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# Verbal Learning and Memory Abilities in Children with Brain Tumors: The Role of the Third Ventricle Region

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VERBAL LEARNING AND MEMORY ABILITIES IN CHILDREN WITH BRAIN  
TUMORS: THE ROLE OF THE THIRD VENTRICLE REGION

by

JACKIE L. MICKLEWRIGHT

Under the Direction of Tricia Z. King

ABSTRACT

The third ventricle region houses several neuroanatomical structures that are primary components of the human memory system, and provides pathways through which these brain regions communicate with critical regions of the frontal and medial temporal lobes. Archival data was obtained for 42 children with cerebellar or third ventricle tumors, and was examined for tumor and treatment related confounds. Children with third ventricle tumors were hypothesized to exhibit; 1) better performance on a measure of auditory attention, 2) greater impairment in learning across trials, 3) greater memory loss over a 20-minute delay, and 4) greater impairment across delayed memory tests than the cerebellar group. Children with third ventricle tumors demonstrated significantly better auditory attention, but greater impairments in verbal learning, and greater verbal memory loss following a 20-minute delay. In contrast, children with third ventricle tumors did not demonstrate significantly greater memory impairments across long delay memory tests.

INDEX WORDS: brain tumors, children, cerebellum, third ventricle, learning, memory, attention

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TUMORS: THE ROLE OF THE THIRD VENTRICLE REGION

by

JACKIE L. MICKLEWRIGHT

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

Master of Arts

in the College of Arts and Sciences

Georgia State University

2005

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College of Arts and Sciences  
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December 2005

In loving memory of Cyrus A. Spear

In loving dedication to David

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## **Introduction**

Brain tumors comprise approximately 22% of childhood cancers and tumors originating in the central nervous system and are second only to leukemia in cause of death among childhood cancers (Linnet et al., 1999; Fuemmeler, Elkin, & Mullins, 2002). Although survival rates among children with brain tumors have risen over the last two decades due to improvements in neuroimaging and treatment options, brain cancer continues to be a life-threatening and chronic ailment for many children (Packer et al., 1989; Finlay & Goins, 1987). A 1994 review by Ris and Noll suggested that the prognoses for pediatric brain tumor patients ranged from almost certain death to almost certain survival and that outcome was related to a variety of factors including tumor site, treatment type, age at diagnosis, medical complications and a myriad of tumor and treatment related factors.

Previous research on the impact of tumors on brain functioning has produced a virtual laundry list of impairments spanning cognitive, emotional and behavioral domains. The severity of these impairments is complicated by diversity in tumor type and location. Over the years, multiple studies have reported a progressive decline in IQ scores after diagnosis which may affect several domains of the patient's life (Morris et al., 2000). Other neuropsychological findings have indicated significant difficulties with memory, executive abilities, fine motor coordination, and perceptual-motor abilities, as well as disturbances in emotional functioning (Morris et al., 2000). When considered in the context of a child's life, the widespread implications of a brain tumor on a child's

ability to learn, succeed in the classroom environment, and connect with peers becomes apparent.

One concern for parents and health care providers is how cognitive difficulties will affect the child's school performance and their ability to learn and remember information. Learning is the primary way in which we acquire knowledge, and occurs when experiences in the environment change our nervous system and subsequent behaviors (Carlson, 20004). These changes are referred to as memories. A brain tumor can have innumerable effects on a child's attentional, learning and memory abilities. The impact of attentional, learning, and memory dysfunction is widespread, affecting both the daily activities of childhood and the attainment of scholastic strategies. Much of school-taught information builds on itself and early identification of specific difficulties could facilitate the development of compensatory skills. The value of research within this field lies in its ability to guide remedial efforts and individualized curriculum that will capitalize on each child's strengths. Therefore, in order to design appropriate ability-based skills, it is of utmost importance to understand the impact of brain tumors on the structures and pathways of developing learning and memory processes.

A number of tumor and treatment related variables have consistently been shown to impact intellectual and memory abilities in children with brain tumors. These variables include age at the time of diagnosis and neuropsychological evaluation, presence of hydrocephalus, seizure medication, and hormone deficiency, time since completion of treatment, and type and amount of treatment received (whole brain vs. focal radiation, chemotherapy, neurosurgery, or multiple treatments). Because these

variables may mediate or moderate cognitive outcomes, they are considered to be potential confounds. For the purposes of this study, these variables were examined for their impact on memory abilities and unequal representation across groups. This was done in an attempt to prevent these potentially confounding variables from obscuring the true relationship between brain regions and learning and memory processes.

#### Time since diagnosis

Traditionally, studies of children with brain tumors have focused on age-dependent effects on cognitive processes. In general, findings have illustrated that children who are diagnosed and treated for brain tumors at a younger age are at a higher risk for neuropsychological problems (Packer et al., 1989). Age at diagnosis and treatment are thought to be important variables because differential impairments in intellectual and emotional functioning may result as a function of the developmental stage at which the tumor appeared and was treated.

In 1994 Ris & Noll warned against neglecting a time since diagnosis variable when examining the abilities of children with brain tumors. They posited that the exclusion of this variable may function to overestimate the effects of age at diagnosis and treatment on outcome variables. The amount of time passed between diagnosis and evaluation has been found to be negatively correlated with performance on cognitive tasks. Potentially vast differences in ability may be observed when children with brain tumors are evaluated at different stages of tumor development, treatment and recovery, therefore making qualitative statements regarding the nature and severity of their impairments difficult.

Ellenburg et al. (1987) measured IQ over a four year period in groups of children with third ventricle, fourth ventricle and hemispheric tumors. The children in the third and fourth ventricle groups experienced an increase in IQ in the interval from diagnosis to four months post-diagnosis. The third ventricle group experienced a steady decline in IQ from four months to one year, but experienced an increase in IQ in the one to four year interval. In contrast, the fourth ventricle group displayed a consistent and significant decline in IQ over the one to four year interval. These findings illustrate group differences in the pattern of cognitive decline over time, while highlighting the utility of the time since diagnosis interval as a variable in neuropsychological research. The relationship between the time since diagnosis interval and cognitive abilities is thought to primarily result from the early disruption of brain regions and pathways that are instrumental in the acquisition and development of skills and higher cognitive processes. In the current study, the amount of time passed since diagnosis was examined for potential group differences that could obfuscate the relationship between tumor location and memory performance.

While advancements in the treatment of brain tumors have helped to increase survival rates in this population, complications resulting from these procedures are known to cause significant and permanent cognitive deficits (Packer et al., 1989). This fact makes it difficult for researchers to determine if certain deficits primarily result from the tumor type and location, or long-term side effects of the medical treatments. In their 1994 review, Ris & Noll concluded that previous research has lent strong support to the hypothesis that cognitive and emotional impairments primarily result from an interaction

between tumor pathology and location, and the treatment modalities utilized. Regarding cognitive impairments often seen in this population, the authors stated “the fact that these diseases and their treatments affect the organ of adaptation/adjustment means that the survivors are at increased risk for such problems,” (p. 37).

### Whole-brain radiation

Over the years, countless research endeavors have demonstrated a robust relationship between whole-brain radiation therapy and damage to brain structures and their associated functions (Fletcher & Copeland, 1988). Of particular relevance to the current study, are the findings of Dennis and colleagues (1992) which reported that, in a sample of 46 children with brain tumors, severe deficits in working memory were found when individuals with tumors located in thalamic/epithalamic regions were treated with radiation therapy. In 1989, Packer et al. noted that children who had received whole-brain radiation therapy displayed, 1) a significant decline in IQ, and 2) a wide range of dysfunction that included deficits in memory, fine motor, visual-motor and visual-spatial skills. They noted that children who had not received whole-brain radiation did not demonstrate consistent or significant declines in any of the aforementioned domains over time. Due to the consistently documented impact of whole-brain radiation therapy on memory and various aspects of cognitive functioning, participants within the two tumor location groups were evaluated for the differential impact of whole-brain radiation therapy on memory processes.

### Focal Radiation, Chemotherapy, & Neurosurgery

Focal radiation, chemotherapy and surgical interventions are known to have less of a global impact on intelligence and memory abilities. Ris & Noll (1994) reviewed a number of investigations into the effects of focal radiation therapy on cognitive abilities. The authors reported that the majority of studies found “no discernable neurobehavioral deficits” associated with this type of treatment. However, they noted that despite the precision of focal radiation, the potential still exists for this type of treatment to cause damage to brain regions surrounding the tumor site. Additionally, the amount of radiation received has been shown to be related to greater declines in intellectual functioning (Sibler et al., 1992).

Regarding the effects of chemotherapy on the CNS, Riva and colleagues (1990) reported that the impact of this treatment modality on cognitive abilities is far less significant than that caused by radiation. Additionally, a 1987 study by Ellenberg et al. found virtually equivalent declines in IQ from post-diagnosis to follow-up between children treated with and without chemotherapy. Regarding the effects of neurosurgery, Moore et al. (1992) reported that children who underwent neurosurgery or chemotherapy performed significantly better on a battery of neuropsychological tasks, with the exception of those within the visual-spatial domain, than did children treated with radiation therapy.

A recent study by Carpenteri et al. (2003) reported that memory disturbances, difficulties with problem solving, visuospatial deficits and psychomotor slowing were observed in pediatric brain tumor patients who had undergone neurosurgery only. The

sample was taken from a population of 106 children with brain tumors and included participants with tumors in a variety of locations. Participants received partial or total tumor resection based on the characteristics (histology and location) of their tumor. Although significant impairments were found across a number of domains, the authors acknowledged that there is the potential for the observed deficits to be the result of the disruptive presence of the tumor, the impact of the neurosurgery, or factors related to the surgical procedure (Carpenter et al., 2003). Research findings attempting to define a role for neurosurgery, chemotherapy, and focal radiation in the cognitive decline of children with brain tumors have been mixed. Therefore, these treatment-related variables were examined for their differential representation across groups and relationship with memory abilities.

### Multiple Treatments

While combining various treatment modalities has been shown to increase survival rates in some populations of children with brain tumors, this strategy also poses a significantly greater risk for global cognitive impairment. The most commonly observed combination of treatment for pediatric brain tumors is radiation plus chemotherapy. In 1988, Copeland and colleagues demonstrated that children displayed significantly greater impairments in cognitive performance when treatment included both intrathecal chemotherapy and cranial radiotherapy. Riva and colleagues (1990) investigated the effects of multiple treatments on cognitive functioning. They reported that the combination of chemotherapy and cranial irradiation more frequently results in serious brain damage than chemotherapy alone. Furthermore, Carlson-Green, Morris &

Krawiecki (1995) demonstrated that the number of treatment modalities a child is exposed to is a significant predictor of later intellectual functioning and achievement. The current study examined the use of multiple treatments in order to determine if group differences exist, and if this variable is significantly related to participants' memory abilities.

#### Time since initiation of treatment

The amount of time passed since the initiation of treatment has been found to be related to declines in cognitive abilities, and multiple studies have cited the relationship between variables of this type and declines in intellectual abilities (FSIQ) (Packer et al., 1989). These "late effects are usually thought to be a function of the vulnerability of the developing brain," (Chapman et al., 1995). Children treated with radiation "show a progressive decline in IQ compared to those children treated without it," however, time since the initiation of chemotherapy has been less explored in the literature (Chapman et al., 1995). Packer and colleagues (1989) reported that memory was "frequently impaired" in children who received whole-brain radiation therapy, and the authors noted a significant decline in memory performance over time in one third of participants. Therefore, the time since the initiation of radiation and chemotherapy variables were examined for group differences and a relationship with participant's memory abilities.

#### Hormone Deficiency

The plasma concentration of several hormones has been shown to be significantly related to cognitive abilities, including memory (Whean et al., 1980). Some of the hormones that have been implicated in memory function include the anterior pituitary

peptide hormone, adrenocorticotropin (ACTH), the adrenocortical steroid hormone, cortisol and the posterior pituitary peptide hormone (Dennis et al., 1992). There are three primary ways in which the occurrence of a brain tumor can lead to endocrine dysfunction including; the compression of structures that are directly involved in the release and regulation of hormones, damage caused by the surgical removal of the tumor, and damage caused by radiation treatment. Because the structures of the third ventricle region are located in close proximity to a number of brain regions that regulate hormone levels, it is likely that children with tumors of the third ventricle will account for a significantly higher percentage of the hormone deficiency group, than will children with cerebellar tumors. Therefore, hormone deficiency was examined for potential group differences and a relationship with memory abilities.

### Hydrocephalus

Hydrocephalus, as defined by Erickson et al. (2001), is a condition in which an excess amount of cerebral spinal fluid accumulates within the ventricles of the brain and results in an increase in intracranial pressure. It is commonly observed in children with brain tumors, particularly when the tumor is located near the fourth ventricle/cerebellum or third ventricle region, and can lead to diffuse impairments in cognitive abilities (Ris & Noll, 1994). Erickson et al. (2001) reviewed the effects of hydrocephalus on neuropsychological functioning and reported that children with hydrocephalus secondary to a brain tumor had greater intellectual deficits than did children without secondary hydrocephalus. This can be partially explained by the fact that hydrocephalus is characterized by diffuse cortical and subcortical damage which affect a wide range of

cognitive abilities (Erickson et al., 2001). These researchers reported that memory and attentional difficulties are a common complaint of children with hydrocephalus. Specifically, they cited several studies illustrating that children with hydrocephalus display impaired verbal short-term retrieval when assessed with word lists (Cull & Wyke, 1984; Scott et al., 1998; Yeates et al., 1995). On average, these individuals recalled fewer words on both initial and subsequent trials. Learning difficulties were also noted, with children with hydrocephalus taking longer to acquire information and skills across a variety of domains. Further evidence was provided by Fletcher 1992, who reported verbal and nonverbal memory deficits in children with hydrocephalus of varying etiology. Due to a number of reports of learning and memory impairments in children with hydrocephalus, the presence of hydrocephalus was examined for group differences and its relationship with memory abilities.

### Seizure Medications

Individuals with brain tumors often experience the additional complication of recurrent seizures, which can result from the location of the tumor or the toxic effects of chemotherapy. Although the long-term outcome of treatment induced seizures is unknown, many children have experienced cognitive decline as a result (Khan, Marshman, & Mulhern, 2003). A primary concern for families and health care providers are the deleterious effects of a handful of seizure medications. In 1991, Forsythe et al. (1991) documented the impact of anti-epileptic medication on cognitive abilities in a sample of 64 children with epilepsy. At the time of the study, participants had remained seizure free for one year after being randomized to one of three anti-epileptic drug

groups. Results were mixed, only participants on carbamazepine displayed impairment in memory function. While impairments were observed after 6 months of carbamazepine treatment, the authors stated that the impairments were definite after the full 12 months. Participants taking valproate or phenytoin did not display consistent difficulties in memory performance. Regardless of the etiological nature of the epileptic syndromes observed in these patients, many studies have documented the negative effect of both the seizures and seizure medications on cognitive integrity (Vining et al., 1987; Farwell et al., 1990). The presence of seizure medication is considered a potential confound in research within this domain and was examined for group differences and a relationship with memory abilities.

The results of multiple investigations into age and treatment related variables, as well as associated medical complications (hydrocephalus, epilepsy, and hormone deficiency), have illustrated that a potential exists for each of these factors to be 1) differentially represented in the two groups, and 2) related to memory abilities. Due to the potential for and unequal representation of these factors within samples of children with brain tumors, researchers must evaluate and control for the relative effects of all confounds prior to offering an interpretation of their findings. Neglecting to take confounds into consideration has the potential to render any inferences drawn from the sample invalid, as there would be less certainty that significant results are due to the variables of interest. This investigation examined learning and memory abilities in children with tumors of the cerebellum and third ventricle region after examining the

relationship between previously cited potentially confounding variables and verbal memory abilities.

Brain tumors are heterogeneous in both location and histology. Many of the clinical samples used in research of this type include participants with varied tumor histologies and locations, making a distinct neuropsychological profile of pediatric brain tumor patients virtually impossible. The predominant effects of a brain tumor are imposed on the structures or pathways to which it is in closest proximity. Therefore, research focusing on pediatric brain tumors has the ability to help psychologists and other medical professionals to better understand the specific impairments that result from damage to particular regions of the brain. The current study focuses on supratentorial tumors of the third ventricle and infratentorial tumors of the cerebellar region in an attempt to better understand the role of these neuroanatomical regions in attentional, learning and memory processes.

In general, supratentorial tumors have been found to be more disruptive to cognitive functions than infratentorial tumors (Ris & Noll, 1994). Studies have found two to three times the incidence of neurological deficits and disability in children with supratentorial tumors compared to children with infratentorial tumors and approximately twice the incidence of intellectual and emotional disability (Mulhern et al., 1983). The third ventricle of the brain is a narrow ventricle surrounded by the diencephalon and is the most common location for supratentorial tumors in the pediatric population. While it has long been known that damage to the medial temporal lobes and hippocampal formation severely disrupts memory processes, there is strong support for the hypothesis

that a tumor in the closely interconnected structures and pathways of the third ventricle region also causes memory impairment (Crosson, 1992).

Diencephalic structures that have been proposed to play a critical role in memory processes include the thalamus, hypothalamus, basal forebrain, mammillary bodies, fornix, and mammillothalamic tract. The role of the structures in the third ventricle region in memory processes is partially based on the white matter pathways which provide connections to the structures of the medial temporal lobes. These structures of the third ventricle region and medial temporal lobe are strongly interconnected and damage to any one of these components or the fiber tracts that connect them, can have a severe effect on memory functions (Mayes & Montaldi, 2001).

#### Basal Forebrain

One area of particular relevance within the third ventricle region is the basal forebrain, which contains large clusters of neurons that provide cholinergic innervation to the prefrontal cortex and temporal lobes (Hendelman, 2000). The basal forebrain is considered imperative to memory processes because of the nuclei that it contains and the connections it provides to the amygdala and hippocampus (Crosson, 1992). A 1985 study by Damasio et al. examined five adults with damage to the basal forebrain who were suffering from amnesia. None of the five patients had damage in the regions classically associated with major amnesic syndromes (medial temporal lobes or the dorsomedial thalamus). These patients exhibited a deficit in the recall of previously presented information. The deficit was supported by clinical observations and an examination of the patients' performance on the Rey Auditory Verbal Learning Test. An

impaired learning curve was observed during the recall trials of the RAVLT, however patients improved to normal or near normal on the recognition trial.

These individuals were suffering from a type of amnesia primarily associated with the basal forebrain portion of their lesions. Specifically, it was concluded that this amnesia resulted from “interference with medial temporal function in the hippocampal formation proper, amygdala, and parahippocampal gyrus caused by the basal forebrain lesion,” (p. 661). Due to the interconnectedness of these brain structures, and the finding that basal forebrain damage is associated with diminished activity in the medial temporal regions, it was concluded that damage to the basal forebrain can lead to a reduction of cholinergic input into the temporal lobes and association cortices which results in memory impairments. Therefore, it is proposed that one way in which a brain tumor in the basal forebrain of the third ventricle region can affect memory and learning is by preventing the flow of information between these critical components of the human memory system.

### Hypothalamic Nuclei

Evidence for the role of third ventricle structures in memory, particularly the nuclei of the hypothalamus, has been provided through the study of Korsakoff's Syndrome. While chronic alcoholism is the most common cause of this disorder, this syndrome has been observed in individuals suffering from tumors that apply pressure to the mammillary bodies of the hypothalamus, causing lesions to the hippocampus and septal areas (Kahn & Crosby, 1972). The study of the role of the mammillary bodies of the hypothalamus in memory processes has indicated that damage to this area can result

in significant impairments in recall abilities. The hippocampus is greatly dependent on the activation of the cyclic limbic arcs which involve the septal areas and mammillary bodies, therefore damage to either of these areas will produce difficulties in memorizing and recalling recently acquired information (Kahn & Crosby, 1972). Therefore, it follows that a tumor or lesion in this region of the hypothalamus would also negatively impact an individual's memory system and learning ability.

### Fornix

As the mammillary bodies of the hypothalamus have been implicated in human memory processes, so has damage that threatens the ability of these structures to convey information to and from the structures of the medial temporal lobe. Heilman and Sybert (1997) illuminated the role of the fornix, the fiber tract that provides a pathway for hippocampal input to the mammillary bodies and dorsomesial thalamic nucleus, in memory processes. It follows that damage to the pathway that allows the flow of information between the hippocampus, mammillary bodies and thalamus would impair memory abilities. Heilman & Sybert (1977) reported that a lesion of the fornix resulted in an inability to recall verbal stimuli after being distracted, and a virtual inability to learn a list of 41 common words (Heilman & Sybert, 1977). This finding is consistent with the results of a 1996 meta-analysis of human recognition data, which suggested that there is a single dissociation in which patients with damage to the hippocampus, fornix, mammillary bodies, or thalamus are relatively unimpaired on item recognition, but equally impaired as more generally deficient global amnesiacs, on measures of free recall (Tulving & Craik, 2000). Together, these findings provide further evidence for the role

of the structures of the third ventricle region in memory processes that include learning ability, recall, and recognition.

### Thalamus

Research into the role of the thalamus in memory has led to the implication of this structure primarily in verbal memory processes. Specifically, it appears that greater verbal-memory deficits are observed in adults with damage to the left medial thalamus. Speedie & Heilman (1982) reported greater impairment of verbal than nonverbal memory in a patient with left dorsal medial thalamic infarction. In 1989, Brown & colleagues observed a greater impairment in verbal versus visual memory in patients with damage in the same region. These results indicated that there is a lateralization of verbal memory functions at the level of the medial thalamus. Further evidence provided by Mori and colleagues (1986), indicated a relationship between left thalamic infarction and significant impairments in immediate recall, delayed recall, and delayed recognition trials on a test of verbal memory. In the last twenty years, multiple studies have documented the role of this thalamic region in memory processes while providing evidence for the hypothesis that “lateralization of verbal and visual memory abilities extends, in most cases, to the level of the medial thalamus,” (Crosson, 1992 p. 229).

In a series of three studies focusing on brain tumors in children and adolescents, Dennis and colleagues (1991a, 1991b, 1992) examined the impact of brain tumors on working memory task performance. Three memory tasks were administered to 46 children with tumors in 13 brain regions. The distribution of the tumors was primarily subcortical and infratentorial, with the most common locations being the cerebellum and

diencephalon (Dennis et al., 1991a). The memory tasks included a measure of recognition, content, and sequential memory, however the authors stated that all three tests qualify as recognition measures because each included a list of exhaustive responses from which the participant chose. These researchers utilized “a CT scan transcription system that was designed to identify the brain regions affected by the tumor and associated damage,” (p. 832). Multiple regression analyses were then completed for each of the three memory tasks to determine the patterns of brain damage that were most predictive of memory deficits.

The researchers found that damage to the putamen or globus pallidus impaired performance on all memory tasks. They also reported that “performance on the recognition memory test was impaired by damage in the diencephalon,” specifically the anterior thalamus, medial-midline thalamus and pineal gland. In contrast, they reported that “performance on the sequential memory test was impaired by tumor damage in both diencephalic and telencephalic components of the limbic system,” with specific damage to the pulvinar, hypothalamus, the neuro-hormonal pathways of the tuber cinerium and pituitary, and the uncus. No specific sites of tumor damage significantly predicted deficits in content memory. These findings highlight the role of structures of the third ventricle region in children’s learning and memory processes, while noting the distinct nature of these three types of memory tasks at a neuroanatomical level.

The way in which memory systems are disrupted depends on which structures or pathways are primarily affected by the tumor or lesion. Because focal damage is difficult to attain in clinical samples, there is significant diversity in the methodology and results

of the aforementioned studies. The role that specific diencephalic structures play in memory processes also remains elusive due to difficulties identifying the contributions of small structures and pathways in learning and memory tasks.

A growing body of literature has highlighted the importance of the structures of the third ventricle region in learning, recall, and recognition in adult samples. However, few studies have examined the role of these structures in children, and significant differences in impairment may be observed when underdeveloped memory systems are damaged at a young age. In one of the few studies of examining these abilities in children, King et al. (2004) compared performance on auditory verbal learning and memory measures in a sample of children with third ventricle and cerebellar tumors. Drawing from research on adults with diencephalic insult, the researchers hypothesized that verbal memory abilities would be more impaired in children with third ventricle tumors than in children with cerebellar tumors. Specifically, it was hypothesized that the third ventricle group would display; 1) a more impaired rate of list learning, 2) a larger decline in recall after a delay, and 3) a greater impairment on both delayed memory tasks, but a greater rate of improvement on the recognition task.

The King study followed methodological guidelines for the study of children with brain tumors set by Ris & Noll (1994) through the utilization of theory driven hypothesis testing and consideration of the many potential confounding variables that plague research of this type. The results provided considerable support for the role of the third ventricle region in children's learning and memory processes. In the study, the third ventricle group demonstrated significantly worse learning ability over the five trials.

They displayed greater impairment on immediate and delayed recall trials, but displayed improved performance on delayed recognition. Additionally, the cerebellar group performed significantly worse than the third ventricle group on digit span, a measure of auditory attention and working memory for number sequences.

Learning and memory are important outcome variables in the study of children with brain tumors. Dennis et al. (1991) reported that examinations of memory abilities are of utmost importance in these populations because “many of the tumors that characteristically occur in childhood are located in brain regions, such as those surrounding the third ventricle, which have been demonstrated to be important for memory functioning in older individuals,” (p. 814). Continual examination of damage to these structures during development is warranted in order to fully elucidate their role in learning and memory and later academic functioning. The findings by King and colleagues (2004) highlight the severity of learning and memory difficulties in a sample of children with third ventricle tumors. Replication of these findings would provide further support for the role of these structures and pathways in children’s learning and memory processes, and would help to provide parents and health care providers with a greater understanding of the difficulties experienced by these children. By attempting to replicate and extend the findings of King et al. (2004), the current study hopes to provide further evidence for the role of diencephalic structures in the verbal learning and memory abilities of children.

## Cerebellum

Unlike the third ventricle region, research has not demonstrated a consistent role for the cerebellum in verbal memory and learning processes, and for many years it was believed to be solely involved in motor activity (Courchesne et al., 1997). This is due in part, to past observations of the effects of cerebellar damage on posture, gait, and voluntary movement (Fiez et al., 1992). More recent studies have implicated the cerebellum in multiple cognitive abilities including the voluntary shift of selective attention (Akshoomoff & Courchesne, 1992), executive functioning (Appollonio et al., 1993), associative learning (Bracke-Tolkmitt et al., 1989), and the skilled manipulation of information (Leiner et al., 1986). The cerebellum has been called “one of the busiest intersections of the human brain,” (Courchesne et al., 1997). Researchers have proposed that the cerebellum’s connections with the prefrontal cortex and association cortices may be responsible for “frontal-like” cognitive impairments observed in individuals with cerebellar tumors (Appolonio et al., 1993).

Research into the role of the cerebellum in verbal learning and memory abilities has produced mixed findings. A 1992 case study by Fiez et al. reported that a patient with a large right cerebellar hemisphere lesion was severely impaired on a series of tasks that included learning abilities and the retrieval of verbal information. Helmuth, Ivry & Shimizu (1997) attempted to replicate these findings with twelve cerebellar lesion patients. In this study, the cerebellar lesion patients displayed a learning rate on the semantic association task equivalent to that of the control subjects. The equivalence of their performance was noted through the examination of the learning curve of the two

groups when tested with the same stimuli used by Fiez et al. (1992). The researchers reported an initial deficit in verbal discrimination learning in the cerebellar patients, however, when age was entered as a covariate in the analysis, the difference in learning ability between the cerebellar and control groups disappeared. Inconsistency regarding the participation of the cerebellum in learning and verbal retrieval may be the result of the limitation of Fiez et al.'s single patient approach. Therefore, this incongruity in results between studies justifies further investigation into a potential role for the cerebellum in verbally based learning and memory processes.

Attention can be thought of as the direction of resources in the active processing of incoming information (Crosson, 1992). In 1992, Akshoomoff and Courchesne examined the role of the neocerebellum, the evolutionarily newest piece of the cerebellum, on attention. The researchers found a significant role for this region of the cerebellum in the voluntary shift of selective attention between sensory modalities. They proposed that this portion of the cerebellum is involved in tasks that require quick, successive changes or adjustments of neural activity in order to proceed from one motor or cognitive condition to another. A 1997 follow up study by Courchesne et al., further elucidated the relationship between the cerebellum and attention. The researchers found that the cerebellum was activated by attentional processes without the engagement of any component, physical or imagined, of the motor system. The results demonstrated that attention to sensory information was enough to activate the cerebellum in their sample of adolescents and children with autism. They reported that their results highlighted the “functional independence of cerebellar activation by attention,” (p. 1941). However, a

1997 attempt by Helmuth et al. to replicate these findings was unsuccessful and led the researchers to question the generalizability of Courchesne's findings.

Many researchers have posited that the role of the cerebellum in cognitive processes may be best explained through examination of the connections it forms with other brain regions. A 1992 study by Riva et al. reported significant attentional difficulties in children with posterior fossa tumors. They hypothesized that these deficits were the result of the proximity of the tumor to the ascending activating system. The ascending activating system travels through the brainstem and works with thalamic and cortical structures to mediate attention and arousal in humans. These researchers concluded that brain tumors of the posterior fossa may lead to attention deficits during routine tasks in children. Other researchers have posited that the cerebellum plays a role in cognitive abilities through its modulation of higher brain regions such as the frontal and parietal association cortices (Lalonde & Botez-Marquard, 2000). The idea that multiple cortical areas project to, and communicate with, the cerebellum through the cortico-ponto-cerebellar pathway has been widely accepted (Middleton & Strick, 1998). However, until recently it was thought that the cerebellar output to the thalamus had an influence solely on regions of the primary motor cortex (Middleton & Strick, 1998). However, through the use of neuroanatomical tracing techniques, Middleton & Strick (1998) have demonstrated that the cerebello-thalamocortical connections project to regions of the premotor and prefrontal cortex, as well as to regions of the cingulate gyrus involved in the regulation of attention and emotion. Findings from neuroimaging studies have led to the hypothesis that these cerebello-prefrontal connections contribute to

various cognitive and language abilities in normal populations (Desmond & Fiez, 1998). Furthermore, it is believed that damage to the cerebellum has the potential to reduce activation in cerebellar efferent target regions, thereby contributing to cognitive and executive impairments (Lalonde & Botez-Marquard, 2000).

Research examining the relationship between the cerebellum and attention has led to an interest in the potential role for this brain region in more severe attentional impairments, such as Attention-Deficit Hyperactivity Disorder (ADHD). ADHD is characterized by attentional impairments, impulsivity and hyperactivity (American Psychiatric Association, 2000). Brain regions typically associated with ADHD include the prefrontal cortex and basal ganglia, however, a growing body of literature has highlighted the correlation between cerebellar volume and attentional impairments consistent with a diagnosis of ADHD (Berquin et al., 1998). Berquin and colleagues (1998) examined differences in cerebellar and vermal volumes in 46 right-handed boys with ADHD and 47 healthy control children. The researchers documented a significant reduction in cerebellar vermis in males with ADHD. This finding was replicated by Mostofsky and colleagues (1998) in a sample of 12 boys with ADHD. These findings support a potential role for the cerebellar vermis in clinical disorders of attention. However, due to the correlational nature of these studies, the researchers note that the exact contribution of the cerebellum to attentional processes remains unclear and call for further examination into this issue.

Evidence for the cerebellum's role in auditory attention was provided by King and colleagues (2004), who reported that children with cerebellar tumors performed

significantly worse than children with tumors in the third ventricle region on the digit span task of the Wechsler Intelligence Scale for Children-III. In contrast, the researchers did not find a significant difference in performance between the cerebellar and third ventricle group on the first trial of the auditory verbal learning tests. The lack of a consistent impairment in the cerebellar group's performance across two tasks of auditory attention indicates that the additional sequencing demand of the digit span task may account for this discrepancy. The first trial of the two word lists of the Rey Auditory Verbal Learning Test (RAVLT) differ from the digit span task in their supraspan format, lack of a sequencing component, and utilization of words as stimuli. Trial 1 of list A has demonstrated negligible correlations with subsequent learning trials (A, 2-5 of the Rey) as a result of its supraspan format and large attentional component (Macartney-Filgate & Vriezen, 1988). Furthermore, neuropsychological findings have demonstrated that the immediate memory span for digits and the numbers of words recalled on trial 1 should be within one or two points of each other (Lezak, 1995).

The inconsistency in results yielded by these two tasks which require the use of auditory attentional abilities warrants further investigation and highlights the need for additional research into the role of the cerebellum in attentional processes. The current study attempted to replicate the King et al. (2004) finding of decreased performance on measures of auditory attention in the cerebellar group. However, instead of evaluating auditory attentional abilities based on the digit span task, performance on trials A, 1 and B of the Rey Auditory Verbal Learning Test (RAVLT) were examined. Utilizing trials A, 1 and B of the Rey allowed the researchers to determine if the cerebellar group would

demonstrate consistent impairments on attentional tasks that utilize verbal stimuli and do not require sequencing abilities.

Multiple studies have reported a role for the structures of the third ventricle region in memory processes that underlie the acquisition of knowledge. Damage to any component of these critical diencephalic structures or pathways may result in impairments in learning and memory. In contrast, the cerebellum has not been consistently implicated in learning and memory processes, and mixed results have been reported regarding its role in basic auditory attention processes. The current study examined whether or not children with cerebellar tumors demonstrate a greater impairment in auditory attention for words. The current study also compared pediatric patients with third ventricle tumors to those with cerebellar tumors in an attempt to determine if children with tumors of the third ventricle region would exhibit a greater degree of difficulty on a measure of verbal learning and memory abilities.

The first aim of the study was to examine differences in auditory attentional abilities across the two tumor location groups. Specifically, it was hypothesized that due to attentional difficulties, the cerebellar group would demonstrate a greater impairment than the third ventricle group on trials A, 1 and B of the Rey AVLT. The second aim of the study was to examine differences in verbal auditory learning and memory abilities across the two tumor location groups. Specifically, participants of the third ventricle group were hypothesized to exhibit; 1) a greater impairment in learning across trials 2-5, 2) a greater memory loss over the 20 minute delay and, 3) a greater impairment across

delayed memory tests than the cerebellar group, but to demonstrate a greater benefit in performance when presented with the recognition test format.

## **Methods**

### **Participants**

A subset of 51 children were selected from 191 participants in a longitudinal study that focused on cognitive, emotional and behavioral changes in children diagnosed and treated for a brain tumor. Participants were recruited from the hospital at which they were seeking treatment in the metropolitan area of Atlanta. Informed consent was obtained from all families. In most cases, the children participating in the study underwent neuropsychological assessment shortly after their diagnosis and annually during the anniversary month of their diagnosis. At each assessment, the children completed a battery of neuropsychological tests and parents were asked to complete several questionnaires that inquired about the functioning of the child and family.

For inclusion in the current analyses, participants had to be between 5 and 17 years old at the time of the evaluation and speak English as their first language. Participants were required to have been diagnosed with a brain tumor in the cerebellum, posterior fossa, or third ventricle region of the brain. They also were required to have completed the Rey Auditory Verbal Learning Test and the Stanford-Binet Intelligence Test-IV as part of their participation in the longitudinal study. Participants were excluded from the current analyses if they had comorbid neurological conditions, auditory impairments, had experienced a traumatic brain injury or stroke, or if their tumor extended to the brain region of the comparison group.

After reviewing the medical records of the original 51 participants, nine individuals were excluded from participation in the current study. Three participants were excluded due to incomplete medical records, three were excluded because of hearing difficulties, and two participants had co-morbid neurological conditions (hypoxic encephalopathy, meningitis). One participant was excluded because of a verbal reasoning IQ score below 70 on the Stanford-Binet Intelligence Scale-IV. The excluded sample was comprised of four individuals with third ventricle tumors and five with cerebellar tumors. The mean age of the excluded participants was 11.2 and did not differ significantly from the study sample ( $p = .72$ ). The excluded group was comprised of seven females and two males. Seven of the nine excluded participants were Caucasian and two were African-American. The Hollingshead Two-Factor Index of Social Position (Hollingshead, 1957) was used to estimate family socioeconomic status. The Hollingshead is scored on a 1-5 point scale (1 = high, 5 = low) and calculates SES as a function of occupation and years of education of the child's parents (Ater et al., 1996). A significant difference in mean SES was noted between the excluded and study samples ( $p = .04$ ), with the study sample having a mean SES of 3.11 and the excluded sample a mean of 3.77.

Within the study sample, the cerebellar/posterior fossa group was comprised of nine males and nine females and the third ventricle group was comprised of sixteen males and eight females. Within the cerebellar group, sixteen children were Caucasian and two were African-American. Within the third ventricle group, nineteen children were Caucasian and five were African-American. The mean SES fell near the midpoint of the

Hollingshead scale for both the cerebellar ( $M = 3.16$ ,  $SD = 1.29$ ) and third ventricle groups ( $M = 3.08$ ,  $SD = 1.41$ ). The pathology of the tumors observed in the cerebellar and third ventricle group are listed in Table 1. See Table 2 for the demographics of the two tumor location groups.

The average age at the time of evaluation was 10.7 years. A significant ( $p = .006$ ) difference was observed in the age of participants within the two tumor location groups at the time of the neuropsychological evaluation. The average age at the time of the evaluation was 8.9 for the cerebellar group and 12.1 for the third ventricle group. The average time between diagnosis and first neuropsychological evaluation in the longitudinal study did not differ significantly ( $p = .72$ ) between the cerebellar ( $M = 1.72$ ,  $SD = 2.38$ ) and third ventricle groups ( $M = 2.23$ ,  $SD = 3.33$ ). Because each tumor location group contained a small number of individuals who were seen years after their original diagnosis, and who were likely to increase these time estimations, medians were also calculated. The results revealed that the median time between diagnosis and first evaluation was .29 years (105 days) for the cerebellar group and .75 years (274 days) for the third ventricle group.

## **Procedure**

### Medical Information

Neuroanatomical verification of the location of the tumor was completed in the longitudinal study by radiologists and neurologists in the Atlanta area. Radiological and surgical reports were obtained from participants' medical records in order to confirm the

Table 1

## Tumor Pathologies by Tumor Location Groups

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Third Ventricle Region	
Craniopharyngioma	9
Fibrillary Astrocytoma	7
Glioma	3
Germinoma	3
Pineoblastoma	1
Ependymoma	1
Cerebellar & Posterior Fossa	

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Medulloblastoma	8
Astrocytoma	8
Ganglioglioma	2

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Table 2

## Demographic Variables by Tumor Location

Demographic Variables	Tumor Location	
	Third Ventricle Region	Cerebellar/Posterior Fossa
Number of participants	N = 24	N = 18
Mean age at evaluation	12.1*	8.9*
Mean time from diagnosis to evaluation	2.23	1.72
Male to female ratio	16:8	9:9
Caucasian to non-Caucasian ratio	19:5	16:2
Mean SES estimate (Hollingshead)	3.08	3.16

\*  $p < .05$ \*\*  $p < .01$ \*\*\*  $p < .001$

location and extent of the tumor. Information about tumor location and potentially confounding variables was gathered from archival data and medical records provided by the participants' primary treatment institution. Access to the medical records of the study participants was granted during their participation in the longitudinal study.

Additionally, a HIPAA waiver of authorization was obtained from Georgia State University (IRB No. H04405) and Emory University (IRB No. 672-2004).

### **Neuropsychological Measures**

The Rey Auditory Verbal Learning Test (RAVLT) was designed to assess learning ability across 5 trials, interference, memory span, and recognition memory. A list of 15 nouns (list A) was read aloud to each participant for five consecutive trials. Each trial was immediately followed by a free-recall test. After completion of the learning trials, an interference list of 15 nouns (list B) was read aloud to the participant and was followed by a free recall test. Immediately thereafter, participants were given a free recall test of list A. After a 20-minute delay period, participants were again asked to recall the words from list A. The final component of the Rey AVLT involved the examiner reading a list of fifty words (15 target words, 35 distracter words) and asking the participant to state whether or not each word was included in list A.

Evaluations of the RAVLT's psychometric properties have demonstrated good reliability and validity. The majority of studies that have examined test-retest reliability of the RAVLT employed an alternate-form test-retest format in order to avoid practice effects (Groth-Marnat, 2000). Correlations of scores between parallel forms (A and C) have been found to range from .61 to .86 for trials 1-5, and from .51 to .72 for recall trials

(Delaney et al., 1992). Stallings et al. (1995) examined the convergent validity of the Rey AVLT and the California Verbal Learning Test. Raw scores for all trials (1-7) were found to be significantly correlated ( $p < .001$ ) and ranged from .49 for Trial 1 to .83 across trials 1-5. Additionally, Guilmette & Rasile (1995) examined the ability of the Rey AVLT to discriminate between sixteen adults with mild brain injuries and controls matched for age, gender and education. The Rey demonstrated overall accuracy rates of about 70% with moderate sensitivity (range of 38% to 75%) and good specificity (69% to 100%). The RAVLT has been found to correlate well with other measures of learning and memory and is sensitive to neurological impairment, laterality of damage, and deficits in verbal memory in an array of patient groups (Crossen & Wiens, 1994).

Comprehensive normative data from a sample of control subjects age 5-17 was not available for the Rey AVLT, therefore norms from a number of studies were compiled to allow for the conversion of participants' raw scores to Z-scores. Normative data for a sample of children and adolescents reported by Forrester & Geffen (1991), was used to calculate Z-scores for the following age ranges; 7-12, 14-15. Normative data from a large sample of Midwestern children ages 5-6 was utilized in the calculation of Z-scores for the current analyses. Munson's (1987) data on a sample of adolescents was used to calculate Z-scores for participants ages 13, 16, and 17. Compiling normative data from several samples, which have variable sample sizes and differing methodology increases the likelihood that variability in performance will be observed both within and across age groups. However, because of an inability to locate a single study that reported

comprehensive normative data for children ages 5-17, this method was utilized and interpreted with caution.

The following variables of the RAVLT were included in the current study:

List A Recall Trial 1: The first trial of the RAVLT is thought to measure auditory attention and immediate memory (Lezak, 2004). Trial 1 of list A was used to determine if there were significant differences in attention across the two tumor location groups. It was hypothesized that children with tumors in the cerebellum would have greater difficulty with attention, and would therefore display greater impairment on list A, trial 1 than members of the third ventricle group.

List A Recall Trials 2-5: Free recall tests provide a good measure of memory in children with learning impairments because they are similar to tasks encountered in the classroom and allow for responses to be free of structure (Talley, 1995). Performance on list A trials 2-5 was examined in order to evaluate the hypothesis that the third ventricle group would demonstrate greater impairment in auditory verbal learning abilities.

List B: List B requires participants to attend to, and immediately recall a new word list after being presented with five trials of list A. It is considered a measure of auditory attention and susceptibility to proactive interference. This trial was compared to trial A, 1 to determine if the cerebellar group demonstrated consistent impairments in attention across these two trials.

Short Delay Free Recall Trial (Trial A, 6): Trial 6 of the Rey AVLT requires the child to recall the original words from list A, after being exposed to the interference list. This trial is typically administered 1-3 minutes after trial A, 5 and does not include a

presentation of the word list. It is considered to be a measure of short-term verbal memory and will be compared to long delay free recall to determine the extent of memory loss over the 20-minute delay in each tumor location group.

Long Delay Free Recall Trial: This trial provided a measurement of the participants' free recall of list A after a 20 minute delay. No interfering material was presented during the 20 minute delay. This variable was examined to determine if third ventricle participants demonstrate impaired verbal recall abilities and a greater memory loss after a delay.

Long Delay Recognition: This task was completed approximately 20-25 minutes after list A, 5 and was compared to performance on the long delay free recall trial. The two long delay variables were examined to determine if the third ventricle group exhibited a greater impairment across delayed memory trials, and a greater benefit in performance than the cerebellar group when presented with the recognition test format.

## **Results**

### Potential Confound Analyses:

In the current analyses, a confound was defined as a variable that is

- 1) significantly differentially represented in the two tumor location groups, and
- 2) significantly related to delayed memory performance. Participants' performance on the long delay free recall trial was the dependent variable used to determine if a confound was significantly related to memory performance. Parallel confound analyses were computed with delayed recall Z-scores and age-covaried raw scores.

Two-tailed t-tests were completed to determine if the potentially confounding continuous variables were differentially represented in the tumor location groups. In

order to determine if the potentially confounding continuous variables were significantly related to memory abilities, each was correlated with performance on the long delay free recall trial of the RAVLT (Z-scores and age-covaried raw scores).

Prior to running the analyses, the continuous variables were examined for normality. The time since diagnosis, amount of radiation, and time since the initiation of radiation and chemotherapy variables were found to be positively skewed.  $\text{Log}_{10}$  transformations were completed on these variables, and resulted in closer approximations of the normal curve. In the instances in which a continuous variable was non-normally distributed, two correlations were completed and compared for consistency. Specifically, Spearman two-tailed correlations were used to correlate non-transformed (positively skewed) independent variables with delayed memory abilities, and Pearson two-tailed correlations were used to correlate transformed (normally distributed) independent variables with delayed memory abilities. See Table 3 for an overview of the significance levels for the correlations and chi-square analyses.

Chi-Square Analyses or Fisher Exact Tests were used to examine differential representation of the categorical variables across the two tumor location groups. The decision regarding which of the independent sample tests to use was determined by the total number of individuals falling within each of the cells. If the value of any cell was less than 5, a Fisher Exact Test was completed in the place of a Chi-Square. Table 4 lists the Chi-Square/Fisher Exact Test values, phi coefficients and significance levels. Table 5 lists the number of participants within each tumor location group who were exposed to each of the potentially confounding categorical variables.

Table 3

## Significance Levels of Variables Examined to Determine Confound Status

Variable	Tumor Location	Delayed Recall	
		Age-Covaried Raw Score	Z-score
Time since Diagnosis	$p = .65$	$p = .15$	$p = .20$
Radiation Treatment	$p = .53$	$p = .05^*$	$p = .16$
Whole-brain Radiation	$p = 1.0$	$p = .76$	$p = .75$
Amount of Radiation	$p = .11$	$p = .14$	$p = .28$
Time since Radiation	$p = .79$	$p = .04^*$	$p = .07$
Chemotherapy	$p = .44$	$p = .16$	$p = .11$
Time since Chemotherapy	$p = .09$	$p = .20$	$p = .09$
Neurosurgery	$p = .00^{***}$	$p = .31$	$p = .09$
Multiple Treatments	$p = .07$	$p = .16$	$p = .07$
Growth Hormone Deficiency	$p = .01^*$	$p = .96$	$p = .21$
Hydrocephalus	$p = .21$	$p = .82$	$p = .59$
Seizure Medication	$p = .71$	$p = .67$	$p = .32$

\*  $p < .05$ \*\*  $p < .01$ \*\*\*  $p < .001$

Table 4

## Chi-Square Analysis and Fisher Exact Tests for Categorical Variables

Variable	$\chi^2$	$p$	$\phi$	$p$
Radiation Treatment	.66	.53	.13	.42
Whole-brain Radiation	.05	1.0	.04	.83
Chemotherapy	.70	.44	-.13	.40
Neurosurgery	9.8***	.00	-.48	.00
Multiple Treatments	7.07	.07	.41	.07
Hormone Deficiency	7.64*	.01	.43	.00
Hydrocephalus	1.96	.21	-.22	.16
Seizure Medication	.42	.71	.10	.52

\* $p < .05$ \*\* $p < .01$ \*\*\* $p < .001$

Table 5

Number of Participants Exposed to Potentially Confounding Tumor and Treatment Related Variables by Tumor Location Group

	Cerebellar	Third Ventricle
	N = 18	N = 24
Radiation	9	15
Whole-Brain Radiation	5	9
Chemotherapy	4	3
Neurosurgery	18***	14***
Radiation & Surgery	5	8
Radiation & Chemotherapy	0	2
Chemotherapy, Radiation & Neurosurgery	4	0
Hormone Deficiency	5*	17*
Hydrocephalus	17	19
Seizure Medications	3	6

\* $p < .05$

\*\* $p < .01$

\*\*\* $p < .001$

The relationship between the potentially confounding categorical variables and delayed recall memory abilities was examined using both *Z*-scores and age-covaried raw scores. (See Table 3). T-tests and analyses of covariance were chosen for these analyses. The relationship between the covariate (age) and the delayed recall variable was examined and found to be linear in nature ( $F(1, 39) = 14.50, p = .00$ ). The assumptions of analysis of covariance were examined and met by the data.

#### Time since Diagnosis

The amount of time since diagnosis was not significantly different between the two tumor location groups ( $t(40) = -.45, p = .65$ ). The average time since diagnosis in the third ventricle group was 1330 days ( $SD = 1827$ ), and 1120 in the cerebellar group ( $SD = 848$ ). A Spearman correlation coefficient was calculated on the non-normally distributed time since diagnosis variable and age-covaried raw scores ( $r = -.17, p = .27$ ). A Pearson correlation was calculated on the transformed continuous variable and age-covaried raw scores ( $r = -.23, p = .15$ ). Parallel Spearman ( $r = -.20, p = .20$ ) and Pearson correlations were completed ( $r = -.12, p = .44$ ) on delayed recall *Z*-scores and the time since diagnosis variable and were found to be nonsignificant. Although time since diagnosis was not significantly related to performance on the delayed recall trial, it was noted that as time since diagnosis increased, performance on the delayed recall memory task decreased. Time since diagnosis is not considered a confound in the current sample.

#### Radiation Treatment

There was no significant difference in the number of participants who underwent radiation treatment between the two tumor location groups ( $\chi^2(1, N = 42) = .66, p = .53$ ).

Specifically, 9 out of 18 of the cerebellar participants and 15 out of 24 of the third ventricle participants had received radiation treatment as a result of their tumor diagnosis. Radiation treatment was found to be significantly related to age-covaried raw scores ( $F(1, 39) = 4.24, p = .05$ ) but not delayed recall Z-scores ( $t(40) = 1.44, p = .16$ ). Radiation treatment accounted for 7.0% of the variance in participants' age-covaried raw scores and 4.9 % of the variance in delayed recall Z-scores, but is not considered a confound in the current analyses.

Within the group of participants who had undergone radiation, the presence of whole-brain radiation treatment was examined. The number of patients who underwent whole-brain radiation treatment was comparable across the two groups ( $\chi^2(1, N = 24) = .05, p = 1.0$ ). Specifically, 5 out of 18 cerebellar participants and 9 out of 24 of the third ventricle participants received whole-brain radiation therapy. Furthermore, the presence of whole-brain radiation treatment was not significantly related to age-covaried raw scores ( $F(1, 21) = .10, p = .76$ ) or delayed recall Z-scores ( $t(22) = .33, p = .75$ ). Therefore, the presence of radiation or whole-brain radiation are not considered to be confounding variables in the current sample.

Time since the initiation of radiation (in days) was not significantly different between the two tumor location groups ( $t(40) = .27, p = .79$ ). On average, the mean time since the initiation of radiation was 918 days ( $SD = 1029$ ) for the third ventricle group and 801 days ( $SD = 1598$ ) for the cerebellar group. Spearman correlation coefficients calculated on the non-transformed time since initiation of radiation variable and age-covaried raw scores ( $r = -.30, p = .05$ ), and delayed recall Z-scores ( $r = -.28, p = .07$ ),

were found to cluster near significance. Pearson correlation coefficients calculated on the transformed time since the initiation of radiation variable and age-covaried raw scores ( $r = -.31, p = .04$ ), and delayed recall Z-scores ( $r = -.28, p = .07$ ) resulted in comparable findings. Time since the initiation of radiation accounted for .4% of the variance in delayed recall Z-scores, and 4.9% of the variance in age-covaried raw scores.

The amount of radiation received (in rads) was not significantly different between the two tumor location groups ( $t(40) = -1.65, p = .11$ ). The average amount of radiation in the third ventricle group was 3665 rads ( $SD = 2435$ ), and the average in the cerebellar tumor location group was 2393 rads ( $SD = 2527$ ). Pearson correlation coefficients were calculated on the amount of radiation received and age-covaried raw scores ( $r = -.23, p = .14$ ) and delayed recall Z-scores ( $r = -.16, p = .31$ ). Additional Spearman correlation coefficients calculated on age-covaried raw scores ( $r = -.23, p = .15$ ) and delayed recall Z-scores ( $r = -.17, p = .28$ ), confirmed that the amount of radiation received was not significantly related to delayed recall performance. Therefore, neither the amount of radiation received or time since the initiation of radiation, are considered to be confounds in the current analyses.

### Chemotherapy

There was no significant difference in the number of participants undergoing chemotherapy between the two tumor location groups ( $\chi^2(1, N = 42) = .70, p = .44$ ). Specifically, 4 out of 18 cerebellar participants and 3 out of 24 third ventricle participants received chemotherapy treatment. Furthermore, the presence of chemotherapy treatment was not significantly related to age-covaried raw scores ( $F(1, 39) = 2.02, p = .16$ ) or

delayed recall Z-scores ( $t(40) = 1.65, p = .11$ ). The presence of chemotherapy accounted for 3.5% of the variance in participants' raw scores and 6.4% of the variance in Z-scores. Therefore, chemotherapy is not considered a confound in the current sample.

A trend was observed for a significant difference in time since the initiation of chemotherapy ( $t(40) = 1.76, p = .09$ ). The mean number of days since initiation of chemotherapy was 433 in the cerebellar group ( $SD = 857$ ) and 66 in the third ventricle group ( $SD = 247$ ). Spearman correlation coefficients were calculated on the non-transformed time since initiation of chemotherapy variable and age-covaried raw scores ( $r = -.20, p = .20$ ), and delayed recall Z-scores ( $r = -.27, p = .09$ ). Pearson correlation coefficients were calculated on the  $\log_{10}$  transformed variable and age-covaried raw scores ( $r = -.17, p = .26$ ) and delayed recall Z-scores ( $r = -.05, p = .77$ ), and indicated that the time since initiation of chemotherapy was not significantly related to delayed recall performance. Time since the initiation of chemotherapy accounted for less than 1% of the variance in delayed recall Z-scores and age-covaried raw scores. Time since the initiation of chemotherapy is not considered a confound in the current sample.

### Neurosurgery

A significant difference was found in the number of participants undergoing neurosurgery between the two tumor location groups ( $\chi^2(1, N = 42) = 9.84, p = .00$ ). The number of participants undergoing neurosurgery in the third ventricle group was significantly lower than in the cerebellar group. Specifically, 14 of 24 (58.3%) participants in the third ventricle group underwent neurosurgery compared to 18 of 18 (100%) in the cerebellar group. Undergoing neurosurgery was not significantly related to

delayed recall Z-scores ( $t(40) = -1.73, p = .09$ ), or age-covaried raw scores ( $F(1, 39) = 1.08, p = .31$ ). Neurosurgery accounted for 2.7% of the variance in age-covaried raw scores and 7.0% of the variance in delayed recall standard scores. However, neurosurgery is not considered a confound in the current sample.

### Multiple Treatments

A nominal variable was created in order to determine if the number of children receiving multiple treatments was significantly different across tumor location groups. The variable had 4 levels and each child was coded based on their membership in one of the 4 treatment groups. Prior to the creation of this variable, participants' treatment records were examined for the purpose of defining the multiple treatment groups. It was determined that within this sample of 42 children with brain tumors, 3 distinct treatment combinations were utilized. Children receiving combination treatment fell into one of the three following categories; 1 = radiation and surgery, 2 = chemotherapy and radiation, 3 = chemotherapy, radiation and surgery. The fourth level of this variable included children who experienced only one treatment modality as a result of their brain tumor diagnosis.

A trend for a significant difference was found in the number of participants who experienced multiple treatments across the two tumor location groups ( $\chi^2(1, N = 42) = 7.07, p = .07$ ). Specifically, five of the cerebellar and eight of the third ventricle participants experienced the radiation and surgery treatment combination. Two participants in the third ventricle group experienced the chemotherapy and radiation

treatment combination. Four participants in the cerebellar group experienced the radiation, chemotherapy and surgery treatment combination.

The multiple treatment variable was not significantly related to delayed recall Z-scores ( $F(3, 38) = 2.64, p = .07$ ) or age-covaried raw scores ( $F(4, 37) = 1.84, p = .16$ ). The multiple treatment variable accounted for 10.7% of the variance in participants' delayed recall Z-scores, and 3.6% of the variance in age-covaried raw scores. However, the exposure to multiple treatment modalities is not considered to be a confound in the current analyses.

#### Hormone Deficiency

A significant difference was found in the number of participants experiencing hormone deficiency between the two tumor location groups ( $\chi^2(1, N = 42) = 7.64, p = .01$ ). The number of participants experiencing hormone deficiency in the cerebellar group was significantly lower than in the third ventricle group. Specifically, 5 of 18 (24.7%) participants in the cerebellar group experienced hormone deficiency compared to 17 of 24 (70.8%) within the third ventricle group. However, hormone deficiency was not significantly related to delayed recall Z-scores ( $t(40) = 1.27, p = .21$ ) or age-covaried raw scores ( $F(1, 39) = .00, p = .96$ ). Therefore, hormone deficiency is not considered a confound in the current sample.

#### Hydrocephalus

No significant difference was observed in the number of participants with a hydrocephalus diagnosis between the two tumor location groups ( $\chi^2(1, N = 42) = 1.96, p = .21$ ). Specifically, 17 out of 18 of the cerebellar participants and 19 out of 24 third

ventricle participants had received a diagnosis of hydrocephalus. Furthermore, a diagnosis of hydrocephalus was not significantly related to age-covaried raw scores ( $F(1, 39) = .05, p = .82$ ) or delayed recall standard scores ( $t(40) = .54, p = .59$ ). Therefore, hydrocephalus is not considered a confound in the current sample.

#### Seizure Medications

No significant difference was observed in the number of participants prescribed seizure medications between the two tumor location groups ( $\chi^2(1, N = 42) = .42, p = .71$ ). Specifically, 3 out of 18 cerebellar participants and 6 out of 24 third ventricle participants had been prescribed seizure medication. Furthermore, seizure medications were not significantly related to age-covaried raw scores ( $F(1, 39) = .17, p = .67$ ) or delayed recall Z-scores ( $t(40) = 1.01, p = .32$ ). Therefore, the presence of seizure medications is not considered a confound in the current sample.

#### Attention Deficit/Hyperactivity Disorder and Learning Disabilities

Participants' medical records and data from the longitudinal study were examined for the presence of pre-morbid diagnoses of learning disabilities and Attention Deficit-Hyperactivity Disorder. This was done in an attempt to control for the effects of pre-existing attentional or learning difficulties on participants' performance on the Rey AVLT. However, a review of the files indicated that none of the participants in the current sample had preexisting diagnoses of Attention Deficit-Hyperactivity Disorder or learning disabilities.

### Trial A, 1 vs. Trial B

In order to address the auditory attention hypothesis, and determine if children with cerebellar tumors would show consistent impairment in performance on tasks of auditory attention and immediate memory, a 2 x 2 ANCOVA was completed. The 2 x 2 ANCOVA examined participants' age-covaried raw score performance on list A, trial 1 and list B of the RAVLT. A significant effect was found for the tumor group by list type interaction, and accounted for 13.6% of the variance in participants' performance ( $F(1, 39) = 6.16, p = .02$ ). A trend for a significant difference in performance between the two tumor location groups was also observed ( $F(1, 39) = 2.41, p = .13$ ). However, no significant effect was found for list type among the two groups ( $F(1, 39) = .90, p = .35$ ). See Figure 1, and Table 6 for age-covaried raw score means and standard deviations for trials A,1 and B.

A significant difference in performance was observed between groups on trial A, 1 of the RAVLT ( $F(1, 39) = 7.16, p = .01$ ). Tumor location accounted for 15.5% of the variance in participants' performance on trial A, 1. On average, participants in the cerebellar group recalled fewer words ( $M = 4.16, SD = 1.69$ ) than participants in the third ventricle group ( $M = 5.50, SD = 1.51$ ). These results indicate that participants with cerebellar tumors performed significantly worse than participants with third ventricle tumors, on a measure of auditory attention and immediate memory. However, no significant difference in performance was found between groups on trial B of the RAVLT ( $F(1, 39) = .00, p = .96$ ). Performance on trial B was strikingly similar across the cerebellar ( $M = 4.45, SD = 1.76$ ) and third ventricle groups ( $M = 4.42, SD = 1.57$ ).

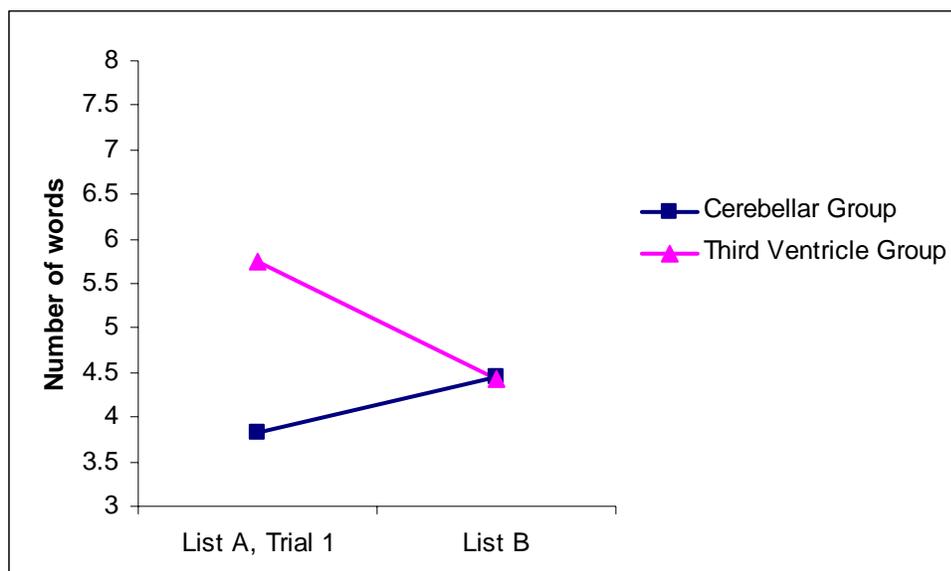


Figure 1

Performance on List A, Trial 1 and List B across the Two Tumor Location Groups, in Age-Covariied Raw Scores

Table 6

Age-Covariied Means and Standard Deviations of Words Recalled on List A, Trial 1 and List B by Tumor Location

	Cerebellar		Third Ventricle	
	M	SD	M	SD
List A, Trial 1	4.16*	1.69	5.50*	1.51
List B	4.45	1.76	4.42	1.57

\*  $p < .05$

\*\*  $p < .01$

\*\*\*  $p < .001$

Within each tumor location group, simple effects analyses were completed to compare performance on trial A, 1 and trial B. Within the third ventricle group, the attention list variable accounted for 13% of the variance in performance. The third ventricle group's performance declined significantly across trials A, 1 and B ( $F(1, 45) = 6.7, p = .01$ ). In contrast, the cerebellar group demonstrated roughly equivalent impairment across trials A, 1 and B ( $F(1, 33) = .18, p = .68$ ). This finding is inconsistent with the proposed hypothesis which stated that the children with cerebellar tumors would demonstrate a greater impairment in performance than children with third ventricle tumors across both trials of auditory attention.

Parallel analyses completed on participants' Z-scores revealed a strikingly different pattern of results than observed with age-covaryed raw scores. The 2 x 2 ANOVA indicated significant main effects for the trial type ( $F(2, 40) = 9.87, p = .00$ ) and the attention trial by tumor location interaction ( $F(1, 40) = 6.20, p = .01$ ). No significant main effect was observed for tumor location ( $F(1, 40) = .84, p = .36$ ). Simple effects analyses were completed and indicated that participants differed significantly in performance on trial A, 1, but that this difference diminished in trial B ( $F(1, 40) = .00, p = .96$ ). On trial A, 1, tumor location accounted for 10% of the variance in performance. On this trial the cerebellar group performed in the mildly impaired range ( $M = -1.41, SD = 1.21$ ), and the third ventricle group performed in the average range of functioning ( $M = -.69, SD = .99$ ). On trial B, both the cerebellar ( $M = -.27, SD = 1.36$ ) and third ventricle groups performed in the average range ( $M = -.56, SD = 1.16$ ). Simple effects analyses also indicated that the third ventricle group's performance did not differ significantly

across trials ( $F(1, 46) = .23, p = .64$ ). In contrast, to the proposed hypothesis, the cerebellar group performed significantly worse on trial A, 1 than on trial B ( $F(1, 34) = 10.57, p = .003$ ). See Figure 2 and Table 7.

### List Learning

To address the list learning hypothesis, which proposed that the third ventricle group would perform significantly worse than the cerebellar group across trials 2-5 of the RAVLT, a 2 x 4 ANCOVA was completed. A 2 x 4 ANCOVA was chosen in order to examine differences in age-covariied raw score performance in the two groups unaffected by differences in attention on trial A, 1. Therefore, trial 1 was entered as a covariate into the analysis and was found to account for 29.5% of the variance in participants' performance ( $F(1, 38) = 15.88, p = .00$ ).

After controlling for differences in performance on trial 1, a significant effect was demonstrated for tumor location ( $F(1, 38) = 4.39, p = .04$ ). Tumor location accounted for 10.4% of the variance in participants' performance across trials 2-5 of the RAVLT. In contrast, no significant effect was observed for learning trial ( $F(3, 114) = 0.68, p = .57$ ) or the interaction of learning trial by tumor group ( $F(3, 114) = 0.96, p = .41$ ). These findings are consistent with the list learning hypothesis, and indicated that after accounting for initial differences in attention, children with cerebellar tumors display superior learning across trials 2-5 of the RAVLT than children with third ventricle tumors. See Figure 3 and Table 8 for the age-covariied raw score means and standard deviations for trials 1-5. See Figure 4 and Table 9 for the age-covariied raw score means and standard deviations for trials 2-5 (after covarying out performance on trial A, 1).

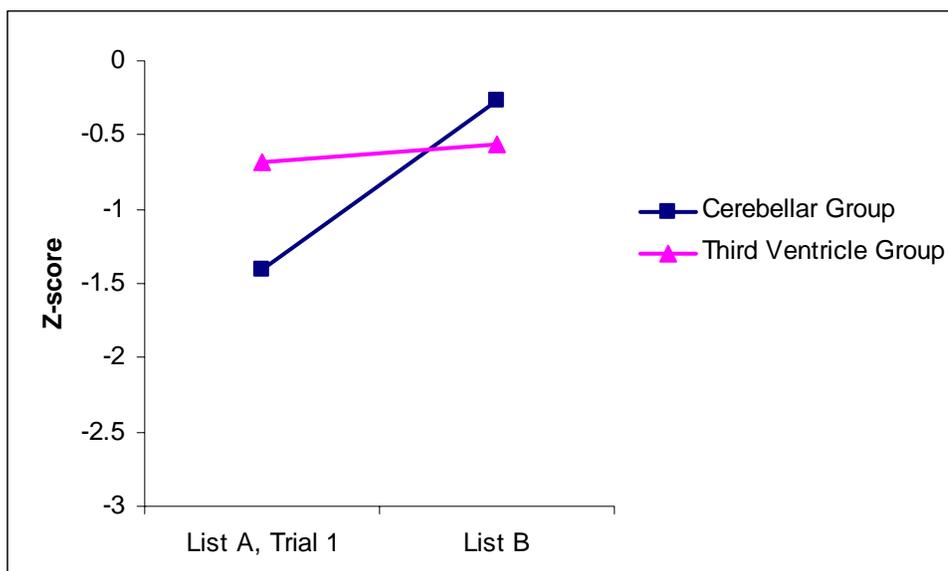


Figure 2

Performance on List A, 1 and List B across the Two Tumor Location Groups, in Z-Scores

Table 7

Mean Z-Scores and Standard Deviations of Words Recalled on List A, Trial 1 and List B by Tumor Location

	Cerebellar		Third Ventricle	
	M	SD	M	SD
List A, Trial 1	-1.41*	1.21	-0.69*	.99
List B	-.27	1.36	-.56	1.16

\*  $p < .05$

\*\*  $p < .01$

\*\*\*  $p < .001$

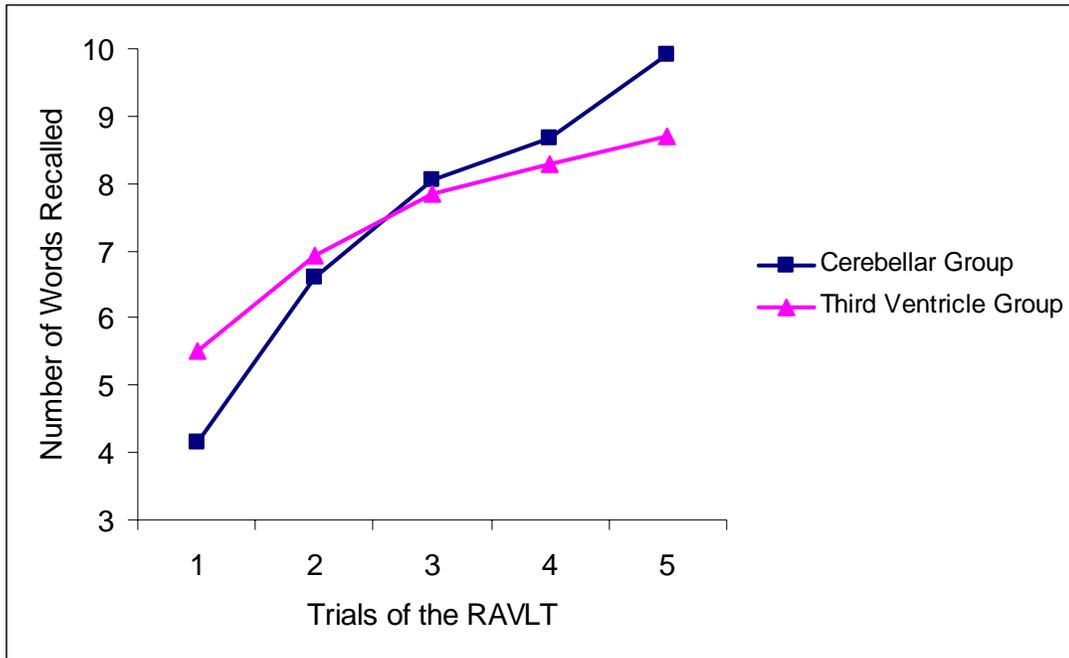


Figure 3

Learning Across Trials 1-5 of the RAVLT by Tumor Group, in Age-Covaried Raw Scores

Table 8

Age-Covaried Mean and Standard Deviation of Words Recalled Across Trials 1-5 of RAVLT by Tumor Location

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Trial 1	4.16**	2.33	5.50**	2.00
Trial 2	6.59	3.43	6.93	2.91
Trial 3	8.06	3.79	7.83	4.08
Trial 4	8.67	4.27	8.29	3.63
Trial 5	9.91	4.47	8.69	3.82

\* $p < .05$

\*\* $p < .01$

\*\*\* $p < .001$

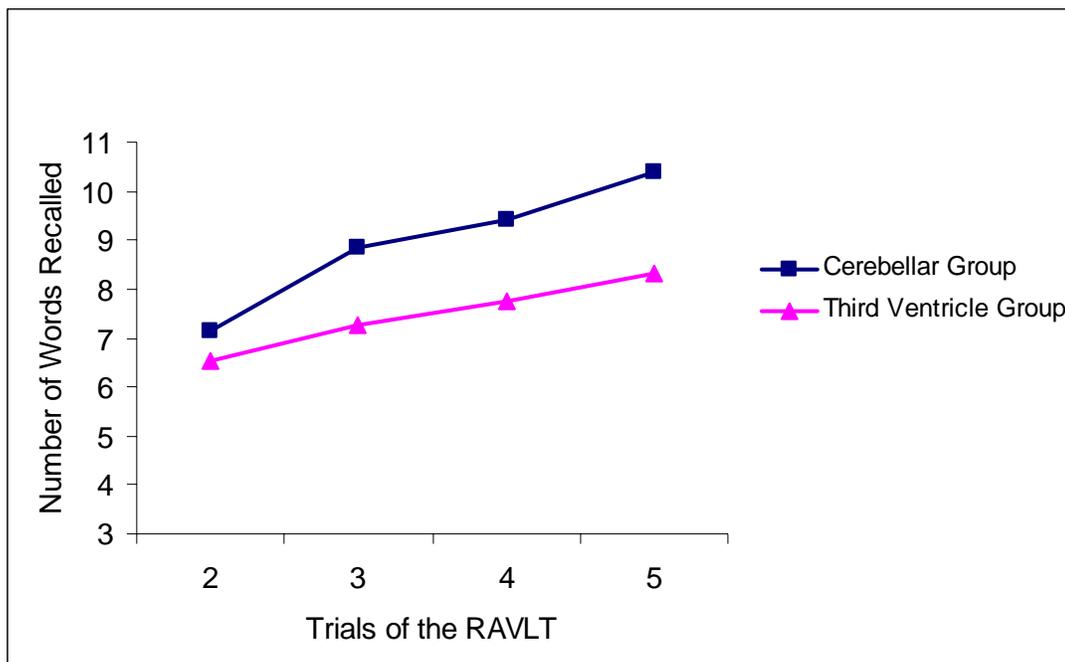


Figure 4

Learning across Trials 2-5 of the RAVLT after Controlling for Performance on Trial 1, in Age-Covaried Raw Scores

Table 9

Mean and Standard Deviation of Words Recalled Across Trials 2-5 of RAVLT after Controlling for Age and Performance on Trial 1

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Trial 2	7.13	3.24	6.52	2.78
Trial 3	8.83	3.82	7.25	3.75
Trial 4	9.4	3.82	7.74	3.30
Trial 5	10.4	4.53	8.33	3.82

\* $p < .05$

\*\* $p < .01$

\*\*\* $p < .001$

In order to compare the performance of the two groups on each trial of the RAVLT, a series of five simple effects analyses were completed (See Tables 8 & 9). As previously reported, a significant difference in performance was observed between groups on trial A, 1 of the Rey AVLT ( $F(1, 39) = 7.16, p = .01$ ). No significant difference in performance was observed between the tumor groups on trial 2 ( $F(1, 38) = 0.73, p = .40$ ). However, both the cerebellar ( $F(1, 33) = 8.95, p = .00$ ) and third ventricle groups ( $F(1, 45) = 12.45, p = .00$ ) demonstrated their only significant gain in the number of words recalled between trials 1 and 2. A trend for a significant difference in performance between the two tumor location groups was observed on trial 3 of the RAVLT ( $F(1, 38) = 2.57, p = .12$ ), and the difference in performance between the two groups closely approached significance on trial 4 ( $F(1, 38) = 3.83, p = .06$ ). Tumor location accounted for 9.2% of the variance in performance on trial 4. A significant difference in performance was observed on trial 5 of the RAVLT ( $F(1, 41) = 4.33, p = .04$ ), with tumor location accounting for 10.2% of the variance in participants' performance.

Parallel analyses completed on participants' Z-scores indicated a comparable pattern of results for the 2 x 4 ANCOVA. Trial 1 was entered as a covariate and was found to account for 24.3% of the variance in participants' performance ( $F(1, 39) = 12.5, p = .001$ ). After controlling for this initial difference in performance on trial 1, a significant effect was observed for tumor location ( $F(1, 39) = 4.05, p = .05$ ). Tumor location accounted for 9.4% of the variance in participants' performance across trials 2-5 of the RAVLT. On average across trials 2-5, the performance of the cerebellar group (M

=  $-.89$ ,  $SD = 1.55$ ) fell in the low average range, while the performance of the third ventricle group fell in the mildly impaired range ( $M = -1.57$ ,  $SD = 1.36$ ). No significant effect was observed for learning trial ( $F(3, 117) = .15$ ,  $p = .91$ ) or the learning trial by tumor group interaction ( $F(3, 117) = .50$ ,  $p = .68$ ). These findings provide further support for the list learning hypothesis and indicate that children with tumors of the cerebellum display verbal learning abilities superior to those of children with tumors of the third ventricle region (See Tables 10 & 11, Figures 5 & 6).

As previously reported, simple effects analyses completed on participants' Z-scores revealed that the two groups differed significantly on trial A, 1 of the Rey AVLT ( $F(1, 39) = 4.44$ ,  $p = .04$ ). On this trial, tumor location accounted for 10% of the variance in performance. A series of four simple effects analyses revealed no significant difference in performance between groups on trial 2 ( $F(1, 39) = .57$ ,  $p = .46$ ), a trend for a significant difference in performance between groups on trial 3 ( $F(1, 39) = 2.98$ ,  $p = .09$ ), and a significant difference on trial 4 ( $F(1, 39) = 4.07$ ,  $p = .05$ ). In contrast to the results from the age-covariied raw score analyses, the Z-score analyses revealed that the third ventricle group improved from the mildly impaired range on trial 4, to the low average range on trial 5. This improvement in recall between trials 4 and 5 was also seen in the cerebellar group, and resulted in only a trend for a significant difference between groups on the last list learning trial ( $F(1, 39) = 2.29$ ,  $p = .14$ ).

### Delayed Memory

In order to examine memory loss over time within each group, a 2 x 2 ANCOVA was completed to examine age-covariied raw score performance on short and long-delay

Table 10

Mean Z-Scores and Standard Deviations of Trials 1-5 of RAVLT by Tumor Location

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Trial 1	-1.41*	1.21	-.69*	.99
Trial 2	-1.1	2.20	-1.08	1.87
Trial 3	-1.17	2.40	-1.57	2.07
Trial 4	-1.30	2.27	-1.69	2.00
Trial 5	-.85	2.07	-1.29	1.81

\* $p < .05$ \*\* $p < .01$ \*\*\* $p < .001$ 

Table 11

Mean Z-Scores and Standard Deviations of Words Recalled Across Trials 2-5 of RAVLT after Controlling for Performance on Trial 1

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Trial 2	-.89	1.55	-1.23	1.81
Trial 3	-.93	2.27	-1.75	1.94
Trial 4	-1.02	2.07	-1.90	1.81
Trial 5	-.72	2.07	-1.38	1.81

\* $p < .05$ \*\* $p < .01$ \*\*\* $p < .0$

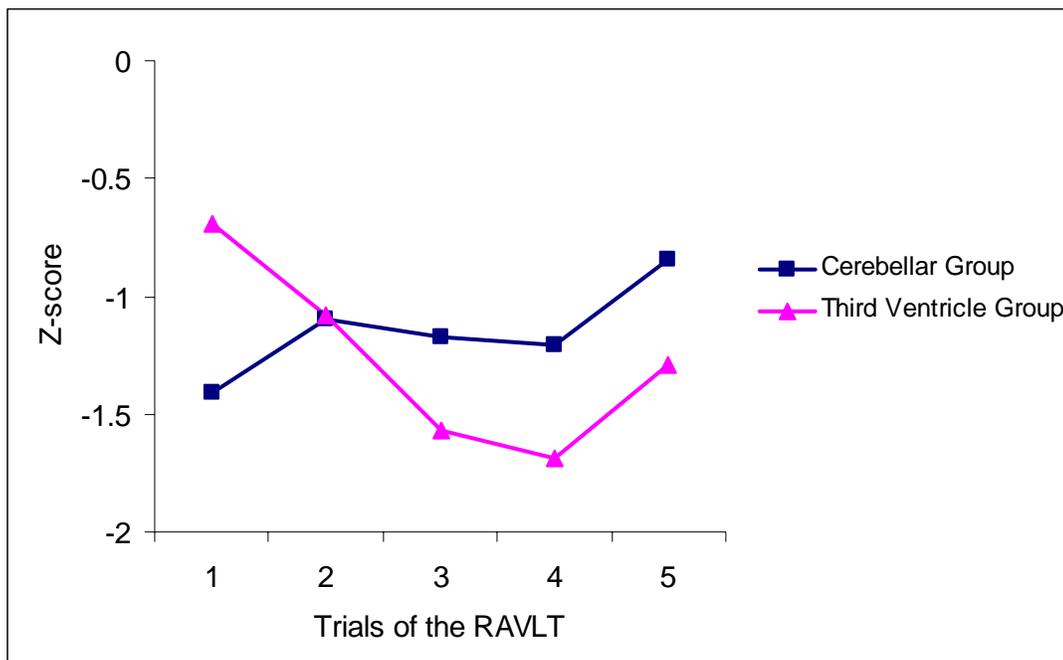


Figure 5

Learning Across Trials 1-5 of the RAVLT by Tumor Group, in Z-Scores

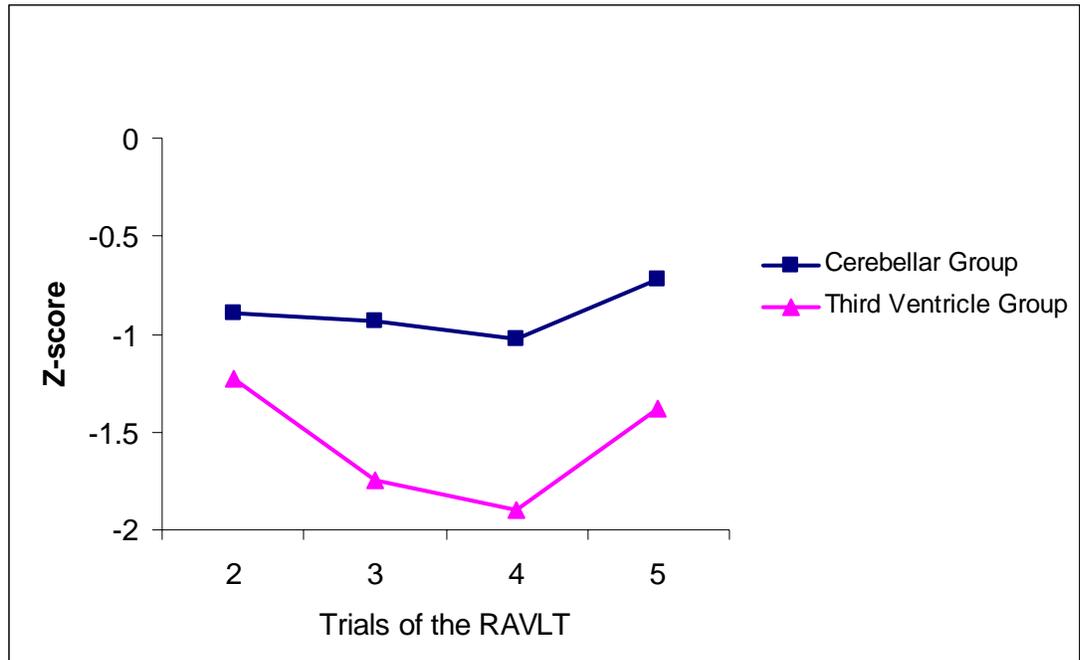


Figure 6

Learning Across Trials 2-5 of the RAVLT after Controlling for Performance on Trial 1, in Z-Scores

free recall trials. After controlling for differences in learning abilities by covarying out performance on trial 5 ( $F(1, 38) = 41.73, p = .00$ ), no significant main effect was found for tumor location ( $F(1, 38) = .00, p = .96$ ), or trial type ( $F(1, 38) = .66, p = .42$ ). No significant effect was found for the trial by tumor interaction ( $F(1, 38) = .50, p = .48$ ). Additionally, simple effects analyses revealed that neither the cerebellar ( $F(1, 33) = .03, p = .87$ ) or the third ventricle group ( $F(1, 45) = .03, p = .86$ ) demonstrated a significant decline in memory performance between the short and long delay free recall trials. See Figure 7, Table 12.

A 2 x 2 ANCOVA was completed on participants' performance on the long delay free recall and recognition trials. It was hypothesized that the third ventricle group would be more impaired than the cerebellar group on both delayed memory tasks, but would show a greater rate of improvement when presented with the recognition test format. In order to examine differences in memory performance unaffected by differences in learning abilities, trial 5 of the RAVLT was entered as a covariate. Performance on trial 5 accounted for a significant amount of the variance ( $\eta^2 = .36$ ) in delayed memory performance ( $F(1, 38) = 21.19, p = .00$ ).

Results of the 2 x 2 ANCOVA illustrated a significant effect for delayed memory trial type ( $F(1, 39) = 20.92, p = .00$ ), which accounted for 35.5% of the variance in performance. Participants across tumor location groups performed significantly better on the delayed recognition memory task ( $M = 13.07, SD = 2.98$ ) than on the delayed recall

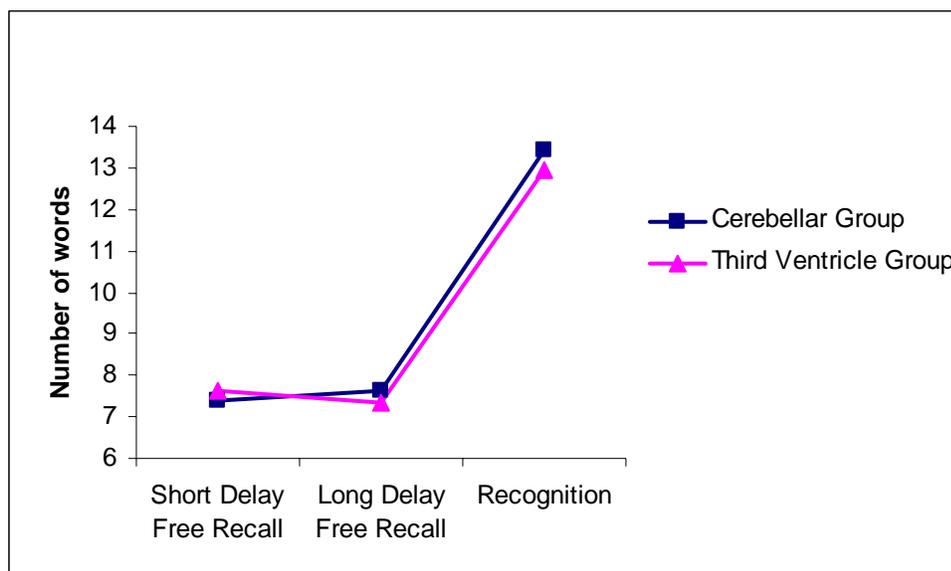


Figure 7

Performance on List A, Trial 6, Delayed Recall and Recognition trials in Age-Covaried Raw Scores

Table 12

Age-covaried Raw Score Performance on Short and Long Delay Free Recall and Recognition Trials by Tumor Location

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Short Delay Free Recall	7.4	3.75	7.62	3.18
Long Delay Free Recall	7.65	4.08	7.36	3.56
Delayed Recognition	13.44	4.80	12.96	4.15

\*  $p < .05$

\*\*  $p < .01$

\*\*\*  $p < .001$

task ( $M = 7.38$ ,  $SD = 2.48$ ). Simple effects analyses indicated that the tumor location groups did not differ significantly in their performance on the long delay free recall ( $F(1, 39) = .24$ ,  $p = .63$ ) or recognition trials ( $F(1, 39) = .04$ ,  $p = .64$ ) when controlling for age and trial 5. A significant effect was not observed for tumor location ( $F(1, 38) = .41$ ,  $p = .53$ ), or the interaction of trial by tumor ( $F(1, 38) = .09$ ,  $p = .77$ ). In contrast to the proposed hypotheses, the third ventricle group did not demonstrate a greater impairment than the cerebellar group across delayed memory tasks, nor did they demonstrate a greater benefit in performance when presented with the recognition test format. (See Table 12, Figure 7).

Participants' standard scores were examined for outliers prior to completing the delayed memory analyses. One member of the third ventricle group was excluded from the analyses because of a delayed recognition Z-score of -10.71, because of the potential for this value to unduly skew the results of the analyses.

Parallel analyses completed with Z-scores indicated a somewhat different pattern. A 2 x 2 ANCOVA was completed to examine memory loss over the 20-minute delay (short delay vs. long delay free recall). Trial 5 was entered as a covariate to control for differences in learning ability ( $F(1, 39) = 15.88$ ,  $p = .00$ ), and accounted for 28.9% of the variance in participants' performance. No significant main effect was observed for tumor location group ( $F(1, 39) = .54$ ,  $p = .47$ ). A significant effect was observed for the memory trial ( $F(1, 39) = 7.63$ ,  $p = .009$ ), with participants across the two groups performing significantly better on the short delay free recall trial ( $M = .15$ ,  $SD = 1.10$ ) than on the long delay free recall trial ( $M = -.76$ ,  $SD = 1.62$ ). A trend for significance

Table 13

Z-Score Performance on Short and Long Delay Free Recall and Recognition Trials by Tumor Location with Trial 5 as a Covariate

	Cerebellar		Third Ventricle	
	M	SD	M	SD
Short Delay Free Recall	.10	1.68	.19	1.43
Long Delay Free Recall	-.48*	2.20	-1.04*	1.94
Delayed Recognition	-.69	3.30	-.61	2.91

\* $p < .05$

\*\* $p < .01$

\*\*\* $p < .001$

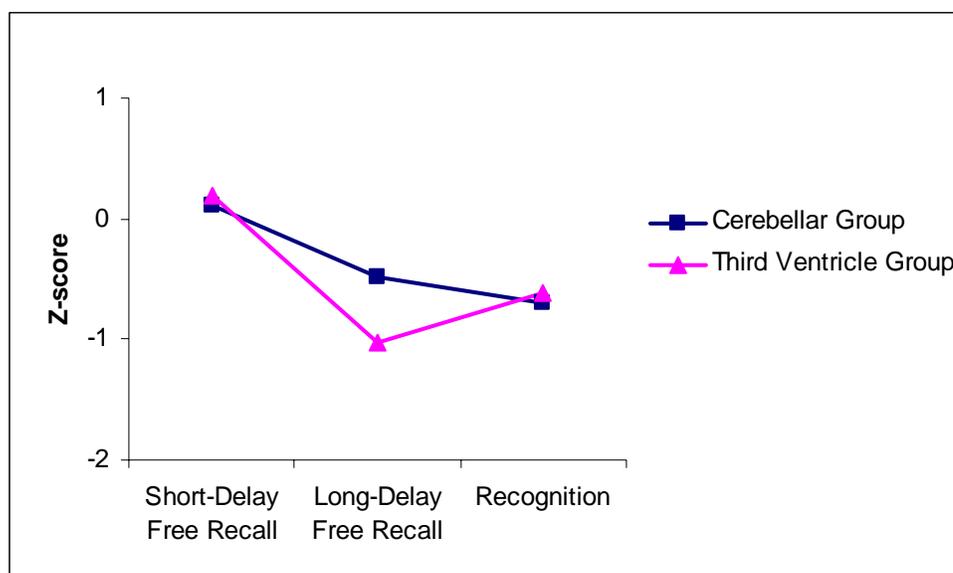


Figure 8

Performance on List A, Trial 6, Delayed Recall and Recognition Trials in Z- Scores with Trial 5 as a Covariate

was noted for the memory trial by tumor group interaction ( $F(1, 39) = 3.74, p = .06$ ).

See Table 13, Figure 8.

Simple effects analyses were completed to examine differences between groups on the two memory trials. No significant difference was observed on trial A, 6 of the Rey AVLT ( $F(1, 39) = .07, p = .79$ ). The performance between the two groups on this trial was strikingly similar, with both the cerebellar ( $M = .10, SD = 1.68$ ) and third ventricle group ( $M = .19, SD = 1.43$ ) performing in the average range. A trend for a significant difference was observed between groups on the long delay free recall trial ( $F(1, 39) = 1.83, p = .18$ ), with the cerebellar group performing in the average range and the third ventricle group performing in the low average range of functioning. Additional simple effects analyses were used to examine the pattern of performance within each group. The performance of the cerebellar group did not differ significantly across the short ( $M = .10, SD = 1.68$ ) and long delay free recall trials ( $M = -.48, SD = 2.20$ ) of the Rey AVLT ( $F(1, 39) = .11, p = .74$ ). In contrast, the performance of the third ventricle group declined significantly across the short ( $M = .19, SD = 1.43$ ) and long delayed free recall ( $M = -1.04, SD = 1.94$ ) trials of the Rey AVLT ( $F(1, 46) = 8.58, p = .005$ ).

A 2 x 2 ANCOVA was completed on the Z-score of participants' performance on the long delay free recall and recognition trials. Trial 5 was entered as a covariate into the analysis and accounted for 21% of the variance in participants' performance ( $F(1, 38) = 10.11, p = .003$ ). No significant effect for tumor location was observed ( $F(1, 38) = 1.33, p = .57$ ). No significant main effects were observed for trial type ( $F(1, 39) = .002, p = .96$ ), or the trial type by tumor location interaction ( $F(1, 38) = .98, p = .33$ ).

Simple effects analyses were utilized to compare performance between groups on the long delay memory trials. A previously completed simple effects analysis revealed a trend for a significant difference between groups on the long delay free recall trial (see above). In contrast, the two groups did not differ significantly on the delayed recognition trial ( $F(1, 38) = .01, p = .91$ ). On average, participants in both the cerebellar ( $M = -.69, SD = 3.30$ ) and third ventricle groups ( $M = -.61, SD = 2.58$ ) performed in the average range on the delayed recognition memory trial.

To examine the performance of each group across the delayed memory trials, two one-way ANOVAs were completed. The cerebellar group's performance did not differ significantly across the two delayed memory test formats ( $F(1, 34) = .23, p = .64$ ). The performance of the cerebellar group was in the average range on both the long delay free recall trial ( $M = -.48, SD = 2.20$ ), and the delayed recognition trial ( $M = -.69, SD = 3.30$ ). The third ventricle groups' performance did not differ significantly across the delayed memory trials ( $F(1, 44) = .78, p = .38$ ). However, as a result of the recognition test format, the performance of the third ventricle group improved from the low average ( $M = -1.04, SD = 1.94$ ) to the average range of functioning ( $M = -.61, SD = 2.91$ ).

#### Memory for Sentences

As a secondary analysis, a t-test was completed on the standard scores of participants' performance on the memory for sentences subtest of the Stanford-Binet Intelligence Scale-IV. This was completed as a collateral measure of verbal auditory attention abilities. One member of the third ventricle tumor group was excluded from these analyses, due to missing data on the memory for sentences subtest of Stanford-

Binet Intelligence Test-IV. No significant difference in performance was observed among the two groups on the memory for sentences subtest ( $t(39) = .66, p = .51$ ). On this task, members of both the cerebellar ( $M = -.16, SD = .81$ ) and third ventricle groups ( $M = -.39, SD = 1.30$ ) performed in the average range. Little overall differences in performance were observed between groups; however, the third ventricle group demonstrated greater variability in performance on this subtest (See Table 14).

Table 14

Performance on the Memory for Sentences of the Stanford-Binet Intelligence Scale-IV by Tumor Location

	Memory for Sentences			
	Standard Age Scores		Z-Scores	
	M	SD	M	SD
Cerebellar Tumor Group	48.72	6.51	-.16	.81
3 <sup>rd</sup> Ventricle Tumor Group	46.87	10.43	-.39	1.30

\* $p < .05$

\*\* $p < .01$

\*\*\* $p < .001$

## Discussion

Examinations of cognitive abilities in children with brain tumors are complicated by a multitude of treatment and diagnosis related variables, which have the likelihood to interact and exert diverse and widespread affects on the developing neural structures. The consideration and statistical control of the differential effects of these variables on cognitive abilities is a primary means by which researchers can increase the internal validity of their findings. The current study considered both the individual and combined effects of treatment and diagnosis related variables on memory abilities in a sample of children with brain tumors. Surprisingly, the examination of these potentially confounding variables within the cerebellar and third ventricle groups revealed minimal group differences. This finding was unexpected, as tumor pathology, and therefore tumor characteristics, the presence of diagnosis related conditions, and treatment modalities of choice, vary across the cerebellar and third ventricle regions of the brain.

Within this sample, two variables were found to be differentially represented in the two tumor location groups; the presence of neurosurgery and hormone deficiency. The third ventricle region of the brain is located deep in the cerebral hemispheres and is surrounded by subcortical structures that are sensitive to disruption. The high prevalence of hormone deficiency in children with tumors of the third ventricle region is thought to be due to tumor and treatment-related disturbances of diencephalic brain structures (e.g. hypothalamus, pituitary gland), which are responsible for the modulation of a variety of hormones. In an attempt to minimize damage to these surrounding brain structures that may result from surgical removal, tumors of the third ventricle region are frequently

treated with radiation therapy. In contrast, surgical resection is frequently utilized in the treatment of children with cerebellar tumors. Surgical resection is favored in this population because of its high success rate. Additionally, the location of the cerebellum reduces the risk of disrupting surrounding brain structures and pathways during the surgical procedure. The significant differences observed between groups in the prevalence of hormone deficiency and neurosurgery, are consistent with the literature regarding co-morbid conditions and treatments of choice in children with brain tumors. An examination of these two differentially represented variables revealed that they were not significantly correlated with performance on the delayed recall memory task, and therefore were not considered to be confounds in the current analyses.

Two treatment related variables, the presence of radiation treatment and the time since the initiation of radiation, were found to be significantly related to performance on the long delay free recall measure. Specifically, participants who had received radiation performed significantly worse on the long delay free recall memory trial than participants who had not received radiation therapy. Furthermore, as the amount of time that had passed between the initiation of radiation and the neuropsychological evaluation increased, participants' performance on the delayed recall memory trial decreased. These findings are congruent with studies citing radiation "late effects," or notable increases in cognitive impairment that may occur weeks, months and years after the initiation of radiation treatment (Chapman et al., 1995). Although both radiation variables were found to be significantly related to memory abilities, no significant group differences were noted. Therefore, after a comprehensive review of participants' medical records, it

was concluded that none of the 12 tumor or treatment related variables met criteria ( $p < .05$ ) to be considered a confound in the current analyses.

Deficits in executive functioning, including attention, have been repeatedly documented in the literature on children with tumors in the cerebellum/posterior fossa region of the brain. In 2004, King et al. reported that children treated for cerebellar tumors performed significantly worse than children treated for third ventricle tumors on the digit span subtest of the Wechsler Intelligence Scales for Children-III. Additionally, a role for the cerebellum has been implicated in selective attention tasks in normal populations. Specifically, posterior sites of the cerebellum have been shown to become activated in a visual shape detection task that was free of a motor component (Allen et al., 1997).

The current examination of attention in a sample of children with brain tumors supported the findings of King et al. (2004), and other studies citing a role for the cerebellum in attentional abilities. Specifically, children with cerebellar tumors performed in the mildly impaired range on the first trial of the Rey AVLT. Impaired performance on trial A, 1 of the Rey AVLT has typically been thought to be due to inattention and a slowness in shifting from one task to another (Lezak, 1995). Furthermore, when poor performance on trial A, 1 is observed in a sample of individuals with attentional impairments, but whose immediate verbal memory abilities are within normal limits, it is expected that, 1) the performance of these individuals will improve to within normal limits on list B, and 2) performance will improve significantly between trials A, 1 and A, 2 (Lezak, 2004).

The Z-scores of the cerebellar group revealed a pattern that was consistent with the profile of individuals exhibiting attentional impairments. The cerebellar group demonstrated its only significant increase in word recall between trials A, 1 and A, 2. An examination of the raw number of words recalled by the cerebellar group revealed that the group's average raw scores did not increase significantly on trial B. However, an examination of norm generated Z-scores indicated that their performance on this trial fell in the average range of functioning, a pattern more consistent with the profile of individuals with attentional impairments cited by Lezak (2004). The inconsistency in the pattern of results between the raw scores and Z-scores can be partially explained through an examination of the normative data. Across ages, the individuals comprising the normative sample performed better on trial A, 1 than on trial B. When individuals demonstrate this pattern of performance, the decreased number of words recalled in trial B is typically attributed to the effects of proactive interference. Proactive interference occurs when previously learned material (list A) interferes with an individual's acquisition of new material (list B) (Lezak, 2004). As the performance of the normative group declined across trials A, 1 and B, the slight increase in raw number of words recalled by the cerebellar group translated to a significant increase in standard Z-scores (resulting in the mean Z-score that fell in the average range of functioning). This indicates that the cerebellar group demonstrated consistent performance across trials, but that this performance did not consistently fall in the mildly impaired range of functioning when compared to same aged peers. Similarly, the significant decline in the third ventricle group's word recall between trials A, 1 and B, paralleled the performance of the

normative sample. This resulted in a stability of the third ventricle group's standard scores across tasks, and indicated that individuals in this group demonstrate susceptibility to proactive interference that is within normal limits.

The pattern of performance observed across trials A, 1 and B indicates that the mildly impaired performance of the cerebellar group on trial A, 1 may be due to inattentiveness and a slowness of shifting to the new task, and is consistent with some of the literature citing a role for the cerebellum in attentional and executive abilities. The majority of evidence for the cerebellum's role in executive functioning has been provided by neuroanatomical demonstrations of indirect cerebellar connections with frontal and parietal association cortices (Riva & Giorgi, 2000). Cerebrocerebellar pathways that link the cerebellum with frontal and prefrontal areas through the pons, and reciprocally through the thalamus, have been identified in a number of studies (Schmahmann & Pandya, 1995, 1997 a, b; Middleton & Strick, 1997; Riva & Giorgi, 2000). Examinations of these neuroanatomical substrates have been used to define the cerebellum as a primary component in the widely distributed neural pathways that play a role in cognitive and executive abilities (Levisohn et al., 2003). Difficulties in attention and executive functioning may result from the reduced metabolism in cerebellar efferent target regions, as a result of the tumor or treatment related damage (Lalonde & Botez-Marquard, 2000).

As a collateral measure of attention and verbal short-term memory abilities, the performance of the tumor location groups was compared on the Memory for Sentences subtest of the Stanford-Binet Intelligence Scale-IV. In contrast to performance on trial A,1 of the Rey AVLT, no significant difference was observed in the performance of the

tumor location groups on the Memory for Sentences subtest. On this task the performance of the cerebellar group was slightly superior to that of the third ventricle group, however, on average members of both the cerebellar ( $M = -.16$ ,  $SD = .81$ ) and third ventricle groups ( $M = -.39$ ,  $SD = 1.30$ ) performed in the average range.

A lack of a notable difference in performance on this measure between groups could be partially attributed to its additional language comprehension component. Factor analyses of the Stanford-Binet IV have indicated that this measure loads more highly on “verbal ability” than on “memory” (Sattler, 1992). Strong language abilities in children often function to improve otherwise impaired skills, such as attention and auditory-verbal memory abilities (McGrew & Flanagan, 1998). It is reasonable to postulate that children who comprehend the sentences with ease, will demonstrate superior performance when asked to recall the sentences. Furthermore, it is important to note that performance on the memory for sentences subtest may be influenced by the meaningfulness of the sentences. The more meaningful a sentence is, the higher the likelihood that a child will attend to, and recall, the sentence (Lezak, 2004). As a result, performance on this subtest may be influenced by differences in oral language comprehension abilities and the meaningfulness of the stimuli, which have the potential to mediate the relationship between tumor location and performance, and obscure any real effects of the tumor location.

Consistent with previous findings, a significant role was found for the structures and pathways of the third ventricle region in children’s auditory verbal learning abilities. In this sample, children treated for tumors in the third ventricle region demonstrated

significantly greater impairments in learning across trials 2-5 of the Rey AVLT than did children with cerebellar tumors. Results indicated that the learning abilities of the third ventricle group across the trials of the Rey AVLT were in the low average to mildly impaired range ( $Z$ -scores between -1.90 and -1.23).

The pattern of results observed in the current study suggests that children with tumors of the third ventricle region demonstrated average auditory attention and immediate memory on trial A, 1. However, the  $Z$ -scores of the third ventricle group's performance proceeded to decline across trials, as participants in this group demonstrated minimal gains in the number of words recalled as a result of repeat exposure. Non-neurologically impaired children who comprised the normative sample used in the current study demonstrated significant improvements in performance as a result of repeat exposure to the learning material. As the average number of words recalled by the normative sample increased with each exposure, so too did the discrepancy between the performance of "normals" and children with tumors of the third ventricle region, thereby resulting in a significant decline in the  $Z$ -scores of the third ventricle group over trials.

An examination of the standard scores illustrates the growing discrepancy in performance between the third ventricle group and same aged peers across trials 2-5 of the Rey AVLT (See Figure 6). After controlling for differences in attentional abilities on trial A, 1, the third ventricle group performed in the low average range on trial 2, and in the mildly impaired range on trials 3 and 4. On trial 5, the performance of both groups increased relative to the normative sample, placing the cerebellar group in the low average range and the third ventricle group in the mildly impaired range. On average

across trials 2-5 of the Rey AVLT, the performance of the third ventricle group was in the mildly impaired range and differed significantly from the performance of the cerebellar group.

On average, the performance of the cerebellar group across trials 2-5 of the Rey was in the low average range. After an initial impairment on trial A,1, the cerebellar group demonstrated an increase in the number of words recalled across subsequent learning trials. However, when the performance of this group was examined relative to the normative population, they appeared to demonstrate a relatively flat learning curve. The Z-score profile of the cerebellar group indicated that these children learned at a normal rate across trials, but on average recalled fewer words than their same-aged peers. The performance of the cerebellar group was superior to that of the third ventricle group, and by the end of the fifth learning trial, the cerebellar group's performance had improved from the mildly impaired to the low end of the average range.

Consistent with the proposed hypotheses, children with tumors of the third ventricle region demonstrated an impairment in verbal memory abilities. A significant decline was noted in their Z-scores between the short and long delay free recall trials. Examination of the Z-scores and age-covariied raw scores demonstrated that both groups performed in the average range on the short delay free recall trial, indicating preserved immediate memory abilities. However, the Z-scores of the third ventricle group declined significantly in the 20-minute delay that separates the short and long delay free recall trials. On the long delay trial, a trend for a significant difference in Z-score performance was observed. On this trial, the cerebellar group performed in the average range while

the third ventricle group's performance declined into the low average range of functioning.

The recognition trial is a measure of how many words the participant learned, unaffected by difficulties with spontaneous retrieval (Lezak, 2004). In contrast to the proposed hypothesis, the third ventricle group's performance (Z-scores) did not improve significantly as a result of the recognition test format. Across these trials, the performance of the third ventricle group improved from the low average to the average range of functioning. Although this finding was not as robust as predicted, the results of the current analyses indicate that the utilization of a recognition test format improves the delayed memory performance of children with tumors of the third ventricle region. These findings indicate that although children in the third ventricle group had mildly impaired learning abilities over trials 2-5 of the Rey AVLT and low average performance on the long delay free recall trial, their performance can improve to the average range of functioning when asked to recognize previously learned material. This pattern of results points to a deficit in verbal memory retrieval in children with tumors of the third ventricle region.

What may appear to be an inconsistency in the tumor location groups' profiles across the age-covaried raw scores and Z-scores is likely due to the characteristics of the normative data. On the short delay free recall trials, age-covaried raw scores and standard scores are consistent. However, between the short and long delay free recall trials this pattern seems to shift. An examination of the normative data used in the analyses indicates that, in general, children ages 5-17 demonstrated an increase in the

number of words recalled between the short and long delay free recall trials. The increase in the cerebellar group's performance across these trials was less than that observed in the normative sample and resulted in a slight decline in the cerebellar group's Z-scores on the long delay free recall trial. Furthermore, the performance of the third ventricle group declined between the short and long delayed free recall trials, and resulted in an even larger drop in standard scores.

Additionally, it is important to note that subtle differences observed in the patterns of results between the age-covariied raw scores and Z-scores are likely due to inherent differences in the way that these two statistical methods account for differences in age. Covariation occurs when one variable (age) consistently and systematically changes relative to another variable (tumor location). When age is covariied out of memory performance scores, the result is an increase in the memory scores of younger children and a decrease in the memory scores of older children. In contrast, the calculation of norm generated Z-scores assigns each child's performance a position (usually between +3 and -3) amongst the performance of same-aged peers. This method of evaluating the child's performance relative to peers is typically considered to be more sensitive to age differences, and allows for the assignment of qualitative labels to the data.

On the recognition trial of the Rey AVLT, both groups demonstrated a significant increase in the raw number of words recalled. Although the raw scores of both groups increased significantly as a result of the recognition test format, so too did the performance of the normative sample. Therefore, the increase in raw number of words

recalled by the two groups did not result in a significant increase in Z-scores. However, it is important to note that the performance of the third ventricle group improved from the low average to the average range of functioning on the delayed recognition trial.

Damage to the structures and white matter pathways of the third ventricle region have been consistently implicated in impairments of learning and memory. Specifically, damage to the structures involved in the transmission of information between the third ventricle region and the prefrontal cortex and medial temporal lobes is proposed to be a primary mechanism that underlies memory impairments in this population. The findings from the current study indicate that when compared to children with tumors of the cerebellum, children with tumors of the third ventricle region demonstrate a greater impairment in auditory verbal learning, and a greater memory loss over a 20-minute delay when tested on a free recall measure.

Overall, the pattern of performance in this sample of children with tumors of the third ventricle region was consistent with learning and memory profiles observed in both adult and pediatric populations with damage to regions of the thalamus and third ventricle. Consistent with expectation, the third ventricle group demonstrated impaired learning abilities across trials 2-5 of the Rey AVLT. However, as observed in the current analyses, when patients with damage to the third ventricle are presented with a recognition test format, they typically demonstrate a pattern of performance that highlights their ability to learn (and therefore recognize) a limited amount of the previously presented material. Normal learning abilities in children with third ventricle tumors are thought to be compromised by defective encoding, which in turn renders

retrieval strategies ineffective, thereby affecting free recall memory abilities (Gazzaniga, 1995). Several studies have demonstrated that impaired free recall performance is associated with a decreased use of organized encoding strategies (Gershberg & Shimamura, 1991). The compromised performance observed on a measure of delayed free recall, relative to average performance on a measure of recognition memory, suggests deficits in encoding and retrieval as primary causes for the learning and memory difficulties within this sample of children with tumors of the third ventricle region (Kopelman, 1989).

The limitations of clinical studies of the cognitive abilities of children with brain tumors must be considered prior to the interpretation of findings. A primary limitation of the current study was the use of normative data compiled from a number of studies differing in inclusionary/exclusionary criteria, methods of recruitment, sample sizes and demographic composition. As a result, this may have introduced some degree of unknown variability into the Z-score analyses. In light of the significant difficulty encountered in obtaining adequate normative data for the Rey AVLT, the current study would have benefited from the inclusion of pre-diagnosis measures of auditory verbal learning and memory abilities or an appropriate control group. An examination of our findings in relation to pre-diagnosis data would allow for a more comprehensive understanding of the decline in attentional and memory abilities that results from the diagnosis and treatment of a brain tumor. However, pre-diagnosis or baseline measures are uncommon in research of this type because of the rarity of the sample and an inability to predict which children may develop such a diagnosis. A promising alternative is the

use of an age-matched control group. Using such a group would allow researchers to make comparisons between participants with brain tumors and normally developing children who were exposed to similar research/testing methods during their participation in the study. In the absence of an age-matched control group, the acquisition of comprehensive normative data for the Rey AVLT would significantly increase the researchers' confidence in the meaning of the qualitative labels applied to participants' performance (*Z*-scores).

When examined in relation to the myriad of research studies examining cognitive abilities of children with brain tumors, the current study stands out for a number of reasons. First and foremost, the current study examined a relatively large sample of children experiencing brain tumors during childhood. The study from which the current data was obtained (Neurological and Neuropsychological Recovery Following Brain Tumors in Children) had a number of strengths including; 1) its utilization of a variety of neuropsychological and behavioral measures, 2) its examination of children at early ages, and 3) the longitudinal or prospective nature of the study. A second way in which the current study sets itself apart from other examinations of this population, is through its meticulous examination of potentially confounding variables. In their 1991 article, Dennis et al. state that, "research investigations have generally failed to explore the systematically interrelated effects of brain-tumor variables on cognitive outcome," (p. 814). Research in the field of pediatric neuro-oncology is rife with treatment and disease related variables that may function to obscure the relationship between the constructs of interest. The current study examined the relationship between several potentially

confounding variables and verbal memory abilities. The absence of a relationship between these variables and the dependent variable of interest serves to increase our confidence in the external validity of our findings.

The current study supports a potential role for the cerebellum in a distributed attentional and executive executive network. Future studies should explore this issue further using a comprehensive attentional battery. Ideally, the neuropsychological battery would be varied in task type, response modality, and cognitive load. Specifically, attentional abilities in children with cerebellar tumors could be examined using measures of sustained and divided attention, and an expanded battery of auditory attention measures (digit span, letter span). Furthermore, examining attention across modalities (visual cancellation tasks, visual span, spatial span) would also aid in our understanding of the cerebellum's role in these processes. A more thorough examination of learning and memory abilities in children with tumors of the third ventricle region could be accomplished through the administration of a measure such as the CVLT, which allows for an examination of serial and semantic encoding strategies, and the effects of cueing on recall performance. Additionally, the use of a story recall measure would help to examine memory abilities using a format that resembles everyday interactions. These measures are beneficial because they examine retention for material that exceeds immediate memory span (Lezak, 2004). Story recall measures also have the power to elucidate the contribution of context and meaning to recall abilities.

Relative to the substantial need for information within this domain, studies such as this can only provide limited insight into the cognitive deficits associated with brain

tumors. In spite of this fact, such studies contribute to the field of neuro-oncology by providing data that can be assimilated into working hypotheses. The active investigation and refinement of these working hypotheses will lay the groundwork for the creation of profiles of cognitive impairment in children with tumors of the cerebellum and third ventricle region. Profiling cognitive dysfunction relative to localized brain damage is a meaningful, yet daunting task. However, through the integration of neuropsychological data, researchers are afforded the ability to weave together the findings from research studies such as this, into a comprehensive conceptualization of the functions of specific brain structures and pathways. Creating profiles of cognitive impairment in this population has the potential to provide families with a better understanding of their child's strengths and weaknesses, which may facilitate the child's adjustment to home and school environments, and aid in the attainment of an optimal level of functioning and quality of life.

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