. hydrocephalus, presence of radiation, chemotherapy, seizures) descriptively and in relationship to findings.

3.4 Verbal Fluency Measures

The Delis-Kaplan Executive Functioning System (D-KEFS) is a series of neuropsychological tests which measure a variety of domains of executive functioning (Delis et al., 2001). The D-KEFS is a validated standardized measure with good psychometric properties that consists of 9 separate subtests. This study focused on two subtests of the verbal fluency section: the letter (phonemic) fluency test and the semantic fluency test.

The verbal fluency subtest of the D-KEFS is a timed task that involves participants naming as many words as possible in 60 seconds based on certain criteria.

Across verbal fluency subtests, participants are informed of specific rules (e.g., no proper nouns, no numbers, none of the same words with different endings). The verbal fluency task starts with phonemic fluency which requires participants to name as many words as possible that start with a specific letter, and consists of three separate letter conditions (F-A-S). Next participants completed the semantic fluency task, which is identical to the phonemic task- except participants are asked to name words in a specific category. The semantic fluency task consists of two separate semantic conditions (animals and boy's names).

Researchers report that the phonemic fluency subtest has a split-half reliability of .68 - .90 (depending on age) and a test-retest reliability of .80 (Homack, Lee and Riccio, 2005). The semantic fluency subtest has a split-half reliability of .37-.68 (depending on age) and a test-retest reliability of .79 (Homack, Lee and Riccio, 2005). The semantic and phonemic fluency subtests also display good validity, and there is some evidence that the D-KEFs fluency subtest can distinguish between Alzheimer's disease and Huntington's disease (Delis et al., 2001). The individuals with Huntington's disease displayed similar impairment across tasks due to difficulties with initiation, whereas the patients Alzheimer's disease only displayed difficulties with the semantic and semantic switching subtests.

Scores on the verbal fluency subtests are standardized based on the normative sample of the D-KEFS. For the current study, Z-scores were calculated based on the normative data in the D-KEFS normative standardization sample (Delis et al., 2001). The average Z-score for phonemic fluency was -.05 (*SD*=1.35) and the average Z-score for semantic fluency was 0.23 (*SD*=1.30). Prior empirical research suggests that

populations with cerebellar insults show particular difficulty with the phonemic (letter) fluency task (Leggio, Silveri, Petrosini, Molinari, 2000) over other fluency tasks. As previously mentioned, this finding may be due to timing or strategy generation. The D-KEFs administration divides the number of words generated by 15 second blocks; thus, the current study also explored the number of words generated in the first and last 15 seconds of the task for both phonemic and semantic fluency tasks.

Across analyses, phonemic fluency was the primary dependent variable of interest. Semantic fluency was included as a dependent variable in analyses to ensure that the results are not due to component skills required for fluency tasks, such as word generation or attention abilities. The number of words generated in the first and last 15 second block for both semantic and phonemic fluency tasks was used to explore whether timing or strategy generation was different across semantic and phonemic fluency tasks.

3.5 Fine Motor and Processing Speed Measures

Participants completed the grooved pegboard test (Trites, 1977) which measures speeded upper limb fine motor ability. During the grooved pegboard test the participant places 25 pins, each with a round peg and a square portion, into a matching keyhole on a board. The participant uses one hand to take each pin from a reservoir of pins on the board and matched the pins one at a time, in order, and as fast as possible. The participant does this task twice, first with their dominant hand, then again with their non-dominant hand. For the current study, Z-scores were calculated for each hand based on normative data in a population standardization sample (Bornstein, 1985). The test-retest reliability for the grooved pegboard test is .94 for the dominant hand and .92 non-

dominant hand, and measures of validity are within an acceptable range (Wang et al., 2011). Z-scores for the dominant hand were analyzed and included as the primary dependent variable for analyses of fine motor functioning. The average Z-score for dominant hand motor performance was -1.89 (*SD*=2.05).

Processing speed was measured using the symbol digit modality test (Smith, 1982). During this speeded number-symbol task, participants were given a sheet of paper with series of symbols, a blank box beneath each one. At the top of the page, there is a key where each symbol corresponds to a number. First, participants were asked to write the number that corresponds to the symbol in the box as fast as possible. The graduate student asked the participant to stop after 90 seconds. Next, participants were given another blank sheet and asked to call out the number that corresponds with the specific symbol according to a provided key. The graduate student wrote down the participants responses and stopped them after 90 seconds. The test-retest reliability for the written portion of the symbol digit modality test is .80 and the test-retest reliability for the oral symbol digit modality test is .76 (Smith, 1982). Additionally, performance on the symbol digit modality test was correlated to performance on the digit symbol subtest of the WAIS-R (Morgan and Wheelock, 1992). The average Z-score for oral processing speed performance was -1.31 (*SD*=1.57), and the average Z-score for written processing speed was -1.73 (*SD*=1.61).

The current study used the participants' symbol digit modality test performance as a measure of processing speed performance in order to determine whether there was specificity of written and oral processing speed with the corresponding regions of interest (crus I, crus II and lobe VI for oral; lobes V and VIII for written). These measures

were selected because the written and oral tasks are identical, thus providing an ideal measure to explore whether it was the oral processing speed or the written processing speed that was disrupted. Therefore, Z-scores on each symbol digit modality test (written and oral) were included as dependent variables in analyses. Z-scores were calculated by subtracting the number of correct answers from the number of mistakes to obtain separate raw scores for both oral and written portions of the test. Then each raw score was subtracted from the mean normative scores (Smith, 1982) and then divided by the mean normative standard deviation, both of which are based on age range and level of education ($\leq$12 or >13).

3.6 Measure of Lesion Size in Each Region

Participants completed an MRI scan using a 3-Tesla Siemens Trio Magnetic Resonance Imaging System which included a T1-weighted 3D sequence (FOV=256mm, voxel size=1x1x1mm, TR/TE=2250ms/3.98 ms, flip angle=9°) and a T2-weighted sequence (FOV=256mm, voxel size=1x1x1mm, TR/TE=3200ms/402 ms). The current study used manual lesion tracing, as some researchers argue that it is the best technique for lesion symptom mapping (Timmann et al., 2008). The brain lesions were drawn and saved as a region of interest for each survivor using MRIcron software (http://www.mricro.com). Lesions were manually drawn on each slice of the T1-weighted image in the coronal view, checked in the axial and sagittal views, and then rechecked in the coronal view. Inspection bilaterally and across different views was used to ensure atrophy, healthy brain space (e.g., fourth ventricle or gyri), and large sulci were not included in lesion masks. Lesions were then verified with the T2 image. All lesion masks were verified and corrected by a neuroradiologist.

All images were converted into SUIT space to improve spatial resolution and normalization of the cerebellum, which is based on 24 healthy brains (Diedrichsen, 2006; http://www.icn.ucl.ac.uk/motorcontrol/imaging/ suit.htm). Using Matlab R2014a, all scripts were run using SPM 8 with the SUIT toolbox, version 2.7. First, images were converted to 3D NifTI images using the DICOM to NIfTI converter (Rorden et al., 2007). Then, the origin was set to the anterior commissure in SPM8. Next, the suit_isolate script was used to segment, crop, and mask the cerebellum. Each cerebellar mask was visually inspected and corrected. At that point, the suit_normalize script was used to normalize the cerebellums and the lesion ROIs into SUIT space, and suit_reslice was used bring the cerebellums and lesions into atlas space. Next, suit_lobuli_summarize nanmean function was used to summarize the lesion size to each lobe of the cerebellum. The lesion size in each region of the cerebellum was divided by the total volume of each region, which resulted in the percent lesion size to each region of the cerebellum. The vermis of lobe V was not included because the SUIT atlas does not define this region due to poor anatomical boundaries relative to the cerebellar hemispheres (Schmahmann et al., 2000; Diedrichsen et al., 2009). For cumulative measures, an average of each region was used (e.g., (% lesion in right crus I + % lesion in right crus II + % lesion in right lobe VI) / 3 = % lesion of phonemic fluency related ROI). The measures were right lateralized for the motor and phonemic fluency related regions, and bilateral for the dentate/vermis regions due to their midline location and importance for cerebellar connectivity. All distinct left and right regions also were explored in the exploratory analyses. Lesion methods were modeled based on prior studies (e.g., Kuper et al., 2013; Kirschen et al., 2008; Ravizza et al., 2006) in which the

lesion ROI overlaid on top of an atlas template to determine the percentage of lesion size to relative to brain regions.

Given the theoretical similarity among phonemic fluency and motor related regions of interest, the current study explored cumulative lesion size in each set of ROIs (i.e. cumulative lesion size in crus I, crus II, and lobe VI; cumulative lesion size in lobes V and VIII; cumulative lesion size in the dentate and vermis). Some researchers might argue that rather than percent lesion to the specific area of interest, the percent lesion to the entire cerebellum would explain the relationships. Thus, total lesion size was calculated as well.

3.7 Atrophy Measure

Visual inspection of the T1 scans revealed possible cerebellar atrophy in the sample. However, cerebellar abnormalities could have been due to factors unrelated to atrophy (e.g., structure collapsing); therefore, an equation was developed to quantify atrophy. Volume of the intracranial vault was included in this measure to correct for any possible premorbid individual brain differences.

Volume of the intracranial vault was calculated using SPM8 with Ashburner and Friston's (2005) unified segmentation program to generate tissue maps of grey matter, white matter, and cerebrospinal fluid. Then the get_total script (Ridgway, 2007; http://www0.cs.ucl.ac.uk/staff/G.Ridgway/vbm/get_totals.m) was used to obtain a 3D voxel count for each image. The sum of the total gray matter, white matter, and cerebrospinal fluid volume was used to calculate the volume of the intracranial vault (Sanfilipo et al., 2007). This measure of intracranial vault is commonly used in

populations, such as multiple sclerosis, who experience both lesions and atrophy (e.g., Chard et al., 2002). For the cerebellar volume, the same script was used with the corrected cerebellar mask for the white and grey matter images. In an effort to quantify atrophy, the following formula was developed and corresponds with the prior literature.

$$Intracranial\ Vault\ (ICV) = White\ Matter + Grey\ Matter + Cerebrospinal\ Fluid$$

Equation 1 Equation for ICV from Sanfilipo et al., 2007

$$Cerebellar(CB)\ Volume = \ Cerebellar\ White\ Matter + Cerebellar\ Grey\ Matter$$

Equation 2 Cerebellar specific absolute parenchymal fraction. Adapted from Sanfilipo et al., 2007; original equation: (total gray + total white matter volume)

$$Healthy\ Controls'\ Cerebellum = \frac{CB\ Volume}{ICV}$$

Equation 3 Cerebellar specific brain parenchymal fraction. Adapted from Sanfilipo et al., 2007; original equation: [gray matter + white matter] / ICV)

$$Survivors' Cerebellum = \frac{CB\ Volume + Lesion + Atrophy}{ICV}$$

Equation 4 Adapted from Chard et al., 2002 atrophy measure with multiple sclerosis patients; original equation: [total white matter + lesion volume (all lesions were in WM)]/ ICV.

$$Atrophy = \ Avg\frac{CB\ Volume_{Controls}}{ICV} - \frac{CB\ Volume_{Survivors} + Lesion}{ICV}$$

Equation 5 Adapted from Chard et al., 2002; Cross sectional comparison between matched controls and MS patients. Original equation: [Controls total white matter]/ ICV – [MS total white matter + lesion volume] / ICV. Lesion size was added back into survivors' volume

$$CB\ \%\ Atrophy = \frac{Atrophy}{(\frac{CB\ Volume_{Controls}}{ICV})} x\ 100$$

Equation 6 Adapted from Chard et al., 2002; Cross sectional comparison between matched controls and MS reports percent decline relative to controls

4 Planned Analyses

Double dissociations help to determine the exact roles of brain structures and how they are involved in behavior, and provide strong evidence for the localization of behavioral functions. The goal of the current study was to localize the cerebellum's contribution to behavioral measures. To dissociate phonemic fluency from motor functioning, the current study included comparison motor related regions and a comparison motor task. The current study also explored whether selective impairment in written or oral processing speed occurred based on lesion size in specific lobes of the cerebellum. Lastly, lesions in the dentate nucleus and the vermis disrupt the aforementioned loops that support both phonemic and motor related regions; therefore, lesions in these regions were hypothesized to negatively affect all measures.

Additionally, treatment factors (e.g., cranial radiation, hydrocephalus, seizure disorder, and hormone disorder) were explored in analyses as potential confounds and covariates.

A confound was defined as a treatment variable that was correlated to both the independent variable (percent lesion size) and the dependent variable (behavioral performance). Confounds were accounted for statistically to ensure they were not misrepresenting the relationship between the independent variable and the dependent variable. A covariate was defined as a treatment factor that was correlated with the dependent variable (behavioral performance) but not the independent variable (ROI lesion size). Covariates were accounted for by using partial correlations.

If findings were not consistent with hypotheses then they would be further probed. First, the individual regions (as opposed to cumulative ROIs) would be explored. Then, analyses would be replicated with the number of words generated during the first and last 15 second time block of the verbal fluency task, to determine whether impaired initiation, impaired word generation, or inflexible search strategies contributed to results. Only medium effect sizes would be reported in exploratory analyses to correct for multiple comparisons. This approach was used for each of the following analyses.

5 Results

5.1 Outliers

Outliers were defined using the outlier labeling rule, in which the interquartile range ($Q3_{75}$-$Q1_{25}$) was multiplied by a factor of 2.2, which was added to or subtracted from $Q2_{50}$ to determine the upper and lower boundary of outliers for each group (Hoaglin and Iglewicz, 1987). Outlier analysis was conducted and 3 survivors were changed to the next lowest score (5.81; Osborne and Overbay, 2004) due to extremely low scores on the grooved pegboard measure (Z-score of -7, -9, and -10). Two of the outliers had damage across all three ROIs, and the third did not have a lesion in the right hemisphere of the cerebellum but did have cerebellar atrophy. Analyses were run both with and without the outliers. The results did not appreciably change when outliers were removed, therefore they were included to increase the overall sample size and power in the analyses.

5.2 Effect Size

Because of the small sample size, the need to explore effect size was critical to ensure that a lack of statistical power was not explaining results. Effect size was defined based on Cohen (1988), who stated that when exploring Pearson's r values, greater than .1 was defined as a small effect size, greater than .3 was defined as a medium effect size, and greater than .5 was defined as a large effect size.

5.3 Descriptive Analyses

A number of participants had some degree of damage across all regions. On average the highest lesion sizes occurred in the dentate and the vermis. Summary of

average lesion size across each lobe of the cerebellum is displayed below in Figures 4-6. On average, participants experienced about 14% total cerebellar lesion size (range 2-28). On average, 10% of the right dentate (0-100), 4% of the left dentate (0-30), 7% of the total dentate (0-50), and 29% of the total vermis (0-72) was lesioned. With regard to the regions of interest (ROIs), average lesion size was 11% of the right phonemic ROIs (0-43), and 10% of the right motor ROIs (0-63). Average lesion size was 18% in the combined dentate and vermis region (0-42). In general, the highest degree of damage occurred in the vermis, whereas the cerebellar hemispheres had smaller amount damage. With regard to lesion laterality, 16 participants had midline lesions, 5 had left lateralized lesions, and 4 had right lateralized lesions.

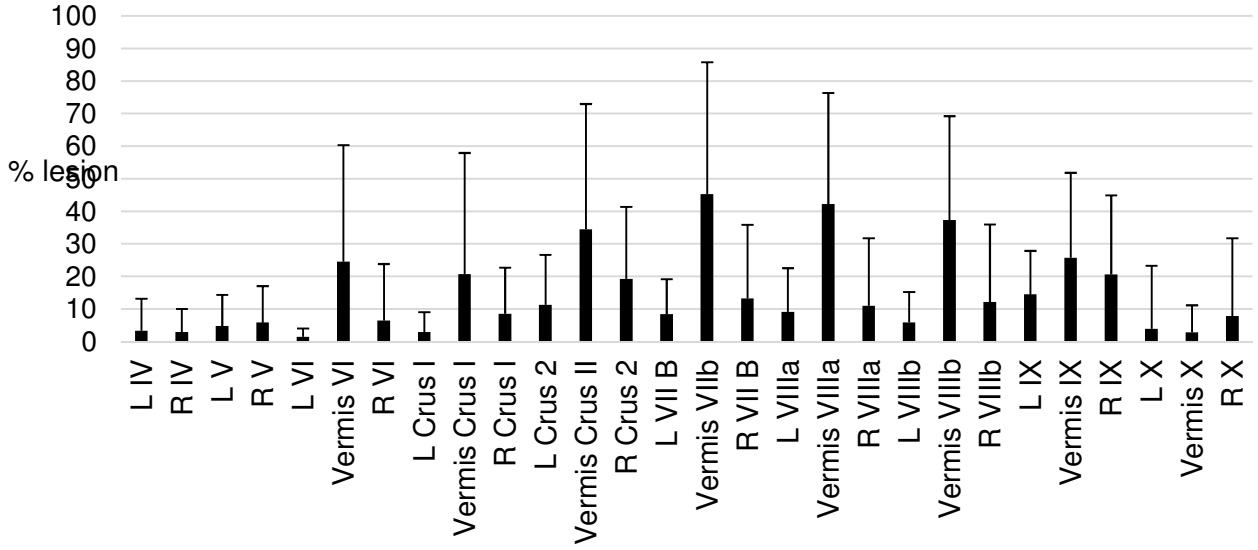


Figure 4 Summary of average cerebellar lesion size

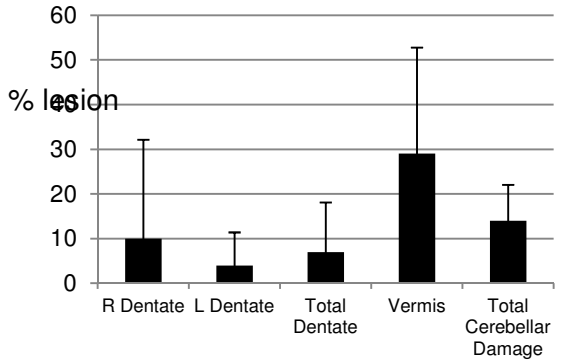


Figure 5 Average lesion size in the dentate & vermis

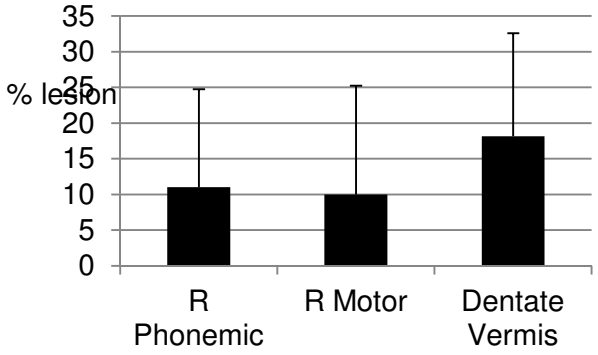


Figure 6 Average lesion size in the ROIs

5.4 Group Comparisons

Data from controls only was included in the atrophy equation. Survivors and controls were matched with regard to gender, age, and level of education. Group comparisons indicated that survivors differed from controls with regard to amount of cerebrospinal fluid (CSF), cerebellar white matter, cerebellar grey matter, total cerebellar volume, whole brain grey matter, and the proportion of the cerebellum relative to the intracranial vault (ICV; see Table 1). Table 2 displays subgroup comparisons. Cohen's D values are reported to reduce bias due to multiple comparisons. Participants with high grade tumors had lower whole brain grey matter, whole brain white matter, cerebellar grey matter, cerebellar volume, and proportion of cerebellar volume relative to ICV when compared to low grade tumors and controls. Participants with low grade tumors had greater CSF, and less cerebellar grey matter, cerebellar white matter, and cerebellar volume when compared to controls. Participants with high grade and low grade tumors had on average the same lesion size, however, individuals with high grade brain tumors displayed significantly greater cerebellar atrophy when compared to individuals with low grade brain tumors.

Table 1 Survivor and control demographic and descriptive comparisons

	Survivors *n*=25	Controls *n*=25	Group differences	Cohen's D
Gender	52% Female	52% Female		
Age at exam (years)	*M*=23.68 *SD*=5.06 Range: 18-34	*M*=23.56 *SD*=4.44 Range: 18-35	*t*=-.09, *p*=.93	*D*=.03, *r*=.01
Years of education	*M*=13.88 *SD*=2.49	*M*=14.59 *SD*=2.16	*t*=-1.08, *p*=.29	*D*=-.30, *r*=-.15
Age at diagnosis (years)	*M*=9.32, *SD*=5.06 Range 1-19			
Radiation & Chemotherapy	*n*=14 56%			
Chemotherapy only	*n*=1 4%			
High grade tumor	*n*=15 60%			
Hydrocephalus	*n*=19 76%			
Seizure medication	*n*=1 4%			
Hormone deficiency	*n*=13 52%			
Whole brain grey matter *	*M*=646 *SD*=80	*M*=687 *SD*=55	*t*=2.09, *p*=.04	*D*=-.60, *r*=-.29
Whole brain white matter^	*M*=442 *SD*=62	*M*=466 *SD*=36	*t*=1.73, *p*=.09	*D*=-.47, *r*=-.23
CSF*	*M*=395 *SD*=138	*M*=287 *SD*=68	*t*=-3.51, *p*<.01	*D*=0.99, *r*=.44
ICV	*M*=1482 *SD*=178	*M*=1440 *SD*=110	*t*=-1.01, *p*=.32	*D*=.28, *r*=.14
Cerebellar grey matter*	*M*=81 *SD*=15	*M*=108 *SD*=9	*t*=-7.46, *p*<.01	*D*=-2.18, *r*=-.74
Cerebellar white matter*	*M*=43 *SD*=8	*M*=53 *SD*=5	*t*=-5.47, *p*<.01	*D*=-1.50, *r*=-.60
Lesion size	*M*=14 *SD*=8			
Cerebellar volume (inc lesion)*	*M*=138 *SD*=23	*M*=161 *SD*=12	*t*=-4.39, *p*<.01	*D*=-1.25, *r*=-.53
Percent of CB atrophy	*M*=11 *SD*=12			
CB Proportion of ICV*	*M*=.10 *SD*=.02	*M*=.11 *SD*=.01	*t*=2.46, p=.01	*D*=-.63, *r*=-.30

Note. ^ indicates trend at p<.10; * indicates p<.05; CSF=cerebrospinal fluid; ICV=intracranial vault; CB=cerebellar; inc=including

Table 2 Subgroup descriptive statistics and effect sizes

	Subgroup descriptive statistics			Subgroup differences Cohen's D		
	High Grade *n*=15	Low Grade *n*=10	Controls *n*=25	High Grade vs. Low Grade	High Grade vs. Controls	Low Grade vs. Controls
Gender	60% Female	40% Female	52% Female			
Age at exam (years)	*M*=23.67 *SD*=5.26 Range:18-34	*M*=23.70 *SD*=5.03 Range: 18-32	*M*=23.56 *SD*=4.44 Range: 18-35			
Years of education	*M*=13.53 *SD*=2.61	*M*=14.40 *SD*=2.32	*M*=14.59 *SD*=2.16			
Age at diagnosis (years)	*M*=9.27 *SD*=5.57 Range 1-19	*M*=9.40 *SD*=4.50 Range 3-17				
Radiation & Chemotherapy	*n*=14 93%	*n*=0 0%				
Chemotherapy only	*n*=1 7%	*n*=0 0%				
Hydrocephalus	*n*=11 73%	*n*=8 80%				
Seizure medication	*n*=1 7%	*n*=0 0%				
Hormone deficiency	*n*=12 80%	*n*=1 10%				
Whole brain grey matter^{+}	*M*=612 *SD*=74	*M*=697 *SD*=64	*M*=687 *SD*=55	-1.21**	-1.20**	0.17
Whole brain white matter^{+}	*M*=419 *SD*=50	*M*=475 *SD*=66	*M*=466 *SD*=36	-0.99**	-1.15**	0.17
CSF^{+}	*M*=434 *SD*=145	*M*=336 *SD*=106	*M*=287 *SD*=68	0.75*	0.49	0.66*
ICV	*M*=1466 *SD*=154	*M*=1507 *SD*=217	*M*=1440 *SD*=110	-0.23	0.20	0.46
Cerebellar grey matter^{+}	*M*=75 *SD*=15	*M*=90 *SD*=11	*M*=108 *SD*=9	-1.10**	-2.85**	-1.88**
Cerebellar white matter^{+}	*M*=39 *SD*=7	*M*=49 *SD*=6	*M*=53 *SD*=5	-1.51**	-2.41**	-0.76*
Lesion size^{+}	*M*=14 *SD*=8	*M*=14 *SD*=9		0		
Cerebellar volume (inc lesion) $^{+}$	*M*=129 *SD*=20	*M*=152 *SD*=21	*M*=161 *SD*=12	-1.13**	-2.07**	-0.60*
Percent of CB atrophy	*M*=15 *SD*=13	*M*=5 *SD*=5		0.94**		
CB Proportion of ICV $^{+}$	*M*=.10 *SD*=.02	*M*=.11 *SD*=.01	*M*=.11 *SD*=.01	-0.59*	-0.69*	0

Note. $^{+}$ indicates significant difference; CSF= cerebrospinal fluid; ICV=intracranial vault; CB=cerebellar; inc= including; Cohen's D: Small=0.2-0.3, Medium=0.5*, Large $\geq$ 0.8**

5.5 Intracranial Vault (ICV)

To examine the possibility that survivors may, in general, have smaller brains due to neurological sequelae that was not captured in the ICV, a *t*-test was conducted between survivor and control groups and ICV. It revealed that survivors and controls were similar with regard to ICV, $t(39.85)=-1.01$, $p=.32$, Cohen's $d=.28$, $r=.14$. The measure of ICV (white matter + grey matter + CSF) is commonly used in healthy individuals, brain tumor populations (Mulhern et al., 1999), and other clinical populations with atrophy (e.g., multiple sclerosis; Vagberg et al., 2013). CSF alone, which is commonly used in other populations with brain atrophy, was not used in the analyses because it does not differentiate between cerebellar lesion and cerebellar atrophy.

5.6 Cerebellar Atrophy

In an effort to quantify atrophy, the aforementioned formula was used. Survivors treated with cranial radiation had on average greater cerebellar atrophy, $t(18.38)=-2.66$, $p=.01$. Survivors treated without radiation therapy on average had 5% cerebellar atrophy ($SD=5$) and survivors who were treated with radiation therapy on average had 15% cerebellar atrophy ($SD=13$). The relationships between radiation and atrophy, atrophy and hormone disorder, and NPS and atrophy were similar ($r=.48$, $r=.39$, $r=.41$, respectively). Of note, radiation, hormone disorder, and NPS are highly collinear (see *5.10 Assumptions of Regression*). ICV was not significantly different among survivors treated with or without radiation $t(23)=.08$, $p=.94$, suggesting that cerebrospinal fluid accounted for volume in atrophied spaces, and negligible differences remained in the estimate of premorbid brain size. Age at diagnosis was negatively related to atrophy, indicating that survivors diagnosed at a younger age had greater levels of atrophy when

compared to survivors diagnosed at older ages. Cerebellar atrophy was not related to total cerebellar lesion size (see Table 3; for a more detailed investigation see section 5.21.1 Relationship between Lesion Size and Cerebellar Atrophy).

Table 3 Correlations among atrophy and medical variables

	Surgery Type	Seizures	Age at diagnosis	NPS	Radiation	Lesion Size	Hormone Disorder
Atrophy	-.09	-.10	-.35	.41*	.48*	-.26	.39

Note. N=25; *p <.05; NPS= Neurological Predictor Scale; Variables defined as: Surgery type (1= subtotal excision, 2= gross total resection), Seizures (0=no seizures, 1= presence of seizures), Age at diagnosis (years), NPS (low treatment 1 to 9 high treatment), Radiation (0=no radiation, 1=presence of radiation), Lesion size (0-100%), Hormone disorder (0= no hormone disorder, 1=presence of hormone disorder)

5.7 Feasibility of Lesion Symptom Mapping

In order to conduct lesion symptom mapping, it was important to have overlapping as well as distinct lesion areas. The first step of determining the lesion overlap was based on a preliminary visual evaluation of each participant's T1 MRI scan. In the preliminary analyses, there was significant overlap in individuals with lesions in both motor and fluency related regions, but a few distinct lesion areas; based on visual inspection, 10 participants had lesions in both motor and fluency related regions, 14 participants had lesions only in fluency related regions, and 4 participants had lesions only in motor related regions. While the preliminary analyses included 28 participants, only 25 survived imaging analyses (2 participants had registration issues and 1 participant had an artifact). Once lesions were drawn and confirmed by a neuroradiologist, the lesion distribution changed due to increased precision and increased ability to distinguish between cerebellar lesion and cerebellar atrophy. After more precise analysis that included atrophy, 20 participants had some degree of damage across all three ROIs. Three individuals had damage outside of the proposed

ROIs, and only two individuals had damage that showed some degree of lesion specificity (see Table 4).

Table 4 Summary of the percentage of cross regional lesion and atrophy

ID	Phonemic Lesion	Motor Lesion	Dentate Vermis Lesion	Total Lesion	Phonemic Atrophy	Motor Atrophy	Dentate Vermis Atrophy	Total Atrophy
1	27	10	14	15	0	0	5	0
2	5	1	3	8	8	14	18	3
3	7	1	23	14	23	19	9	27
4	43	13	35	24	2	15	7	8
5	0	13	5	7	14	1	24	13
6	22	5	3	10	3	10	24	5
7	41	5	38	23	0	0	8	10
8	**0**	**0**	**25**	**14**	**0**	**0**	**9**	**0**
9	1	0	30	19	4	11	9	25
10	2	5	4	6	7	10	25	3
11	12	2	33	21	48	54	16	15
12	4	12	27	16	0	0	10	0
13	11	23	12	11	17	16	30	21
14	**10**	**0**	**0**	**2**	**0**	**0**	**10**	**5**
15	9	11	40	28	4	4	5	0
16	11	2	32	20	13	21	38	9
17	7	3	20	13	0	0	17	3
18	25	63	21	27	0	0	0	0
19	0	2	29	14	34	32	10	13
20	0	4	17	12	12	15	4	20
21	41	45	42	28	19	28	34	0
22	0	0	0	5	0	0	33	0
23	9	23	2	10	14	9	11	42
24	0	0	0	2	0	0	19	14
25	0	0	0	3	37	71	3	33

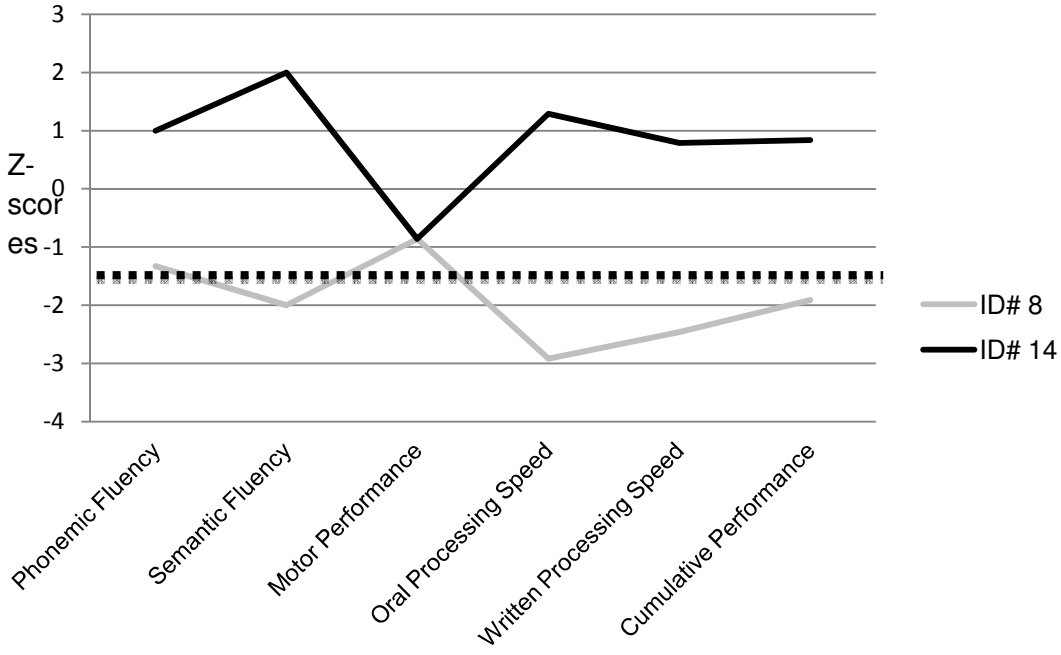
Note. All numbers indicate the percentage of the region that was damaged; IDs 22, 24, and 25 had lesions outside the proposed regions of interest, 16 individuals had lesions that went across all three ROIs, 3 individuals had lesions in the motor and the dentate/vermis ROIs (ID 5, 19, 20), 1 person had a lesion only in the dentate/vermis ROI (ID 8), 1 person had a lesion only in the phonemic ROI (ID 14), and 1 person had a lesion in the phonemic and dentate/vermis ROIs (ID 9). With regard to region specificity with atrophy, only **IDs 8** (dentate/vermis) and **14** (phonemic fluency and dentate/vermis) did not display damage across ROIs.

5.8 Case Series

Descriptive statistics indicated a large degree of diffuse damage and a general lack of regional specificity. Damage across regions makes it very difficult to test the proposed questions. To explore whether any participants showed the expected pattern of results, a case series with individuals who displayed lesion specificity was explored. The only two cases that displayed any specificity were IDs 8 (dentate/vermis) and 14 (phonemic and dentate/vermis). For the case series, significance was defined as greater than or equal to 1.5 standard deviations below the mean on behavioral measures. Thus, the hypothesis was that both participants with damage in the dentate/vermis ROI would have impaired performance across measures. The participant with damage to the phonemic ROI in addition to the dentate/vermis ROI was expected to have a greater degree of impairment on the phonemic fluency measure, when compared to other measures. The last hypothesis was that total lesion size would be related to poorer composite performance (average of phonemic fluency, semantic fluency, right motor performance, oral processing speed, and written processing speed). The planned additional analysis on the number of words generated during the each time block of the verbal fluency task was also explored.

It was important to look at results with consideration for individual differences participant 8 had a high grade tumor that was treated with radiation (whole brain and focal) and chemotherapy. Participant 8 also had secondary complications including hydrocephalus and hormone disorder. Participant 14 had a high grade tumor that was treated with radiation (whole brain and focal) and secondary complications of hydrocephalus and seizures.

Results are presented in Table 5. Participant 8, who had damage to the dentate and the vermis, displayed impaired performance on semantic fluency, oral processing speed, and written processing speed measures. However, unexpected resiliencies were seen in phonemic fluency and motor performance. Participant 14 displayed intact performance across all measures that were hypothesized to be affected. Therefore this case series was not consistent with the hypotheses that individuals with lesions in the phonemic and dentate/vermis ROIs would display corresponding deficits in behavioral performance. It is important to note that 14% of the cerebellum of participant 8 was lesioned, whereas only 2% of the cerebellum of participant 14 was lesioned. Correspondingly, participant 8 displayed more global impairments on behavioral measures, whereas participant 14 displayed intact performance. Therefore the last hypothesis, that total lesion size would be related to cumulative performance, was supported by the case series. With regard to the number of words generated in each 15 second time block (see Figure 8), participant 8 displayed similar trajectories on both the phonemic and semantic fluency measures. Participant 14 appeared to do slightly better at sustaining fluency on the semantic measure, when compared to the phonemic measure. However, this difference did not appear to be substantial enough to conclude that there are differences between semantic and phonemic fluency performance.



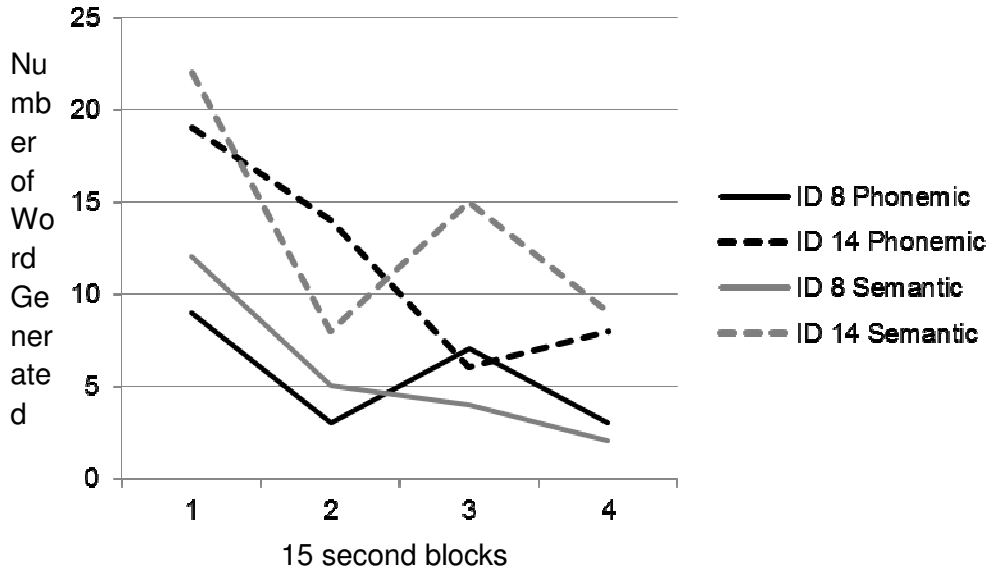
Note. Participant 8 had damage exclusively in the dentate/vermis ROI, and participant 14 had damage exclusively in the phonemic ROI and the dentate/vermis ROI

Figure 7 Case Series: Plot of Z-scores on behavioral measures

Table 5 Case series: Z-score performance across behavioral measures

	N	Phonemic Fluency	Semantic Fluency	Dominant Motor	Oral Processing Speed	Written Processing Speed	Cumulative Performance
ID# 8	1	-1.33	-2.00*	-0.86	-2.92*	-2.46*	-1.91
ID# 14	1	1.00	2.00	-0.86	1.29	0.79	0.84

Note. * indicates significantly impaired Z-score (<1.50); participant 8 had damage exclusively in the dentate/vermis ROI, and participant 14 had damage exclusively in the phonemic ROI and the dentate/vermis ROI



Note. Participant 8 had damage exclusively in the dentate/vermis ROI, and participant 14 had damage exclusively in the phonemic ROI and the dentate/vermis ROI

Figure 8 Number of words generated during the 15-second blocks on the phonemic and semantic fluency measures

Descriptive analyses and case series indicated that the amount of cross regional damage made it impossible to answer the proposed questions with the sample. The aforementioned case series on the participants who displayed some degree of specificity also did not display a consistent pattern of specialization based on behavioral performance. This appears to be related to the high degree of unexpected cerebellar atrophy in the sample. As a result, new hypotheses were developed and tested.

5.9 Revised Hypotheses

Upon finding that most individuals had damage across the phonemic, motor, and dentate/vermis ROIs, the hypotheses were revised. Given a more diffuse degree of cerebellar damage, the current study was only able to determine the impact of diffuse

cerebellar damage. Because the dentate and the vermis are critical regions of connection and damage to these regions has been associated with poorer outcomes (e.g., Szathmari et al., 2010), lesion size in the dentate and the vermis was also investigated. Prior research has not determined the precise causes of cerebellar atrophy, but researchers have suggested that cerebellar atrophy could result from surgery, damage to the dentate, cranial irradiation, seizures, or seizure medication (Poretti, Wolf, and Boltshauser, 2008). There is evidence from multiple sclerosis populations that brain atrophy may be independent of lesion size (Chard et al., 2002). Both cerebellar atrophy and cerebellar lesion size appear to be related to motor and cognitive difficulties (e.g., Schmahmann, 2004); however, due to methodological limitations researchers have not been able to investigate the interaction between the lesion size and the amount of cerebellar atrophy (e.g., Timmann, 2008). Animal models suggest that the cells in the cerebellum are more likely to regenerate if there is a small degree of uniform damage (Rohkamm, 1977). Therefore, cerebellar atrophy was hypothesized to change the relationship between lesion size and behavioral performance, such that individuals with larger lesions would be more affected by cerebellar atrophy, whereas individuals with smaller lesions would be less affected by cerebellar atrophy. After testing assumptions, confounds, and covariates, multiple regressions were used to test the hypotheses.

5.9.1 Hypothesis 1

An interaction between cerebellar lesion size and cerebellar atrophy (such that survivors with larger lesions would be more affected by atrophy than survivors with smaller lesions) would predict cumulative performance and all behavioral measures

(phonemic and semantic fluency, motor performance, and written and oral processing speed).

5.9.2 Hypothesis 2

An interaction between lesion size in the dentate and the vermis and cerebellar atrophy (such that survivors with larger lesions would be more affected by atrophy than survivors with smaller lesions) would predict all behavioral measures (phonemic and semantic fluency, motor performance, and written and oral processing speed).

5.10 Assumptions of Regression

It is important to note when interpreting results that lesion size in the cerebellum and lesion size in the dentate/vermis were highly correlated and could not be modeled in the same equation due to problems with multicollinearity (r=.91, p<.01). Other variables that displayed a high degree of multicollinearity included: radiation and hormone disorder (r=.76, p<.01), tumor grade and hormone disorder (r=.69, p<.01), tumor grade and radiation (r=.92, p<.01), and tumor grade and the neurological predictor scale (r=.86, p<.01). Other assumptions of regression (e.g., normal distribution, homoscedasticity, independence of residuals) were not violated in the regression models. Nonlinear relationships among variables were also explored and did not appear in scatter plots and were not statistically significant when tested quantitatively.

5.11 Potential Confound Analyses

Potential confounds were defined as treatment variables that were correlated to both the independent variable (lesion size) and the dependent variable (behavioral

performance). Potential confounds were chosen based on prior literature which has reported that radiation, hydrocephalus, seizures, hormone disorder, age at diagnosis, tumor grade, cumulative neurological risk factors, and atrophy corresponds with poorer behavioral outcomes (Butler and Haser, 2006; Ris and Noll, 1994; Hardy, Bonner, Willard, Watral, and Gururangan, 2008; Palmer et al., 2003). As previously mentioned, it is important to interpret these relationships with the consideration that some of these variables are highly collinear.

As reported in Table 6, Pearson and Point-biserial correlations revealed that some disease and treatment factors, such as radiation, hormone disorder, age at diagnosis, and cerebellar atrophy, did correlate with lesion size in the cerebellum and lesion size in the dentate/vermis ROI. Radiation, hydrocephalus, seizure disorder, and hormone disorder were defined as dichotomous variables where 0 indicated treatment or disorder was not present and 1 indicated treatment or disorder was present. Age at diagnosis was defined in years; tumor grade was defined as 1 indicating a low grade tumor and 2 indicating a high grade tumor. The Neurological Predictor Scale (NPS; Micklewright et al., 2008) is a cumulative measure that includes treatment complications such as hydrocephalus, hormone deficiency, seizures, as well as amount of brain surgery, presence and type of radiation therapy, and chemotherapy, and values range from 0 (no treatments or complications) to 9 (high degree of treatments and complications). The aforementioned formula for atrophy was used, and provided a measure of the percentage of atrophy in the cerebellum secondary to lesion size. Total cerebellar volume and ICV were also included to verify that the percent lesion was not

highly correlated with the volumetric measures used in the atrophy equation (see Table 6).

For radiation, a small, but statistically non-significant, effect was present between cerebellar lesion size and radiation, such that individuals treated with radiation therapy had slightly smaller lesions in the cerebellum than those without radiation therapy. In contrast, a small, but statistically non-significant, effect was present between hormone disorder and total lesion size as well as lesion size in the dentate and the vermis, indicating that individuals with hormone disorder had slightly larger lesions in the cerebellum and the dentate/vermis ROI than participants without hormone disorder. These findings may, however, be due to radiation therapy considering that only one individual with hormone disorder was not treated with radiation therapy.

With regard to age at diagnosis, there was a small positive relationship between lesion size in the dentate/vermis and age at diagnosis, such that individuals older at diagnosis had larger lesions in the dentate/vermis ROI. For cerebellar atrophy, a small, but statistically non-significant, negative effect was detected between the total lesion size and cerebellar atrophy (r=-.26). This relationship was similar for lesion size in the dentate/vermis ROI and atrophy (r=-.22) and indicated that as lesion size increased total cerebellar atrophy decreased. Additionally, for seizures, the non-significant negative relationships between total lesion size and presence of seizures were based on only one individual who had seizures. Lastly, volumetric correlations indicated that there were small non-significant relationships between the percent lesion measures (total cerebellum and dentate/vermis) and ICV, such that as lesion size increased ICV slightly increased.

Table 6 Correlation coefficients for potential confound analyses

	Rad	Hydro	Seizures	Hormone	Age Dx	Tumor Grade	NPS	Atrophy	CB Volume	ICV
% Lesion in Cerebellum	-.10	-.01	-.31	.12	.02	.03	.02	-.26	.09	.19
% Lesion in Dentate & Vermis	-.03	.02	-.26	.14	.17	-.01	.06	-.22	.14	.22

Note. N=25; all p values>.05; Rad= Radiation Therapy; Hydro= Hydrocephalus; Dx=Diagnosis; NPS=Neurological Predictor Scale; CB=Cerebellum; ICV=Intracranial Vault

5.12 Potential Covariate Analyses

Across behavioral measures, a number of treatment variables were correlated with behavioral outcomes (see Table 7). Therefore, a cumulative measure of total treatments was used as a covariate in all of the following analyses. The Neurological Predictor Scale (NPS; Micklewright et al., 2008) is a cumulative measure that includes treatment complications such as hydrocephalus, hormone deficiency, seizures, as well as amount of brain surgery, presence and type of radiation therapy, and chemotherapy. Cerebellar atrophy also was included as a covariate in all analyses because it had a small to large negative correlation across behavioral measures (-.29 - -.57; see Table 7), indicating that as atrophy increased behavioral performance across measures decreased. Region specific atrophy was explored, but resulted in much smaller correlations among behavioral measures when compared to total atrophy (see Table 8). Therefore, total atrophy was selected as the covariate for the subsequent analyses. Due to a small sample size and limited power, only variables with medium to large effect sizes were included as covariates in the analyses (NPS and atrophy), and because age at diagnosis consistently displayed a small effect size, it was not included as a covariate.

Table 7 Correlation coefficients for potential covariate analyses

	Rad	Hydrocephalus	Seizure	Hormone	Age Dx	NPS	Total Cerebellar Atrophy
Phonemic Fluency	-.38^	-.09	.16	-.30	.23	-.37^	-.32
Motor Performance	-.37^	.15	.11	-.39^	.02	-.21	-.56**
Semantic Fluency	-.43*	-.14	.28	-.52**	.28	-.44*	-.29
Oral Processing Speed	-.39^	.10	.35^	-.38^	.19	-.28	-.46*
Written Processing Speed	-.40*	.15	.33	-.50*	.24	-.31	-.57**
Cumulative Performance	-.46*	.06	.28	.49*	.21	-.37^	-.54**

Note. N=25, ^indicates trend <.10; * indicates p<.05; ** indicates p<.01; Rad=Radiation; Dx=Diagnosis; NPS=Neurological Predictor Scale

Table 8 Correlation coefficients for region specific atrophy

	Phonemic Fluency	Dominant Motor Performance	Semantic Fluency	Oral Processing Speed	Written Processing Speed
Atrophy in Phonemic ROIs	-.35^	-.09	-.27	-.43*	-.29
Atrophy in Motor ROIs	-.25	-.19	-.23	-.43*	-.30
Atrophy in Dentate/Vermis	-.19	-.04	-.12	-.17	-.28
Total Cerebellar Atrophy	-.32	-.56**	-.29	-.46*	-.57**

Note. N=25; ^indicates trend <.10; * indicates p<.05; ** indicates p<.01

5.13 Cumulative Performance: Total Lesion Size and Atrophy

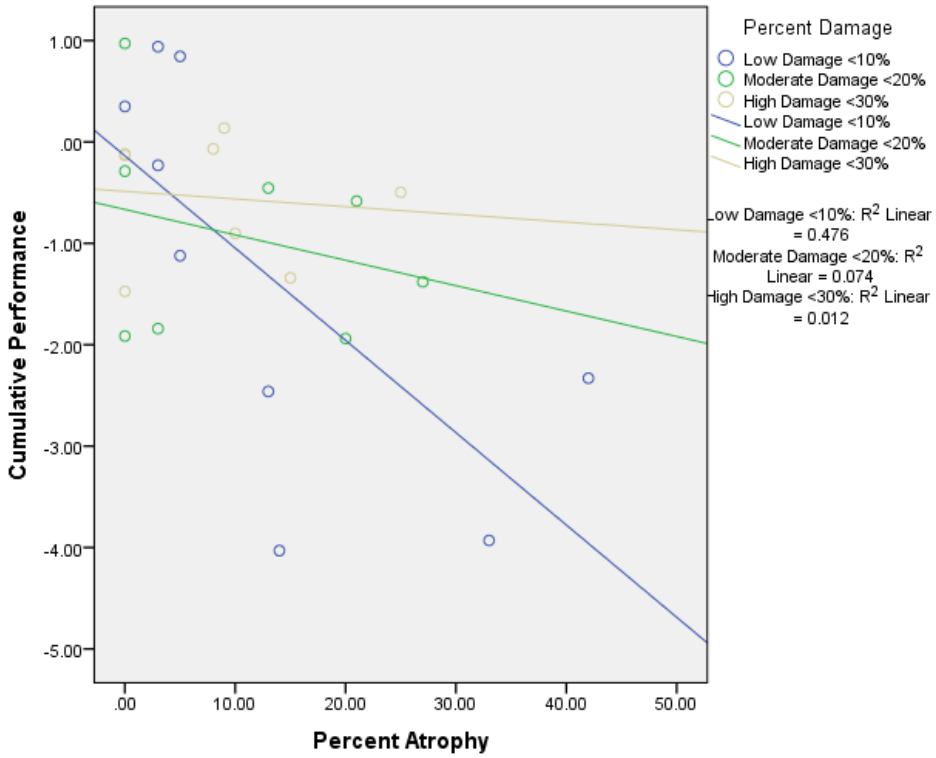
All variables were checked for multicollinearity using variance inflation factor analyses (VIF). VIF values of multicollinearity were within an acceptable range (<5). Unfortunately, lesion size in the dentate/vermis ROI was unable to be included as a covariate in any of the total lesion size analyses due to problems with multicollinearity that would double the standard error (VIF>5); therefore, lesion size in the dentate/vermis ROI was explored separately in subsequent analyses.

The first hypothesis was tested using a four predictor simultaneous entry regression model including the covariates (Neurological Predictor Scale (NPS) and Atrophy), total cerebellar lesion size and the interaction term (Cerebellar Atrophy*Lesion Size) as predictors of cumulative performance. All variables were grand mean centered to aid interpretation. This model accounted for 47% of the variance in cumulative performance (average of all measures), *Adj* R^2=.47,F(4,20)=6.27, p<.01. In the model, NPS was a trending towards significance (Beta=-.30, p=.09). Given the strength of this relationship, it is likely that if the study was replicated with a larger sample size higher NPS scores would result in poorer overall performance (See Table 9 for regression coefficients). A main effect of atrophy on cumulative performance was not significant at the average lesion size, and after controlling for NPS. Larger cerebellar lesion size was associated with higher cumulative performance at the average level of atrophy, B=.07, SE=0.03, Beta=.40, p=.03. Cerebellar lesion size uniquely explained 12% of the variance in cumulative performance. An interaction effect between atrophy and total lesion size indicated that the effect of atrophy was different based on size of the cerebellar lesion, B=.01, SE=0.00, Beta=.54, p=.01, and accounted for 22% of the

variance in cumulative performance. The interaction term indicated that the slope of the regression line between cumulative performance and atrophy varied based on lesion size (see Figure 9). Therefore, the results were inconsistent with the hypothesis that larger lesions would be more affected by atrophy and, rather, analyses suggested that individuals with smaller cerebellar lesions were more negatively affected by (steeper slope) a larger amount of cerebellar atrophy.

Table 9 Regression coefficients for total lesion size and atrophy predicting cumulative performance

Variable	*B*	*SE B*	Beta	*p*	sr^2	*VIF*
NPS (Centered)	-.17	.09	-.30	.09	.07	1.28
Atrophy (Centered)	-.02	.02	-.16	.40	.02	1.60
Total Lesion Size (Centered)	.07	.03	.40	.03	.12	1.33
Interaction (Atrophy*Lesion Size)	.01	.00	.54	.01	.22	1.32



Note. Continuous interaction is probed at three levels (low, moderate, and high damage due to lesion).

Figure 9 Interaction between cerebellar lesion size and atrophy predicts cumulative performance

5.14 Total Lesion Size and Atrophy: Fluency and Motor

The first hypothesis was also tested across dependent variables (motor performance, phonemic fluency, semantic fluency, oral processing speed, and written processing speed) using the same four predictor regression model. The model significantly predicted motor performance (*Adj* R^2=.30, $F(4,20)=3.62$, $p=.02$); however, none of the independent variables were significantly correlated with motor performance. The model did not significantly predict phonemic fluency performance (*Adj* R^2=.21, $F(4,20)=2.64$, $p=.07$). However, the model did predict semantic fluency performance (*Adj* R^2=.35, $F(4,20)=4.20$, $p=.01$). Similar to the results presented in the cumulative

model, NPS (*B*=-.28, *SE*=0.10, Beta=-.52, *p*=.01) and the interaction term (*B*=.01, *SE*=0.00, Beta=.54, *p*=.01) significantly predicted semantic fluency performance. Therefore, overall the first hypothesis was not supported for motor or phonemic verbal fluency performance; however, NPS and the interaction term were found to be predictors of semantic fluency performance.

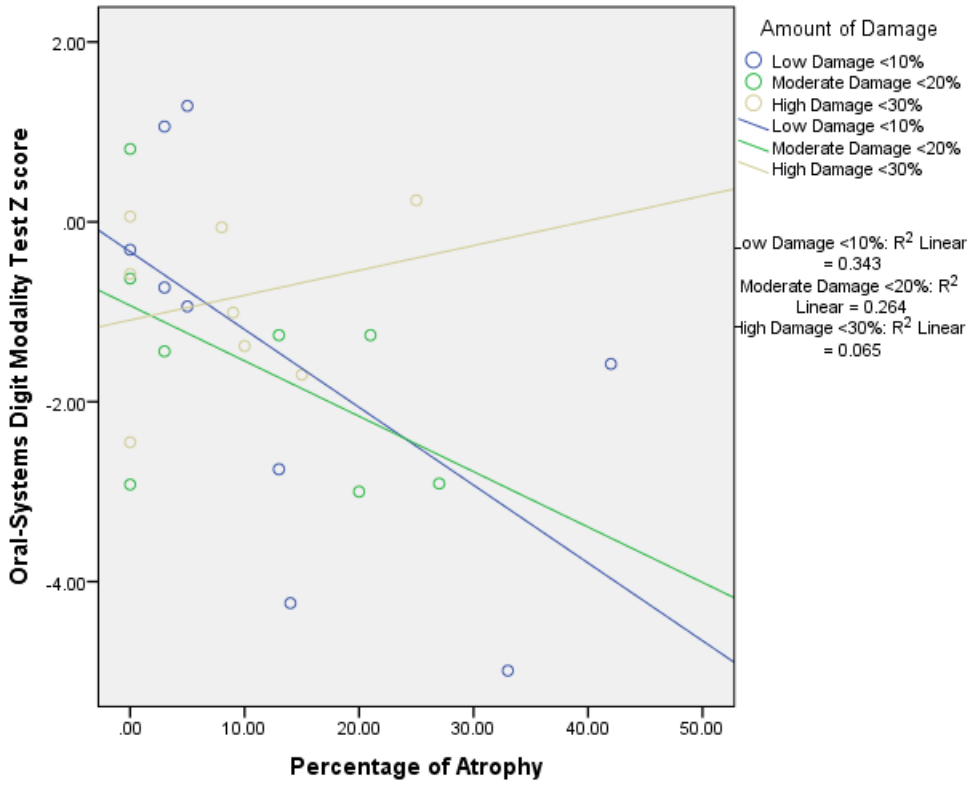
5.15 Total Lesion Size and Atrophy: Oral Processing Speed

The first hypothesis was supported for the oral processing speed measure using the same four predictor regression model (NPS, atrophy, total lesion size, and the interaction term) accounted for 33% of the variance in oral processing speed, *Adj* R^2=.33, *F*(4,20)=3.95, *p*=.02. NPS was not significant, *p*=.25 (See Table 10 for regression coefficients). A main effect of atrophy was not significant at the average lesion size and after controlling for NPS. Total cerebellar lesion size was not significantly associated with oral processing speed performance at the average level of atrophy and after controlling for NPS, *B*=.07, *SE*=0.04, *p*=.10. An interaction effect between atrophy and total lesion size was present and indicated that the effect of atrophy was different based lesion size, *B*=.01, *SE*=0.00, *p*=.01, and accounted for 21% of the variance in oral processing speed. The interaction term indicated the slope of the regression line between oral processing speed and atrophy changed based on lesion size (see Figure 10). Specifically, when estimating oral processing speed, individuals with smaller lesion sizes were more affected by (steeper slope) a greater amount of cerebellar atrophy, whereas individuals with larger cerebellar lesions were less affected by greater atrophy. Similar to the cumulative measure, the results were inconsistent with the hypothesis that larger lesions would be more affected by atrophy and, rather,

analyses suggested that individuals with smaller cerebellar lesions had oral processing speed that was more negatively affected by a larger amount of cerebellar atrophy.

Table 10 Regression coefficients for total lesion size and atrophy predicting oral processing speed performance

Variable	*B*	*SE B*	Beta	*P*	sr^2	*VIF*
NPS (Centered)	-.15	.12	-.22	.25	.04	1.28
Atrophy (Centered)	-.02	.03	-.14	.53	.01	1.60
Total Lesion size (Centered)	.07	.04	.33	.10	.08	1.33
Interaction (Atrophy*Lesion size)	.01	.00	.53	.01	.21	1.32



Note. Continuous interaction is probed at three levels (low, moderate, and high damage due to lesion).

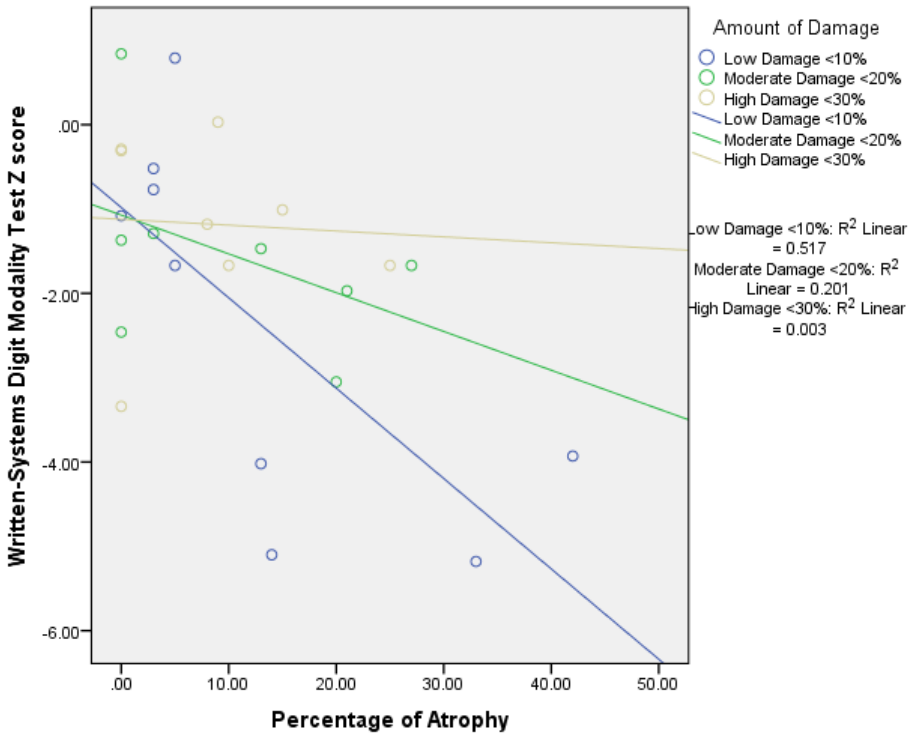
Figure 10 Interaction between total cerebellar lesion size and atrophy predicts oral processing speed performance

5.16 Total Lesion Size and Atrophy: Written Processing Speed

To test hypothesis one, the same model also was tested for written processing speed and accounted for 48% of the variance, *Adj* R^2=.48, $F(4,20)=6.49$, $p<.01$. Main effects of NPS and atrophy were not significant (See Table 11 for regression coefficients). Larger cerebellar lesion size was associated with better written processing speed performance at an average level of cerebellar atrophy after controlling for NPS, *B*=.08, *SE*=0.03, *p*=.03, and uniquely explained 12% of the variance in written processing speed. An interaction effect between atrophy and total lesion size was present in the sample, *B*=.01, *SE*=0.00, *p*=.01, and accounted for 20% of the variance in written processing speed. Similar to the previous models of cumulative performance and oral processing speed, the interaction term indicated that the slope of the regression line between written processing speed and atrophy was changed based on lesion size, and individuals with smaller cerebellar lesion size were more affected by (steeper slope) a greater amount of total atrophy (see Figure 11).

Table 11 Regression coefficients for total lesion size and atrophy predicting written processing speed performance

Variable	*B*	*SE B*	Beta	*p*	sr^2	*VIF*
NPS (Centered)	-.15	.11	-.22	.20	.04	1.28
Atrophy (Centered)	-.03	.03	-.23	.24	.03	1.60
Total Lesion size (Centered)	.08	.03	.41	.03	.12	1.33
Interaction (Atrophy*Lesion size)	.01	.00	.52	<.01	.20	1.32



Note. Continuous interaction is probed at three levels (low, moderate, and high damage due to lesion).

Figure 11 Interaction between cerebellar lesion size and atrophy predicts written processing speed performance

5.17 Dentate/Vermis Lesion Size and Atrophy: Fluency and Motor Performance

To test the second hypothesis identical models were run with lesion size in the dentate/vermis ROI rather than total cerebellar lesion size. The dentate/vermis ROI models did not predict phonemic fluency performance, *Adj* R^2=.09, $F(4,20)=1.61$, p=.21. Whereas, for semantic fluency the model was trending towards significance, *Adj* R^2=.23, $F(4,20)=2.82$, p=.052, NPS was a significant predictor, (NPS: B=-.24, SE=0.11, p=.04), and the interaction term was a trend (dentate/vermis*atrophy: B=.00, SE=0.00, p=.051). However, the dentate/vermis ROI model did predict motor performance, *Adj* R^2=.31, $F(4,20)=3.70$ p=.02, and two variables were trending towards significance: cerebellar atrophy Beta=-.39, p=.08 and the interaction (atrophy*dentate vermis lesion size)

Beta=.37, *p*=.07. Therefore, the second hypothesis was not significant for phonemic fluency performance, but was a trend for semantic fluency and motor performance.

5.18 Dentate/Vermis Lesion Size and Atrophy: Oral Processing Speed and Written Processing Speed

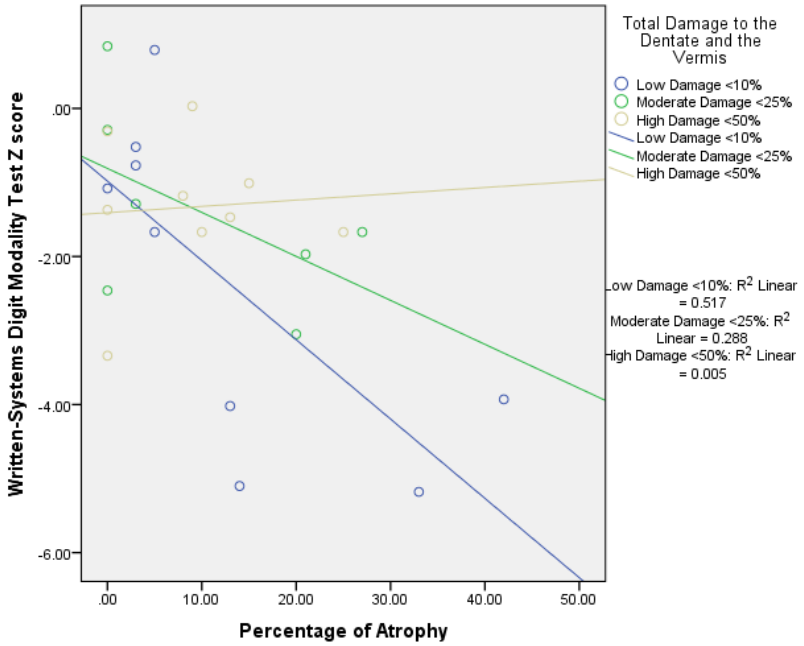
To test hypothesis two, the same four predictor regression model was tested for the dentate/vermis ROI and written and oral processing speed. The dentate/vermis model did not significantly predict oral processing speed although this model was trending towards significance, *Adj* R^2=.18, $F(4,20)=2.33$, $p=.09$.

In contrast, the second hypothesis was supported for written processing speed. The four predictor model included NPS, atrophy, dentate/vermis lesion size, and an interaction term (Atrophy* dentate/vermis lesion size) as predictors, and accounted for 40% of the variance in written processing speed, Adj R^2=.40,$F(4,20)=4.98$, $p<.01$. NPS did not significantly predict written processing speed (See Table 12 for regression coefficients). A main effect of atrophy was not significant at the average lesion size. Lesion size in the dentate/vermis ROI was not associated with written processing speed at the average level of atrophy, and after controlling for NPS, *B*=.02, *SE*=0.02, *p*=.20. However, an interaction effect between atrophy and lesion size in the dentate/vermis ROI was present in the sample, *B*=.00, *SE*=0.00, *p*=.02, and accounted for 15% of the variance in written processing speed. The interaction term indicated the slope of the regression line between written processing speed and atrophy changed based on the size of the lesion in the dentate/vermis ROI, such that individuals with smaller lesion in the dentate/vermis were more affected by (steeper slope) a greater amount of cerebellar atrophy (See Figure 12). Left and right dentate regions (as opposed to

cumulative regions) were tested individually in regression models and did not significantly predict written processing speed.

Table 12 Regression coefficients for lesion size in the dentate/vermis ROI and atrophy predicting written processing speed performance

Variable	*B*	*SE B*	Beta	*p*	sr^2	*VIF*
NPS (Centered)	-.10	.12	-.15	.42	.02	1.24
Atrophy (Centered)	-.04	.03	-.27	.18	.05	1.59
Dentate/Vermis Lesion size (Centered)	.02	.02	-.22	.20	.04	1.11
Interaction (Atrophy*Lesion size)	.00	.00	.43	.02	.15	1.26



Note. Continuous interaction is probed at three levels (low, moderate, and high damage due to lesion).

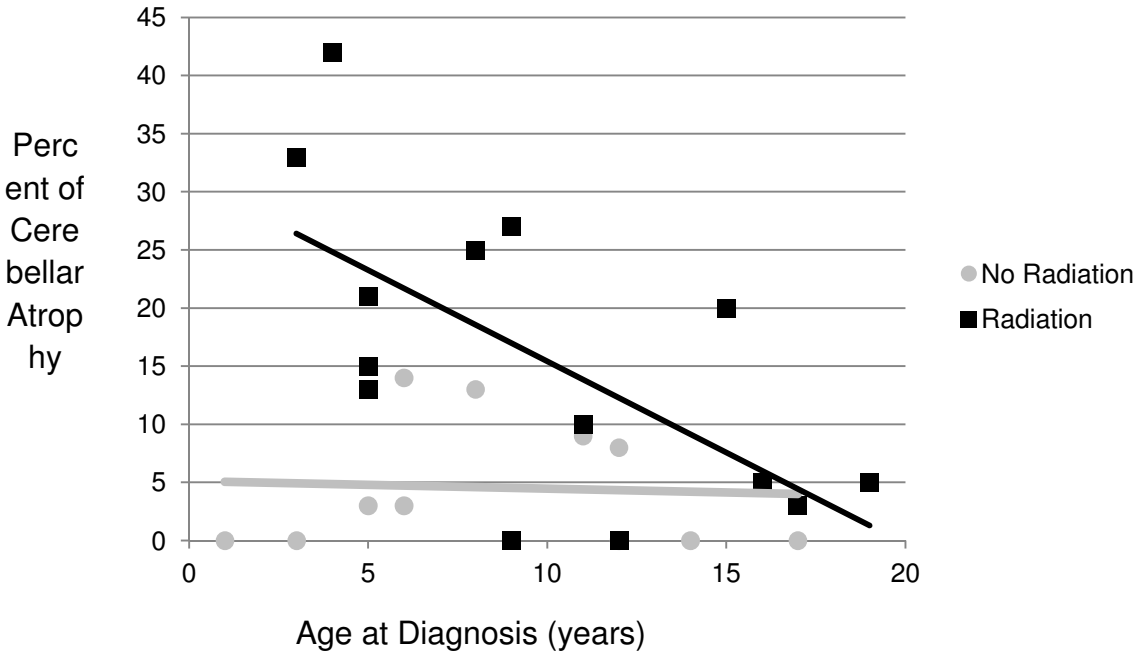
Figure 12 Interaction between dentate/vermis lesion size and atrophy predicts written processing speed performance

5.19 Planned Secondary Analyses: What is Associated with Cerebellar Atrophy?

Due to the possibility that tumor malignancy, age at diagnosis, or presence of cranial radiation was associated with cerebellar atrophy, secondary analyses were used to explore these possible relationships.

5.19.1 Age at Diagnosis and Radiation

Prior research suggests that children diagnosed with high grade brain tumors at a very young age (<5) may delay radiation treatment due to the negative impact on the developing central nervous system and white matter in the brain (Mulhern et al., 1992). In the current sample this was true for one individual (ID 20 diagnosed at age 1, medulloblastoma, no radiation, no cerebellar atrophy). This was the only participant with a medulloblastoma tumor who was not treated with radiation therapy. Other individuals diagnosed at a young age received radiation therapy within one month of diagnosis (ID 16 diagnosed at age 4, medulloblastoma, radiation, 42% cerebellar atrophy and ID 24 diagnosed at age 3 medulloblastoma, radiation, 33% cerebellar atrophy). In the current sample, it is impossible to differentiate treatment from tumor malignancy because no low grade tumors were treated with radiation, and only one high grade tumor was not treated with radiation. However, for participants who received radiation treatment, young age at diagnosis was correlated with greater cerebellar atrophy (n=14, r=-.64, p=.01). In contrast, age at diagnosis was not related to the amount of atrophy for individuals who were not treated with radiation (n=11, r=-.06, p=.86; see Figure 13).



Note. Visual depiction of the interaction between age at diagnosis and radiation as it relates to cerebellar atrophy. For the radiation group, younger age at diagnosis was associated with higher degrees of atrophy; however, in the no radiation group age at diagnosis was not associated with atrophy.

Figure 13 Treatment groups: Interaction between age at diagnosis and cerebellar atrophy

5.19.2 Interaction between Age at Diagnosis and Radiation predicts Cerebellar Atrophy

Based on the evidence from the correlational analyses, an interaction between age at diagnosis and radiation therapy predicting atrophy was explored. A three predictor regression model, which included the simultaneous entry of age at diagnosis, presence of radiation, and an interaction term (age*radiation) as predictors, accounted for 44% of the variance in cerebellar atrophy, *Adj* R^2=.44, $F(3,21)=7.30$, $p<.01$. A main effect of age at diagnosis was not significant. Presence of radiation was associated with higher cerebellar atrophy, $B=11.99$, $SE=3.52$, Beta=.52, $p<.01$. Radiation uniquely explained 27% of the variance in cerebellar atrophy. An interaction effect between age at diagnosis and radiation was present in the sample, $B=-1.51$, $SE=0.72$, Beta=-.50, $p=.049$, and accounted for 10% of the

variance in atrophy. The interaction term indicated that for individuals treated with radiation, younger age at diagnosis was associated with higher cerebellar atrophy. When NPS was added to the model, it was not a significant predictor of cerebellar atrophy (*B*=-.92, *SE*=1.67, Beta=-.19, *p*=.59); therefore it was removed for parsimony.

Table 13 Regression coefficients for age at diagnosis and radiation predicting cerebellar atrophy

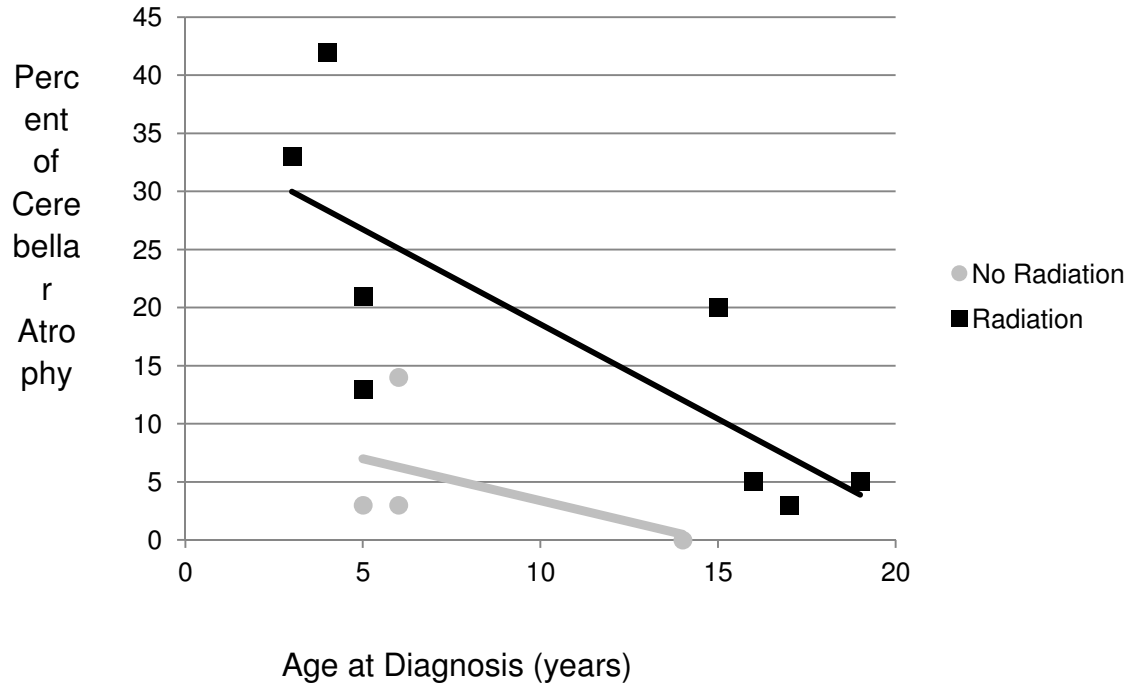
Variable	*B*	*SE B*	Beta	*p*	sr^2	*VIF*
Age at diagnosis (Centered)	-.07	.56	-.03	.91	.00	2.52
Radiation (0=no rad, 1=rad)	11.99	3.53	.52	<.01	.27	2.49
Interaction (age*rad)	-1.51	.72	.50	.049	.10	1.02

Note. Rad= Radiation Therapy; Age=Age at diagnosis

5.19.2 Lesion Size and the interaction between Age at Diagnosis and Radiation

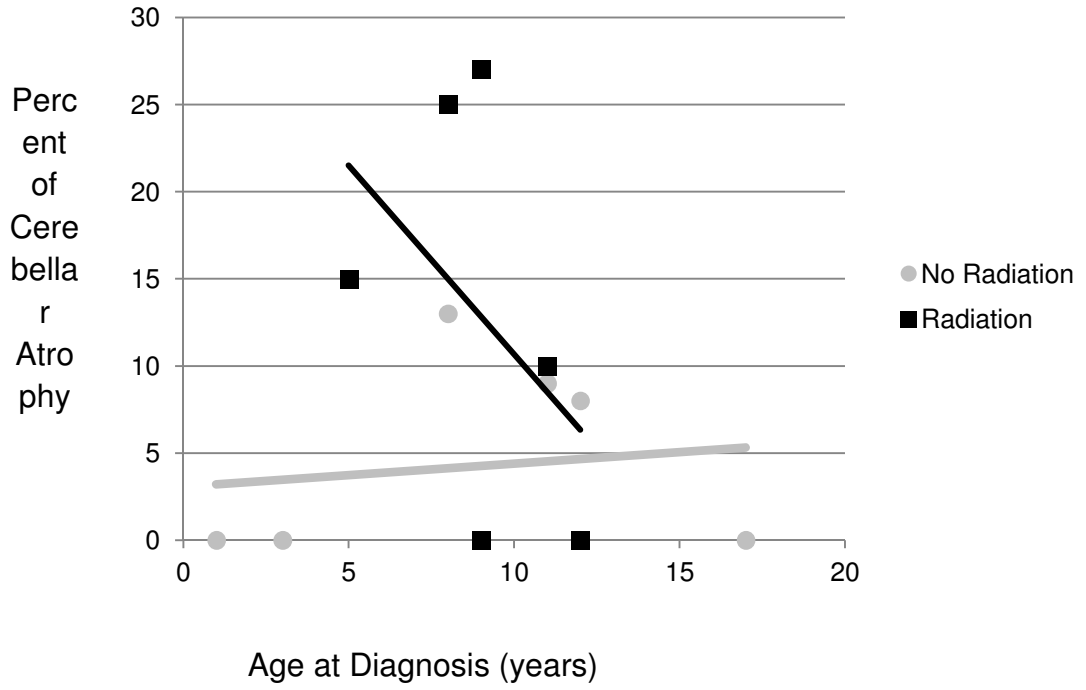
To determine whether lesion size changed the interaction between age at diagnosis and radiation therapy with regard to cerebellar atrophy, the sample was split into small and large lesion groups based on the median lesion size (14%). Individuals with less than 14% of their cerebellum lesioned were placed in the small lesion group (n=12), and individuals with greater than or equal to 14% of their cerebellum lesioned were placed in the large lesion group (n=13). For both groups, radiation therapy appeared to change the relationship between age at diagnosis and cerebellar atrophy; however, individuals in the large lesion group who received radiation displayed a steeper slope between age at diagnosis and atrophy, when compared to the small lesion group (see Figures 14-15). In contrast, correlations

among subgroups (large lesion + radiation and small lesion + radiation) suggested that individuals with smaller lesion sizes and radiation had a stronger correlation between age at diagnosis and radiation therapy (r=-78, p=.02) when compared to the larger lesion group (r=-.45, p=.37); however, these results should be interpreted with caution due to extremely small sample size (n=8 and n=6, respectively).



Note. Visual depiction of the interaction between age at diagnosis and radiation as it relates to cerebellar atrophy for individuals with small cerebellar lesions (<14%). For the radiation group, younger age at diagnosis was associated with higher degrees of atrophy; however, in the no radiation group age at diagnosis was not associated with atrophy.

Figure 14 Small Lesions: Interaction between age at diagnosis and cerebellar atrophy



Note. Visual depiction of the interaction between age at diagnosis and radiation as it relates to cerebellar atrophy for individuals with large cerebellar lesions (≥14%). For the radiation group, younger age at diagnosis appeared to be associated with higher degrees of atrophy and a steeper slope than the small lesion group; however, in the no radiation group age at diagnosis was not associated with atrophy.

Figure 15 Large Lesions: Interaction between age at diagnosis and cerebellar atrophy

5.19.3 Time since Radiation and Atrophy

Age at diagnosis and time since radiation were highly correlated (r=.70, p<.01). Time since treatment was linked to age at diagnosis because younger children are inherently at a longer time since diagnosis when compared to children who were diagnosed when they are older. While results are interpreted as young age at diagnosis and radiation contributing to atrophy, it is important to note that time since radiation also displayed a positive medium effect size (r=.48, p=.09), although non-significant, with cerebellar atrophy (see Figure 16).

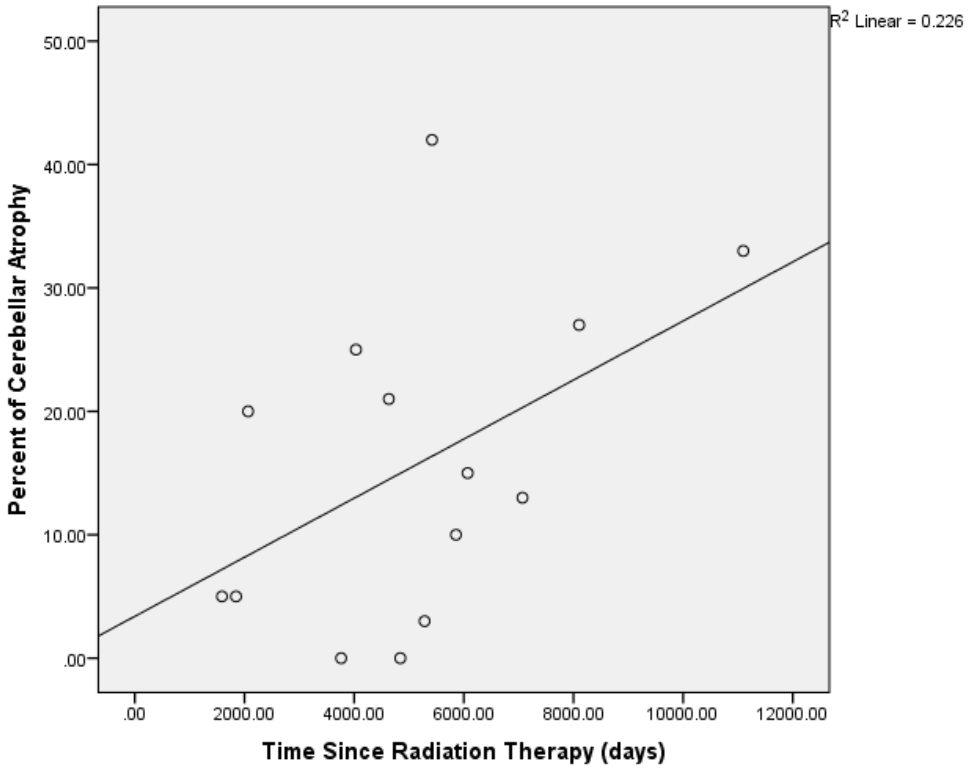
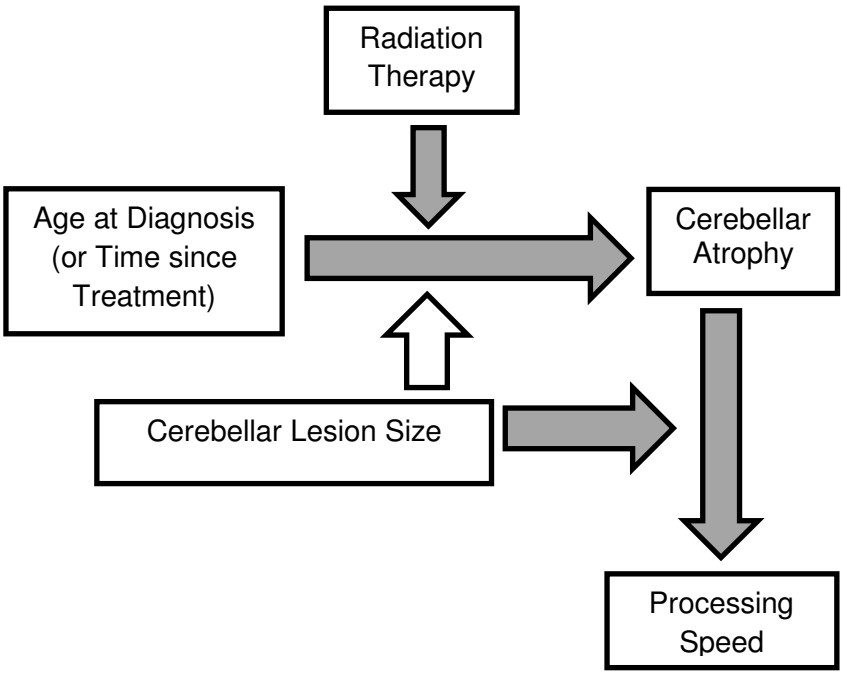


Figure 16 Time since radiation is correlated with cerebellar atrophy

5.20 Relationships among Age at Diagnosis, Radiation Therapy, Atrophy, Lesion Size, and Processing Speed

In summary, the hypotheses that lesions in the cerebellar regions would discriminate based on behavioral performance could not be tested due to a high degree of overlapping lesion locations and the discovery of cerebellar atrophy. Results from the current study suggested that young age at diagnosis and presence of radiation therapy correlated with higher cerebellar atrophy. Furthermore, individuals with smaller cerebellar lesions, and greater cerebellar atrophy displayed lower overall processing speed (oral and written modalities). Figure 17 displays a graphical depiction of the results of the current study.



Note. Grey arrows indicate significant effects, white arrow signifies that there is evidence to suggest that cerebellar lesion size (small vs. large) changes the interaction between age at diagnosis and radiation therapy.

Figure 17 Proposed model based on the relationships among lesion size, age at diagnosis, radiation treatment, atrophy, and processing speed

5.21 Additional Considerations

5.21.1 Relationship between Lesion Size and Cerebellar Atrophy

Given the nature of brain tumor resection and cerebellar atrophy, it was possible that cerebellar lesion size and cerebellar atrophy were related. Survivors of cerebellar brain tumors with larger lesion sizes may have had lower cerebellar atrophy because they had less intact cerebellar volume post-surgery. In the current study there was a small non-significant negative correlation between the cerebellar atrophy and total cerebellar lesion size (r=-.26, p=.21, see Figure 18). The cerebellar atrophy equation attempted to account for lesion size by adding lesion size back into the survivors' cerebellar volume, but the relationship between lesion size and atrophy may have been more nuanced than the equation suggests. Since this

technique has been used with multiple sclerosis populations, it was considered a reasonable proxy for atrophy for the current study (e.g., Chard et al., 2002)**.** Furthermore**,** the cerebellar atrophy measure was highly correlated with cranial radiation (r=.48, p<.05), cerebellar gray matter (r=-.66, p<.01), and a trend for cerebellar white matter (r=-.29, p=.16), which suggested that the atrophy measure was correlated with expected treatment factors and volumetric measures. Cerebellar atrophy also was not related other neurological factors, such as hydrocephalus (r=-.06, p=.77), or damage to the dentate and the vermis (r=-.22, p=.30).

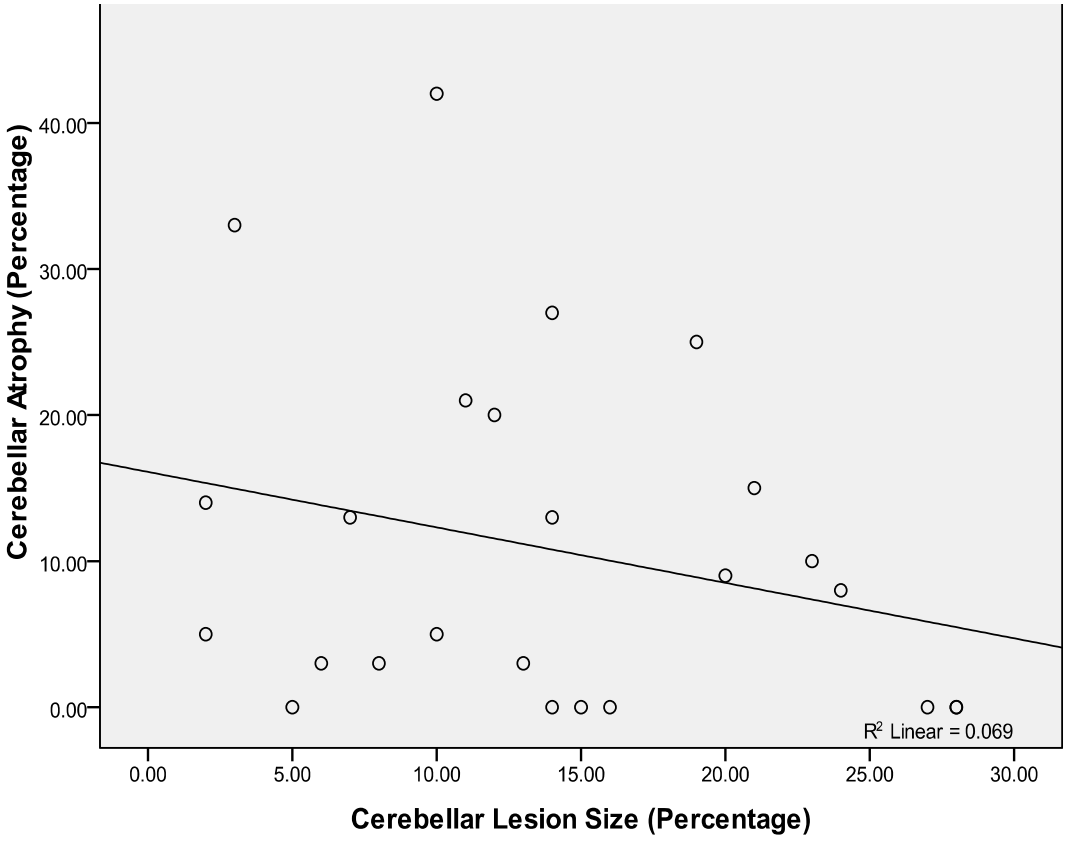


Figure 18 Scatter plot of cerebellar lesion size and cerebellar atrophy

5.21.2 Correction for Intracranial Vault (ICV)

It is possible that the correction for ICV may have explained why atrophy was a stronger predictor of behavior than lesion size. Cerebellar lesion sizes were normalized to the SUIT brain, which by definition accounts for individual differences in volume so there was no correction for ICV. When the analyses were rerun with lesion size divided by ICV, the results were similar and the main effect for cerebellar lesion size was still not significant for oral processing (*B*=79.84, Beta=.28, *p*=.19), and was a trend for written processing (previously significant at *p*=.03; *B*=103.19, Beta=.35, *p*=.07). Unfortunately, correcting lesion size for ICV introduced greater error to the model due to problems with multicollinearity (VIF=5) with the cerebellar atrophy measure (despite centering the variables). These results suggested that the ICV correction did not explain why cerebellar atrophy was a stronger predictor than cerebellar lesion size, likely indicating that cerebellar atrophy caused greater behavioral impairments than lesion size.

5.21.3 Combined Lesion and Atrophy

It is possible that total damage (rather than lesion and atrophy separately) explained results better than the interaction. Therefore an additional regression was run with percent lesion size and percent atrophy added together for a total cerebellar damage measure. A regression that included total damage and NPS did not predict cumulative performance, *Adj* R^2=.10, $F(2,22)=2.28$, $p=.13$, oral processing speed, *Adj* R^2=.04, $F(2,22)=1.47$, $p=.25$, or written processing speed, *Adj* R^2=.07, $F(2,22)=1.93$, $p=.17$. Thus, the interaction effect appeared to better explain processing speed performance than if cerebellar lesion and atrophy were added together.

6 Discussion

The current study found that cerebellar atrophy is important to examine in adult survivors of childhood brain tumors. The results provided evidence that age at diagnosis changed the relationship between radiation therapy and cerebellar atrophy, such that participants who were diagnosed at a young age and treated with radiation therapy displayed the highest amount of cerebellar atrophy, particularly for individuals with large cerebellar lesions. Participants who were not treated with radiation therapy did not display a correlation between age at diagnosis and cerebellar atrophy. The analyses suggested that 44% of the variance in cerebellar atrophy was explained by age at diagnosis and radiation therapy. Furthermore, greater cerebellar atrophy was associated with poorer oral and written processing speed for individuals with smaller lesion sizes. Together lesion size and atrophy explained a large portion of variance in processing speed (33% oral and 48% written). These results provided further evidence that radiation therapy has significant negative ramifications for the developing brain and behavioral performance and should be delayed for young children when medically appropriate.

There was an unexpected finding that participants with larger lesion sizes had processing speed that was less impacted by cerebellar atrophy. This is likely because when greater than 20% of the cerebellum is damaged, participants have reached a maximum threshold of cerebellar damage; whereas, individuals with smaller lesion sizes have more remaining cerebellar volume to be affected by atrophy, and cerebellar atrophy corresponded with the greatest processing speed impairments. An alternative explanation for this finding could be that individuals with larger lesions had a smaller portion of remaining brain volume for volumetric analyses. The atrophy measure assumed the lesion volume due to tumor resection

had 0% atrophy. Therefore participants with large lesions (>20% of the cerebellum) had a smaller portion of intact brain volume to measure atrophy and on average a smaller degree of cerebellar atrophy.

Prior literature suggests that the cerebellum is vulnerable to degeneration but also displays regenerative properties in animal models (Rohkamm, 1977). In particular, Purkinje cells, which are characterized by a high concentration of dendrites, are vulnerable to degeneration after cerebellar damage. In animal models these cells most often regenerate when there is a small degree of uniform damage (applied once) and the animal is at a younger age (Rohkamm, 1977). Additional evidence from human research suggests that the young cerebellum is vulnerable to atrophy following traumatic brain injuries (age at injury: M=9.8 years, time since injury=3.1 years; Spanos et al., 2007), and malignant brain tumors (age at diagnosis: M=8 years, time since injury=9 years; Szathmari et al., 2010). Furthermore, longitudinal research on childhood posterior fossa tumors has found that volume loss in the dentate nuclei following surgery and radiation treatment does not appear to recover $\geq$ 6 months post-surgery (Perreault et al., 2013).

A large body of research looks at atrophy independent of behavioral outcomes (e.g., Dietrich et al., 2001); however, atrophy in brain tumor populations has been related to difficulties sustaining daily tasks (Szathmari et al., 2010). Research on the human brain suggests that subcortical structures are uniquely vulnerable to radiation treatment and correspond with poorer behavioral outcomes. While having a brain tumor generally results in lower whole brain volume relative to controls, researchers have not found significant differences in whole brain volume within survivors groups based on presence of radiation therapy (Jayakar et al., 2015); however, researchers have found significant volumetric differences in

radiation and no radiation groups for the hippocampus and putamen, and these differences are related to poorer verbal memory performance (auditory attention list span and list learning) in adult survivors of childhood brain tumors relative to controls (Jayakar et al., 2015). The results of the current study also are consistent with other literature on brain tumor populations, which suggests that young age at cranial radiation, in particular, has been associated with the largest reduction in whole brain white matter and corresponds with lower attention, intelligence, and academic abilities (Reddick et al., 2005; Reddick et al., 2003; Mulhern, 1998). Furthermore, prior researchers have found that age at radiation therapy has been related to brain atrophy in children who are younger than 5 years old at treatment (Dietrich et al., 2001). Therefore, the finding that young age at diagnosis and radiation therapy is associated with greater cerebellar atrophy and poorer outcomes was consistent with prior research on humans and animals.

The current study was unable to test the original hypotheses because there was a large amount of cross regional damage, with regard to both lesions and atrophy. The majority of the sample had damage across the proposed ROIs making it impossible to draw conclusions about the association between lesion location and behavioral performance. Therefore, the questions regarding heterogeneous functions of the cerebellum were unable to be answered. Distinct lesion groups are critical in lesion based studies in order to correlate lesion location and behavioral impairments. In the context of diffuse damage, correlations between specific lesion locations within the cerebellum and behavioral impairments are less meaningful. Overall, both malignant and benign tumor survivors displayed diffuse cerebellar damage. Prior researchers have successfully done lesion mapping with benign childhood cerebellar tumors, however, they did not include measures of cerebellar

atrophy or dentate damage (e.g., Kirschen et al., 2008). Furthermore, prior research in adult stroke populations does not appear to map onto childhood brain tumor populations who experience more diffuse cerebellar damage, regardless of tumor malignancy.

The case series on the two participants who had more focal cerebellar lesions did not display a pattern of results that were consistent with hypotheses for regional specificity within the cerebellum. Instead, the case series suggested a pattern consistent with the homogenous cerebellum. The case series found that greater total damage to the cerebellum resulted in decreased behavioral performance across measures. It is important to consider that both of these participants experienced damage to the dentate and the vermis, radiation, and treatment complications. Therefore, these factors likely contributed to their presentation. Future studies with participants who have more focal cerebellar lesions and are not treated with radiation may discover a localized presentation.

6.1 Theories

If one were able to interpret the data as supporting a lack of specialization then it is possible that the primary function of the cerebellum is brain efficiency (Bower, 1997). Conversely, one could argue that the cerebellum in young children is functionally plastic, also known as equipotential, and then becomes specialized in adulthood with experience, similar to the theory of neural commitment (Oddy, 1993). One piece of evidence that supports this argument is that in young animals cerebellar lesions are followed by recovery of functions, possibly due to neural reorganization, compensation, or behavioral adaptation (Molinari and Petrosini, 1993; Bower, 1997). Further supporting this argument, Bower (1997) suggests that even with neural adaptation it still takes a longer time to perform tasks (Bower,

1997), due to delays in processing sensory information. However, the data provided in this study could not make a conclusion regarding functional homogeneity because patients had too high a degree of damage to explore functional specialization of the cerebellum. If future research replicated the current findings with a population of children who have focal lesions, then this alternative theory could explain both the lack of structure-functional specification of the cerebellar lobes seen in adults, as well as the processing speed impairments.

6.2 Limitations

The biggest limitation of the current study was the small amount of lesion specificity in the proposed regions of interest, and in general, most participants had diffuse damage. Unfortunately, natural lesion studies do not neatly fall into one cerebellar lobe, and many individuals had lesions and atrophy across ROIs. While there appeared to be enough participants based on the preliminary visual evaluation in the proposed study, the lesion distribution changed due to increased precision of lesion mapping and the methodological addition that allowed the current study to distinguish between cerebellar lesions and atrophy. Therefore, a more precise analysis the sample displayed a great deal of lesion overlap and a smaller portion of individuals with distinct lesion areas. The proposed aims and hypotheses could not have been answered with the current sample due to the high degree of diffuse damage, thus making it impossible to truly differentiate among lesions in specific regions of interest. Even upon looking among individual cases, only two people had damage in distinct regions. Upon looking at these two participants with distinct regions, the results again did not provide sufficient evidence for regional specificity but rather provided evidence for greater diffuse cerebellar damage relating to greater behavioral difficulties. Of note, however, is that both these individuals had malignant

brain tumors, were treated with radiation/chemotherapy, and displayed treatment complications that also could explain the lack of regional specificity.

It is important to highlight that the results presented in the current study are based on brain tumor survivors who were diagnosed and treated on average 15 years prior to participating in this study. One limitation of the study is that caution must be used when making recommendations for current treatment approaches, which have changed over time. The results and implications of this study are inherently embedded in the limitation that this older cohort that may not be generalizable to more recent brain tumor survivors and advancing treatment approaches.

It is important to note that a number of individuals had relatively intact verbal fluency on The Delis–Kaplan Executive Function System verbal fluency subtests (semantic and phonemic). It is possible that this clinical measure of verbal fluency measure is not sensitive enough to determine subtle verbal fluency difficulties. Also of note, the semantic fluency measure is generally considered an easier task, as opposed to the phonemic fluency task, which is slightly more challenging. Therefore, it is possible that with a different and more challenging measure of verbal fluency, survivors would have shown increased levels of difficulty.

Lastly, while the current study had a large number of participants for this patient population, the study was limited by a relatively small sample size which restricted the amount of variables that could be statistically modeled. There were a number of individuals who were not included in the present study because of poor quality imaging data (n=4) or inability to obtain an MRI scan due to medical implant (n=4). An inevitable limitation of using neuroimaging data, particularly with this

population, was difficulties with data acquisition (n=4) and data surviving registration analyses (n=4), which can contribute to small sample size. The participants that were excluded were not significantly different from those that were included with regard to demographic factors, treatment variables, or behavioral performance. Because results are based on a small sample size, future researchers should replicate these findings with a larger sample.

6.3 ICV/Estimate of Premorbid Brain Size

There are both strengths and weaknesses to the measure of ICV employed in the current study. For instance, if individuals had reduced total intracranial volume due to one or many of the aforementioned treatment factors, the results of the current study could have been potentially biased. For example, if cranial radiation reduced grey matter or white matter in a way that was not accounted for with cerebrospinal fluid (e.g., diminished whole brain growth), then total ICV could have been underestimated. Because ICV was a denominator in the atrophy equation, it could have overestimated the amount of cerebellar atrophy. Measures obtained in this study, such as ICV, indicated that there were not statistical differences between ICV that would suggest systematic differences between the overall premorbid estimate of brain size of controls and survivors. Thus, a strength of ICV was the statistical similarities between ICV in survivors and controls, making it a reasonable estimate of total premorbid brain size. This measure also has been previously used in the brain tumor literature and prior researchers have reported that survivors diagnosed with posterior fossa medulloblastoma do not show significant differences when compared to low grade astrocytoma in ICV or grey matter volume (Mulhern et al., 1999). The findings of the current study that indicated similar ICV for survivors with low grade and high grade tumors are consistent with those of Mulhern et al.

(1999) who employed a similar measure of total grey matter, white matter, and cerebrospinal fluid. The finding that ICV is similar for survivors and controls is inconsistent with Jayakar et al. (2015), who found differences in whole brain volume between survivors and controls; however, Jayakar et al. (2015) used a whole brain measure that did not include cerebrospinal fluid. Therefore, the addition of cerebrospinal fluid appears to account for the differences in whole brain volume between survivors and controls. Overall, intracranial vault is a relatively easy and semi-automated method to obtain an estimate of premorbid brain size that appears to be robust in accounting for differences between controls and brain tumor survivors with cerebellar lesions and atrophy.

6.4 Strengths and Innovation

This study was among the first to attempt to explore how damage to specific regions of the cerebellum was related to performance across measures of verbal fluency, motor, and processing speed. Individuals diagnosed with cerebellar brain tumors commonly have exhibited cognitive difficulties, which appeared to be due to cerebellar lesions, and specifically lesions in the dentate and the vermis, as well as cerebellar atrophy. While there is mention of cerebellar atrophy in brain tumor patients in the literature, quantitative measures of atrophy in brain tumor populations are notably absent from neuroimaging studies. This absence is presumably because prior researchers often have excluded cerebellar atrophy or grouped (atrophy vs. no atrophy) patients due to methodological difficulties (e.g., Szathmari et al., 2010; Dietrich et al., 2001). As a result, Voxel-Based Morphometry often is used to measure cerebellar atrophy, and lesion mapping commonly is used with focal lesions (Timmann et al., 2008). However, when both lesion and atrophy are present, qualitative measures are used (Szathmari et al., 2010; Dietrich et al., 2001). Thus,

there is little empirical information regarding the interaction between cerebellar lesions and cerebellar atrophy. The current study used a quantitative measure of cerebellar volume reduction relative to healthy controls that accounted for lesion size by combining Voxel-Based Morphometry and lesion mapping techniques.

Atrophy secondary to cerebellar brain tumors is unique relative to other populations with brain atrophy because it is more difficult to differentiate due to presence of tumor resection. For instance, in Alzheimer's disease and multiple sclerosis, researchers can simply explore the amount of cerebrospinal fluid relative to ICV in order to determine the amount of atrophy. However, cerebrospinal fluid (CSF) does not differentiate between brain lesion and brain atrophy, so the atrophy equation was used to quantify the amount of atrophy secondary to the lesion. Additionally, subtle atrophy was detected in a number of individuals, where these individuals may seem like "focal lesions" subtle atrophy may not be fully captured in the current body of literature.

This study also was able to include data from medulloblastoma and low grade astrocytoma survivors. Prior researchers have reported that survivors diagnosed with posterior fossa medulloblastoma do not show significant differences when compared to low grade astrocytoma in ICV or whole brain grey matter volume. The literature suggests that medulloblastoma survivors do, however, have significantly reduced whole brain white matter, and significantly increased CSF (Mulhern et al., 1999). Furthermore, whole brain white matter, but not CSF or grey matter, is related to intelligence scores (VIQ, PIQ, and FSIQ) in medulloblastoma survivors but not low-grade astrocytoma survivors (Mulhern et al., 1999). Survivors of childhood brain tumors with heterogeneous tumor locations displayed reduced whole brain volume (white matter + grey matter) when compared to controls on average 15 years post

diagnosis (Jayakar et al., 2015). However, findings are mixed and other researchers have reported that whole brain white matter volume and cortical thickness are not associated with performance on measures of executive functioning in survivors of childhood medulloblastoma on average 18 years post diagnosis (Brinkman et al., 2012). The atrophy measure used in the current study provided an objective assessment that detects small amounts of atrophy that may not have been detectable with qualitative ratings and may not be captured in the current body of literature. Future researchers should look at cerebellar atrophy quantitatively and independent of cerebellar lesion size, as it appears that lesion size and atrophy in the cerebellum have a unique relationship to one another that is not captured by simply adding them together. Therefore, this relationship may not be fully captured with volumetric measures of whole brain grey matter, white matter, and cerebrospinal fluid, particularly in subcortical structures.

With a sample of 25, the proposed study was among the largest lesion symptom mapping investigation of cerebellar brain tumors to date. The current study added to prior research by including both written and oral processing speed and having found that these measures were only dissociated with regard to their relationship to the dentate/vermis ROI, but not in relationship to diffuse cerebellar damage. The written and oral processing speed measure in the current study provided a unique opportunity to compare whether the written verses oral expressive modality explained processing speed differences. Taken together, the proposed study makes methodological, theoretical, and empirical contribution to the current understanding of how cerebellar damage due to lesions and atrophy impacted long term outcomes in survivors of childhood brain tumors.

6.5 Future Directions

Lack of regional specificity was likely due to the diffuse nature of brain tumor resection and treatment; therefore, it is possible that with different forms of lesion etiologies, researchers would find lesion specificity. Thus, this study should be replicated with focal childhood cerebellar injuries (e.g., stroke) to determine if the young cerebellum displays functional specialization in focal injury populations. Alternatively, it is possible that longer time since radiation is causing diffuse brain injury in long-term survivors. Another important future direction will be to replicate this study with survivors who have a shorter time since diagnosis to determine if time since radiation contributed to the lack of regional specificity. Future research with each of these populations will be important in determining whether the results of the current study were due to diffuse cerebellar injury or time since diagnosis.

Future research with diffusion tensor imaging may explore the cascading effect of cerebellar atrophy on the corresponding regions in the cerebellar-cortical loops, particularly with regard to motor performance and working memory, two common difficulties seen in populations with cerebellar insults. While difficulties in phonemic fluency is commonly reported in cerebellar lesion populations, difficulties in working memory has been a robust finding in the brain tumor literature (e.g., Law et al., 2011). Therefore exploring a different cognitive construct may provide more robust findings. Spanos et al. (2007) found that the cerebellum and corresponding regions included in cerebellar loops, particularly the pons and the dorsolateral prefrontal cortex, are vulnerable to atrophy following a moderate to severe traumatic brain injury, and resulting cerebellar atrophy. Thus, diffusion tensor imaging studies will be important to understand how cerebellar atrophy impacts important brain networks for motor and working memory performance. To address the diffuse

cerebellar injury in this population, it would be important to design studies that incorporate whole brain volumetric studies and behavioral measures that are resilient to diffuse brain injury as comparison tasks, for instance including verbal or perceptual intelligence and whole brain grey matter as comparison measures (e,g., Law et al., 2011).

Very few studies have looked at white matter connections, measured using diffusion tensor imaging, among cortical-cerebellar loops in brain tumor populations. Although the evidence is limited, there is one study which investigated how the white matter integrity of the dorsolateral prefrontal (DLPF)-thalamo-cerebellar loop relates to working memory performance in children with posterior fossa (cerebellum and brain stem) tumors. Law et al. (2011) found that children with greater treatment (e.g., radiation and chemotherapy) had lower white matter integrity within the DLPF-thalamo-cerebellar loop, when compared to healthy controls. Further, they found that white matter in the left DLPF-thalamo-cerebellar loop was significantly associated with working memory performance, but not verbal or perceptual intelligence, in healthy controls and children with posterior fossa tumors (above and beyond treatment status). Of particular relevance to future studies, Law et al. (2011) establish that diffusion tensor imaging of the loop connecting the right cerebellum-left thalamus- left DLPF is possible with brain tumor populations. Based on the findings of the current study, future researchers should explore how additional treatment factors (e.g., interaction between radiation therapy and age at diagnosis) and cerebellar atrophy relate to white matter integrity in the DLPF-thalamo-cerebellar loop, and how these relationships impact behavioral measures, such as working memory or intelligence.

In our sample, a large number of individuals experienced cerebellar atrophy after tumor surgery and treatment. Given that as many as 43% of individuals with childhood cerebellar medulloblastoma experience atrophy five years post diagnosis (Szathmari et al., 2010), an important future direction will be to explore possible etiologies of cerebellar atrophy in an effort to understand and prevent this disease process where possible. Prior research suggests that cerebellar atrophy could be due to posterior fossa surgery, damage to the dentate, cranial irradiation, seizures, and seizure medication (Poretti, Wolf, and Boltshauser, 2008). In our sample, young age at diagnosis and presence of radiation were related to greater cerebellar atrophy, but no one factor fully explained cerebellar atrophy. Researchers suggest that cerebellar structure is sensitive and may be at high risk for atrophy (e.g., Rohkamm, 1977). Other research suggests that damage to the dentate and vermis, critical regions of connection, would result in disconnection and atrophy in other brain regions (Spanos et al., 2007). Furthermore, advances in surgical techniques using fiber tracking suggests that certain surgical approaches may pose a higher risk to the dentate nucleus; researchers suggest that lower risk methods should be used in elderly populations due to the risk of cerebellar atrophy (Akakin et al., 2014). These are just some of the possible explanations for cerebellar atrophy, and these and other theories should be explored to best identify and prevent cerebellar atrophy.

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