5-9-2015

Practice Effects on a Working Memory Task in Adult Survivors of Pediatric Brain Tumors: An fMRI Investigation

Sabrina Na

PRACTICE EFFECTS ON A WORKING MEMORY TASK IN ADULT SURVIVORS OF PEDIATRIC BRAIN TUMORS: AN FMRI INVESTIGATION

by

SABRINA NA

Under the Direction of Tricia Z. King, PhD

ABSTRACT

Behavioral studies have documented impaired working memory in childhood brain tumor survivors; however, neural mechanisms have yet to be identified using fMRI. The current study investigated BOLD response differences between twenty survivors (Mean age=23.1(4.14), 55% female) and twenty age- and gender-matched controls from the start to the end of a twenty minute 3-back task. There were no differences in task performance between groups or over time. Effects of practice were present in left prefrontal regions, with both groups showing decreases in activation as the task progressed. There were qualitative and quantitative differences in the brain regions that survivors recruited relative to controls in bilateral prefrontal (including the dorsolateral prefrontal cortex) and parietal cortices. Findings suggest that areas under top-down control of the dorsolateral prefrontal cortex become less activated with practice, and that survivors may require more top-down processing and attentional control to perform at similar levels to healthy controls.

INDEX WORDS: Working memory, Magnetic resonance imaging, Neuropsychology, Long-term, Brain tumor survivorship, Dorsolateral prefrontal cortex

PRACTICE EFFECTS ON A WORKING MEMORY TASK IN ADULT SURVIVORS OF PEDIATRIC BRAIN TUMORS: AN FMRI INVESTIGATION

by

SABRINA NA

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

2015

PRACTICE EFFECTS ON A WORKING MEMORY TASK IN ADULT SURVIVORS OF PEDIATRIC BRAIN TUMORS: AN FMRI INVESTIGATION

by

SABRINA NA

Committee Chair: Tricia Z. King

Committee: Robin Morris

Binjian Sun

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

May 2015

DEDICATION

I would like to dedicate this thesis to my loving parents, Jung and Sangsin. They gave everything they had to give me the best education they could, and I am deeply grateful for their years of love, patience and unimaginable sacrifice. I also dedicate this thesis to my sisters, Sarah and Christina, whose bright minds and loving hearts are a constant source of much needed motivation and support.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest appreciation to my committee chair and academic advisor, Dr. Tricia King, who provided essential assistance and conceptual advice at all hours of the day and week. I would also like to thank Dr. Binjian Sun, without whom I would have floundered in an imaging processing haze. He was on hand for every methodological question that I had and I am deeply grateful for his expertise. I am also deeply grateful for the assistance of Dr. Robin Morris, who constantly challenged my work and truly taught me what it meant to think like a researcher.

In addition, my gratitude goes out to the individuals and family members who participated in the study and contributed their time and tireless energies to the research project. Without them, this work would not be possible.

Finally, I am deeply indebted to the individuals in the King Developmental Neuropsychology Laboratory, who have aided with data acquisition and management. Specifically: Alyssa Ailion, Kristen Smith, Ryan Brewster and Reema Jayakar, who provided much needed laughter and support.

This work was supported in part by a Research Scholar Grant, American Cancer Society (#RSGPB-CPPB-114044) awarded to Dr. Tricia Z. King and a GSU Brains & Behavior Fellowship awarded to Sabrina Na.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

1.1 Brain Tumor Survivorship

Cancers of the brain and central nervous system are the second most prevalent type of cancers in children. In the United States alone, over 4200 children are diagnosed with a pediatric brain tumor every year (CBTRUS, 2012). Over the past few decades, medical advances in surgical procedures and cancer treatments have resulted in increased survival rates of children with brain tumors, resulting in more and more of these individuals reaching adulthood (Porter, McCarthy, Freels, Kim, & Davis, 2010). However, improvement in treatment outcomes also necessitate treatments and interventions that address the problems that arise in adult survivors of pediatric brain tumors as they age (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). As such, there has been an increased need to study the long term outcomes and sequelae of adult survivors of pediatric brain tumors.

An emerging body of literature examining the long term outcomes of adult survivors of pediatric brain tumors has demonstrated that these individuals report lower quality of life, and, furthermore, exhibit signs of overall cognitive decline, and deficits in physical, social, psychological, emotional, and adaptive functioning (Lannering, Marky, Lundberg, & Olson, 1990; Mostow, Byrne, Connelly, & Mulvihill, 1991; Pogorzala, Styczynski, Kurylak, Debski, Wojtkiewicz, & Wysocki, 2010; Radcliffe, Bennett, Kazak, & Foley, 1996; Robison, Green, Hudson, Meadows, & Mertens, 2005; Whitton, Rhydderch, Furlong, Feeny, & Barr, 1997). These individuals also frequently report adverse outcomes in health, and experience a lower quality of life, decreased psychosocial adjustment and decreased academic achievement (Anderson et al., 1997; Kelaghan et al., 1988; Lannering et al., 1990; Seaver et al., 1994; Whitton et al., 1997). These findings have been robust, and have been corroborated by reports

from informants, including family members and teachers (Radcliffe et al., 1996). Many of these factors are theorized to contribute to their lower education attainment, lower levels of employment, and subsequent lower experienced quality of life (Macedoni-Luksic et al., 2003; Zebrack, Gurney & Oeffinger, 2004).

Specifically, survivors of pediatric brain tumors exhibit significant impairments in many neurocognitive domains. Previous research has shown that survivors have lower intelligence quotients (IQ) than their healthy peers (Gragert et al., 2011), and, moreover, that full scale IQ drops by a mean level of 2.55 points every year past their age at diagnosis (Palmer et al., 2001). This continued decline is attributed to the inability of adult survivors to acquire new skills and information at a rate comparable to their healthy same-age peers, rather than a loss of previously acquired information (Palmer et al., 2001; Saury & Emanuelson, 2011). Meta-analyses of existing research comparing IQ between survivors of childhood brain tumors to survivors of other malignancies also concluded that adult survivors have lower full scale IQ, lower perceptual IQ, and lower verbal IQ (de Ruiter et al., 2012). These meta-analyses have concluded that the domains of attention, processing speed, working memory, executive function and nonverbal cognitive ability are impaired in adult survivors as compared to healthy controls, with large mean effect sizes (Butler & Copeland, 2002; Robinson et al., 2010).

1.2 Medical and Treatment Complications

Research studies involving adult survivors have a number of methodological complications, as there are a multitude of variables related to the diagnosis and treatment of brain tumors that may contribute to long term outcomes. These include, among others, the histology and location of the tumor, the age at which the child was diagnosed, and the treatment regimen. Several studies have attempted to isolate the contributions of each factor to long-term sequelae.

From these studies, it is widely accepted that radiation (used to shrink tumors and damage cancer cells) contributes to poorer cognitive outcomes (Saury & Emanuelson, 2011). Radiation related neurotoxicity to the brain is hypothesized to prevent normal maturation of late-growing white matter tracts in the brain, as well as cause damage to white matter tracts that already exist in the brain. A number of research studies have supported this model. For instance, a growth curve analysis study of 34 individuals who were diagnosed with malignant posterior fossa tumors, and were treated with radiation found that IQ continued to decline over time, years after treatment had resolved. In addition, survivors exhibited significant declines in visual motor functioning and visual memory. The study concluded that declines in executive function continued over time to the effect of one standard deviation for every five years (Spiegler, Bouffet, Greenberg, & Mabbott, 2004). A meta-analysis studying the cognitive sequelae in adults diagnosed and treated with medulloblastomas as children concluded that survivors treated with radiotherapy had lower IQ scores than survivors who were treated with other types of treatments (de Ruiter et al., 2012). In addition, higher dosages of radiation have been found to be associated with poorer performance in cognitive tests and lower health-related quality of life (Mulhern, Kepner, Thomas, Armstrong, Friedman, & Kun, 1998; Pogorzala et al., 2010).

Other modes of treatments have been found to be associated with poorer outcomes. For instance, a longitudinal review of adult survivors treated with chemotherapy (but not radiation) concluded that attention, executive functioning, visual processing, and visual-motor domains were negatively affected years after treatment (Anderson & Kunin-Batson, 2009). Although chemotherapy is widely accepted to be less neurotoxic than radiation, it nevertheless has been shown to have subtle effects on cognitive outcomes. Finally, the presence of hydrocephalus (cerebrospinal fluid buildup in the ventricles of the brain), which is frequently associated with

brain tumors, has also been implicated as an additional contributor to poorer cognitive outcomes. When compared to adult survivors without shunts (a device used to treat hydrocephalus by relieving pressure from fluid buildup), individuals with shunts were found to have lower IQs and achievement scores, as well as greater impairments in visual-motor functioning (Hardy, Bonner, Willard, Watral, & Gururangan, 2008).

It is worth nothing, however, that there are several studies that have not found any differences in cognitive ability or social adjustment between survivors that had different types of treatments, although there was adequate power to detect differences should they have existed (Radcliffe et al., 1996; Taylor et al., 2007). In these cases, the ways in which the sample of individuals was selected may play a factor in these results. It is clear that there is still a great deal of complexity in studying the individual contributions of the tumor and treatment-related factors when studying long-term cognitive outcomes.

1.3 Role of Working Memory in Outcomes

Researchers have also attempted to identify the deficits that adult survivors exhibit in basic cognitive mechanisms that may underlie higher-order cognitive deficits and deficits in other domains (Butler & Copeland, 2002; Moyer et al., 2012). Studies suggest, for instance, that executive function may play an important role in mediating and developing mature social skills (Wolfe et al., 2012). To that effect, the Palmer (2008) paper provided a conceptual model based on existing literature of adult survivors treated for medulloblastoma, with an emphasis on the neurodevelopmental impact that brain tumors and their treatments have on cognitive sequelae. In this model, Palmer suggests that both processing speed and attention underlie working memory, and that working memory, in turn, acts as a mediator for both intellectual outcome and academic achievement. Although individual contributions and relationships have been established, the

overall model has not been tested as of yet, and more research is needed to parse out the individual contributions that processing speed, attention, and working memory have on broader and more advanced cognitive domains.

Palmer's model emphasizes the importance of working memory as an important mediator between basic cognitive functions and higher-order ones. Furthermore, review papers on cognitive outcomes in adult survivors of brain tumors point to the domain of working memory as a promising area of study. Studies of working memory in healthy populations have demonstrated the importance of this domain for academic learning and aspects of daily living, like mental math and reading comprehension (Gathercole et al., 2004; McClelland & Cameron, 2011; Perna, Loughan, & Talka, 2012; Wolfe, Madan-Swain, & Kana, 2012).

In the adult survivor population, longitudinal studies involving working memory have shown that a longer time period since diagnosis is associated with continued decline in working memory; as survivors age, their working memory was shown to become progressively worse (Edelstein et al., 2011; Fry & Hale, 2000; de Ruiter et al., 2012; Schatz, Kramer, Ablin, & Matthay, 2000). Even fifteen years past their initial diagnosis, adult survivors continued to express progressive declines of working memory (Edelstein et al., 2011). Studies of core cognitive abilities have shown that IQ is insufficient to explain the basis for decline in cognitive function experienced by survivors; working memory was found to explain more of the variance surrounding cognitive function, indicating that working memory is not just a proxy for IQ. Additionally, improvements in IQ have been found to be products of improvements specifically in processing speed and working memory (Palmer, 2008). Therefore, working memory has been shown to be a necessary component of overall cognitive functioning in survivors.

1.4 Neuroimaging in Survivors

To that end, neuroimaging techniques are being utilized to understand the neurological links to behavior. Neuroimaging has been a valuable tool in testing the theories regarding the mechanisms through which brain tumors and their treatments affect long-term outcomes of survivors. As mentioned above, it has been proposed that the neurotoxicity of radiation and chemotherapy disrupt the normal maturation of late-myelinating white matter. A study of white matter tracts showed that the mean white matter integrity was lower in a group of survivors as compared to a healthy control sample, and that this correlated with slower processing speed, slower motor speed (Aukema et al., 2009), and decreased attention abilities (Reddick, White & Glass, 2003). In addition, individuals who experienced cranio-spinal radiation and also had a shunt were associated with reduced white matter volume, when compared to their healthy siblings. This compromise in white matter was shown to be related to deficits in necessary lower functions, such as processing speed and attention, which have been proposed to mediate working memory, and, eventually, IQ and academic achievement (Reddick et al., 2003). These studies have provided much-needed evidence to support the theories linking the neurobiology of the brain and cognitive function. Neuroimaging in this population, however, is still in its infancy; many structural studies evaluating white matter density and volume have been retrospective in nature and did not have access to whole brain scans. Research on normal appearing white matter volumes have been based on a single transverse slice of the brain at the level of the basal ganglia (Reddick, White & Glass, 2003; Reddick et al., 2005; Shan et al., 2006). There have been a few studies that have examined specific tracts and locations of the brain. For instance, the Zhang et al. (2008) study examined survivors before and after months of treatment, and detected reduced white matter density in the internal capsule, hypothalamus, corpus callosum, and the cuneus of

the occipital lobe. This study, however, did not link these changes with cognitive performance. Aukema et al. (2003), in turn, found that the mean white matter integrity was lower in the patient survivor group in both the right inferior fronto-occipital fasciculus and the genu of the corpus callosum. Processing speed was correlated with white matter integrity in the splenium, as well as the body of the corpus callosum. It should also be noted that many of these studies examined patients who were either still undergoing treatment, or had recently completed treatment. True long term outcome studies are few and far between.

As sparse as the literature has been for structural imaging in survivors of pediatric brain tumors, there has been even less for functional imaging. Three studies so far have utilized functional magnetic resonance imaging (fMRI) to study working memory in survivors of pediatric brain tumors. Two of these studies examined working memory networks in survivors who were at least two years past their initial diagnosis and were on average 12.60 years old. Increased activation in prefrontal regions in child survivors was associated with better psychosocial functioning (Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith, Park, & Compas, 2014). A second study using the same sample of child survivors found that differences in working memory network activations existed between child survivors and healthy controls in bilateral frontal regions and left cingulate regions (Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith & Compas, 2014). It should be emphasized, however, that these studies were conducted on child survivors of brain tumors; functional activity in adult survivors requires further examination. Only one published study so far has examined the functional activity involved in working memory in long-term adult survivors, and found that individuals with better cardiorespiratory fitness also exhibited faster performance on a working memory task (Wolfe et al., 2013). Participants with better cardiorespiratory fitness were found to

show less brain activation during an easier load of the working memory task, but recruited more voxels when given a more difficult task, which the authors concluded was evidence of more efficient neural processing. The study exhibited several limitations: most notably, it did not utilize a control group as a basis for comparison, and thus did not explore the question of how survivors differed from controls in brain activation during the working memory task.

A recent poster studied the differences and similarities in brain activation on a parametric working memory task between 13 survivors and 13 healthy controls, matched by age. In the study, there was no significant difference between accuracy and reaction time on the task. However, imaging analyses indicated that the survivor group exhibited less deactivation in the posterior cingulate gyrus, but no significant positive activation differences. These were hypothesized to be due to the fact that survivors required increased cognitive control when working memory loads increased. Conjunction analyses revealed that both groups showed similar activations in the bilateral paracingulate gyrus, frontal, parietal, insula, and cerebellum. Due to the fact that the study had to exclude participants from the study if they had shunts due to artifact or safety reasons, and individuals with substantial structural differences due to surgery, the study concluded that the imaging sample likely were composed of individuals with less medical and treatment complications. As such, the clinical sample had minimal differences from the healthy control sample. The poster discusses the possibility that including participants who had more extensive medical work/complexities would likely lead to discovering greater differences between survivors and healthy controls (King & Smith, 2013).

1.5 fMRI Performance over Time

A potentially more sensitive measure of the differences between the two groups is in practice effects. Recently, a number of studies have used fMRI to understand how brain activity

changes as a result of repeated exposure and practice to certain tasks. This type of examination is particularly useful, as it provides knowledge regarding the basis of mechanisms essential to learning and memory. Kelly et al. (2005) provides an organizational framework for understanding the varied findings regarding brain changes in fMRI studies regarding the effect of practice. The theory posits that the type of effects that can be expected over time (decreases vs. increases vs. combination of decreases and increases in brain activity) depend on the nature of the task, the specific domain that is being tested and the amount of time that the individuals spend learning the task (hours vs. weeks). A number of studies have utilized working memory tasks and have examined the effects of practice that occur in an imaging time-window and learning phase of less than an hour (Landau et al., 2004; Landau et al., 2007; Garavan, et al., 2000; Jansma, et al., 2001; Sayala et al., 2006). All of these studies have evidenced a pattern of *decreased* activation as a result of practice, mostly in the frontal cortex. More specifically, reductions in activity over time have been found in the precentral sulcus, posterior parietal cortex, dorsolateral prefrontal cortex and anterior/posterior cingulate cortex. The finding that practice on a cognitive task decreases activation in these brain areas are quite robust; this network of brain areas have reliably been shown to exhibit decreases in activation after practice on a task (Chein & Schneider, 2005).

Furthermore, decreases in activity in specifically the dorsolateral prefrontal cortex and cingulate cortex have been hypothesized to be due to the fact that these areas play a "scaffolding-storage" role when an individual first learns a task (Kelly et al., 2005). These areas have been implicated with general attention and top-down attentional control. Decrease in activity in these areas indicate that less attention and control is needed for a task as an individual spends more and more time on that task. The activity in the dorsolateral prefrontal cortex and cingulate cortex

is task-irrelevant; a variety of different types of stimuli (i.e. verbal and nonverbal) have been shown to result in the same findings. In essence, a novel task demands activity in the areas of the brain responsible for attention and control; once the task has been practiced, there is a decreased need for the "scaffolding-storage" framework as the task becomes more automatic, and the brain requires less controlled processing. To test the finding that these changes are due to practice and not to fatigue, Landau et al. (2004) bifurcated the study's participant sample into groups with higher error rates versus lower error rates, and reran the analyses checking for differences in activation between the two groups. As there were no reliable differences between the high error versus low error group, the paper concluded that this robust finding of decreased activations were due to practice effects, rather than fatigue.

Most of the studies regarding fMRI investigations of practice effects have used healthy controls as their population of interest, although some studies have also used populations with schizophrenia and compared their performance to controls (Koch et al., 2010; Schlosser et al., 2009). A population already established to have working memory deficits, patients with schizophrenia were compared to healthy controls to test whether they differed in brain activation patterns as they practiced a task; the clinical population showed "abnormally" increased activation early on in the learning process. As practice continued, the activation patterns normalized and became similar to the levels exhibited by the healthy control sample, demonstrating a difference in the overall learning curve between the two populations (Schlosser et al., 2009). A separate study of the same population separated the clinical group into two groups: successful learners versus less successful learners. The group of less successful learners evidenced hyperactivation early on at the beginning of the task before practice; this hyperactivation decreased after practice. Additionally, the authors used an ANCOVA design to

identify the variables that predicted less successful learners, and concluded that more severe symptomatology was associated with smaller learning-related signal decreases in the areas expected in the group of less successful learners (Koch et al., 2010).

This methodology is particularly relevant, as there are known variables in the brain tumor population that are hypothesized to have greater effects on long-term outcomes (e.g. radiation, chemotherapy and hydrocephalus/shunts). This type of analysis allows an additional way to examine the treatment-related variables and individual differences that separate brain tumor populations into higher and lower cognitively functioning groups, and mediate different patterns of learning responses.

Examining performance over time is useful on more than a theoretical level, as studies examining practice effects lead to an "understanding of how individuals repair and recover" following damage to their brain (Kelly & Garavan, 2005). Presently, there is a paucity of research on this topic in populations with a neurological insult; only one study so far has examined the effects of practice on such a population (Medaglia et al., 2012). This study in particular compared learning deactivation patterns in a group with traumatic brain injuries (TBI) and a healthy control group demonstrated that, as expected, the anterior cingulate and right prefrontal cortices had decreased activations after practice on a working memory task. These findings indicate the waning contribution of the areas involved in cognitive control after the task becomes well-learned and automatized in both groups.

More research is necessary to examine how individuals with a neurological insult compare to healthy individuals with regards to working memory capability and learning ability. Examining the neurobiological correlates to these behaviors will allow for an understanding of the quantitative and/or qualitative ways in which survivors of pediatric brain tumors utilize

working memory and learn tasks over time. Examining time dependent processes allows for a more sensitive and nuanced way of exploring biological differences between survivor and healthy populations, and will lend a hand towards understanding how the brain mediates task-dependent processes when learning a task after a neurological insult. A study of this nature using this population not only contributes evidence for existing theories regarding practice effects, but also assists in identifying the functional networks present in individuals who have experienced a neurological compromise, and the ways in which the brain mediate working memory tasks after such an event.

1.6 Specific Aims and Hypotheses

Four aims were proposed to examine the neurobiological correlates of an fMRI working memory task in adult survivors over time. These aims and a priori hypotheses are detailed below:

1.6.1 Aim 1 – Behavioral differences:

- Both groups were hypothesized to show increased performance (i.e. increased accuracy or decreased reaction time) as a result of time.
- We predicted that the survivor group would be less accurate/slower than controls at the beginning of the task, but would not be significantly different from controls at the end of the task.
- In order to understand treatment-related effects, we chose to bifurcate the survivor group into two tumor pathologies: medulloblastomas and low-grade astrocytomas. Based on the fact that the medulloblastoma tumor type requires a more aggressive treatment regimen than astrocytomas, we predicted that the medulloblastoma group would be less accurate/slower at the beginning of the task than the low-grade astrocytoma group.

1.6.2 Aim 2 – Functional neuroimaging differences:

- We predicted that there would be differential effects of practice in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Specifically, we hypothesized that the survivor group would evidence higher levels of activation in these region at the beginning of the task relative to controls due to their increased need for cognitive control. We also hypothesized a decrease in activation in these regions over time and that activation levels would no longer be significantly different between the two groups at the end of the task. Thus, we expected that the survivor group would show a steeper slope with regards to decreases in activation over time in these two regions.

1.6.3 Aim 3 – Brain behavior relationships

- We hypothesized that percent signal change in the two ROIs would be correlated with accuracy on the task, with higher activity in these regions corresponding to worse performance.

1.6.4 Aim 4 – Conjunction analysis:

- Both groups were hypothesized to recruit the same working memory network (i.e. bilateral fronto-parietal areas) at the end of the task. Specifically, we predicted that the lateral premotor cortex, dorsal cingulate dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal poles, and medial and lateral posterior parietal cortex would be similarly activated.

2 Methods

2.1 Participants

The study was reviewed and approved by the local institutional review board, and all participants provided informed consent. The participant samples consisted of survivor and control groups. Adult survivors were recruited using opt-in letters; these letters were mailed to survivors who had been treated for a pediatric brain tumor through the Children's Healthcare of Atlanta. Letters were also mailed to survivors who had participated in a previous longitudinal study, in which they had participated as children. In all, 676 adult survivors were sent mailings. Of these, 127 survivors responded, while 88 letters were returned. Out of the 127 survivors who expressed interest, 74 total survivors met initial criteria for current study. All participants were over the age of 18 and were at least five years after their initial diagnosis, in order to truly assess effects of long-term survivorship in adult survivors of pediatric brain tumors. Characteristics of the sample (including brain tumor type, location, and treatment regimen) are described below in Table 1. Information about the brain tumor and subsequent treatments were obtained from interviews with the participants/participants' families, as well as a full medical records review from Children's Healthcare of Atlanta. All survivors were screened for safety to enter the MRI machine; of the 74 total eligible survivors, 36 individuals participated in the fMRI portion of the study, while the other 38 survivors had no imaging data due to MRI safety exclusions, disinterest, or were lost to follow-up. Of the 36 participants who were scanned, 20 individuals had good quality imaging data for the entire period of scanning.

The control sample was recruited through Georgia State University's psychology department research pool, as well as fliers and advertisements in the Atlanta, GA community. The control sample was matched for age and gender with the survivor sample, and were

administered the SCID-II (First, Spitzer, Gibbon & Williams, 1997) to ensure that they did not currently or in the past meet criteria for psychological or substance abuse disorders. Additionally, all controls had no history of a neurological illness. These steps were to ensure that the control sample truly was representative of a healthy control sample, and that the imaging results would not be influenced by neurological or psychological disorders. All control participants were screened for safety for the MRI scan. Characteristics of the control sample and survivor sample are listed below in Table 1.

Table 1 Participant characteristics

Control and survivor samples in behavioral and imaging analyses

	Sample for Behavioral Analysis		Sample for Imaging Analysis	
	Controls	Survivors	Controls	Survivors
N (Number of participants)	36	36	20	20
Number of Females (%)	21 (58%)	21 (58%)	11 (55%)	11 (55%)
SES^	2.37 (1.29)	2.40 (1.22)	2.31 (1.20)	2.05 (1.03)
Age at Examination Mean years (SD)	22.63 (3.95)	24.53 (4.76)	22.93 (3.67)	23.1 (4.14)
Mean Years of Education (SD)	14.44 (1.53)	13.92 (2.27)	15.05 (1.7)	14.36 (2.65)
Scaled Score for IQ - WASI (SD)	107.25 (6.98)*	100.6 (17.53)*	111 (8.6)	104 (13.5)
Tumor Type (*n*, %)				
Medulloblastoma		10 (28%)		6 (30%)
Astrocytoma		12 (33%)		7 (35%)
Craniopharyngioma		4 (11%)		2 (10%)
Ganglioma		3 (8%)		3 (15%)
Other		7 (19%)°		2 (10%)§
Tumor Location (*n*, %)				
Posterior Fossa		22 (61%)		14 (70%)
Pituitary		5 (14%)		2 (10%)
Frontal Lobe		2 (6%)		0 (0%)
Temporal Lobe		3 (8%)		2 (10%)
Occipital Lobe		2 (6%)		1 (5%)
Other		2 (25%) Ω		1 (20%) Δ
Age at Diagnosis (SD)		8.39 (4.9)		8.75 (5.33)
Hydrocephalus (*n*, %)		26 (72%)		13 (65%)
Radiation Treatment (*n*, %)		18 (50%)		10 (50%)
Chemotherapy (*n*, %)		14 (39%)		8 (40%)
Endocrine Disorder (*n*, %)		20 (56%)		11 (55%)
Neurosurgery (*n*, %)		36 (100%)		20 (100%)
Total Resection		20 (56%)		15 (75%)
Subtotal Resection		11 (31%)		5 (25%)
Seizure medications		2 (5%)		0 (0%)

Note. Intelligence was measured by the Wechsler Abbreviated Scale of Intelligence (WASI). Seizure medications refers to individuals who were still currently on medications at the type of testing *

indicates variables that were significantly different between controls and survivor groups at $p < .05$. ^SES = Current socioeconomic status, calculated using the Hollingshead Four factor Index of Social Status (Hollingshead, 1975). Family SES was used in instances where the individual reported being financially dependent on their family. °1 Brain Stem Glioma, 1 Oligodenroglioma, 1 Pineoblastoma, 1 Meningioma, 1 Germ Cell Tumor, 1 PNET-Not Otherwise Specified, 1 Mixed Astrocytoma Teratoma [§]1 Oligodendroglioma, 1 PNET-Not Otherwise Specified. [Ω] 1 Tectal Plate, 1 Fronto-parietal Lobe. [Δ] 1 Fronto-parietal Lobe.

2.2 fMRI Task Paradigm: Letter n-back task

The n-back has been used to study working memory capabilities in a variety of clinical samples (Owen et al., 2005; Sweet et al., 2006; Shucard et al., 2011; Palacios et al., 2012). This task has been shown to be reliable and valid in a number of studies, especially when using high load levels (Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Jansma, Ramsey, Coppola, & Kahn, 2000). In addition, the n-back task has been able to differentiate between clinical groups that have already demonstrated working memory dysfunction (Bechtel et al., 2012; Lis et al., 2011; Palacios et al., 2012). The n-back task is frequently used in neuroimaging settings due to the ease with which the experimenter can manipulate the difficulty conditions, and the easy mode of response required of the participant. The task is parametric, and can thus be adjusted for difficulty to determine load-sensitive areas of the brain that are specifically involved in working memory (Jansma et al., 2000).

In this task, a series of letters were presented to the participant, one at a time. When the current stimulus was the same as the one presented n trials before (where n is a pre-specified integer), the participant was instructed to respond by pressing the ‘yes’ button with their index finger on the button box. For any stimulus that was not the same as the one presented n trials before, the participant was instructed to respond by pressing the ‘no’ button with their middle finger on the button box. A higher ‘n’ value represented a higher load, and, subsequently, more difficulty in the task. In contrast, the 0-back task was a task testing basic vigilance; the

participant was instructed to watch for the target letter, press the 'yes' button when that target letter appeared on the screen, and press the 'no' button for any other letter. See Figure 1 for an example of the 0-, 1- and 3-back tasks.

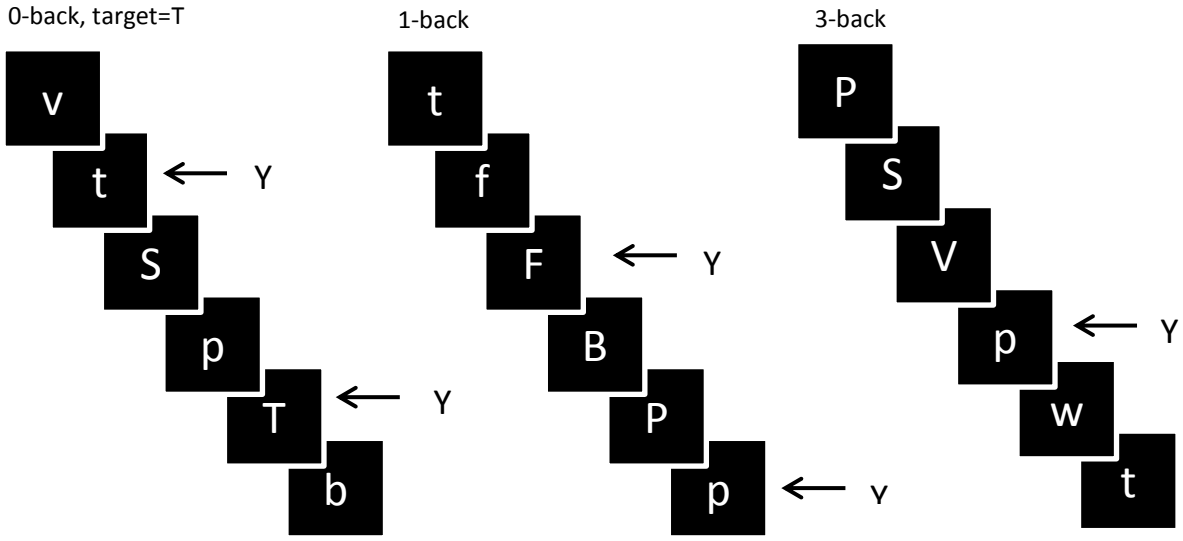

Figure 1 Pictorial representation of the n-back

Arrows represent correct targets

The task was set up as a block design, with five total runs. Each run consisted of a 'fixation' period (where a cross was presented on the screen for 12000 ms, and to allow time for the magnet to homogenize), and five blocks (consisting of the crosshair, 0-, 1-, 2- and 3-back blocks). Blocks were counterbalanced in each run as to minimize order effects. Each block consisted of fifteen letters, where five pre-specified stimuli were the correct targets, and ten were non-targets. Each block was preceded by instructions (which lasted 3000 ms), and each letter stimulus was presented for 500 ms, with an ISI of 2500 ms between each letter presentation. Similarly, the crosshair block consisted of a cross on the screen, which appeared for 500 ms at a time, separated by 2500 ms of blank screen between each cross presentation.

Each run lasted approximately four minutes, with the entire task lasting about twenty minutes (as there were five runs total). Accuracy and reaction times were recorded. As suggested by Haatveit et al. (2010), d' was used as an index of working memory in this task, in order to incorporate the ratios of hits, misses, false alarms, and correct recognition of non-targets into one index of accuracy on the task.

Participants were trained on the n-back task before they entered the scanner. Each participant received a standardized set of instructions, where examples were first supplied on paper; the participant had a chance to work through the task in an untimed setting and were corrected when they made a mistake. Participants were then administered 0- through 3-back conditions on a laptop connected to a button box identical to the one that was used in the scanner. The stimuli on the screen of the laptop were also identical to the screen projected in the scanner in order to increase familiarity with the format of the task. These steps were taken to ensure that the participants understood the instructions of the task (and not to provide extensive practice/training).

The first two runs were averaged and operationalized as the beginning of the task, while the latter two runs were averaged and operationalized as the end of the task. Although this approach does not use data from the third run, it has the advantage of increased reliability and power from averaging two runs together for each time point. The 3-back condition was the only load chosen to be examined for both behavioral and fMRI analysis, as higher loads have been found to be better associated with the construct of working memory (Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Jansma, Ramsey, Coppola, & Kahn, 2000).

2.3 Neuroimaging Parameters

Imaging data was acquired using a 3 T Siemens trio MRI scanner. Participants' head movements were restricted using cushioning around the head, as well as a forehead strap. A total of 620 volumes were collected over twenty minutes. Functional data consisted of gradient-recalled echo-planar-imaging sequence (EPI) sensitive to blood oxygenation level-dependent (BOLD) signals (echo time (TE)=30ms; repetition time (TR)=2130 ms; field of view (FOV)=204 mm and flip angle = 90 degrees). The imaging sequence was acquired as 40 axial slices, with 3.0x3.0x3.0 mm voxel dimensions. 3D T1-weighted images were used for anatomical registration (TR=2250 ms, TE=3.98 ms, flip angle=9 degrees, voxel=1.0x1.0x1.0 mm).

2.4 Neuroimaging Processing steps

Neuroimaging processing consisted of three separate steps: preprocessing, individual level and group-level, which are outlined below in detail.

2.4.1 Preprocessing

fMRI data analysis was conducted using FEAT (fMRI Expert Analysis Tool) Version 6.01, which is part of FSL (fMRIB's Software Library, www.fmrib.ox.ac.uk/fsl).

For individual pre-statistics processing, the following steps were carried out using FEAT: motion correction using MCFLIRT, slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal (brain extraction) using BET, spatial smoothing using a Gaussian kernel of FWHM 5mm, and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0s).

2.4.2 Individual level processing

Registration to high resolution standard space images was carried out using FLIRT. The 0-back was used as the control/comparison task, so as to isolate the areas of the brain that are active for working memory. The 3-back task was operationalized as the working memory task, and [3-back – 0-back] contrasts were utilized for functional imaging analyses.

For each individual, a whole-brain map of z values was created associated with the contrast of interest. Each person's whole-brain map was normalized to a standardized brain template, and each voxel's z value was be tested to see if it was significantly different from zero using the proper threshold. Additionally, all [3-back – 0-back] contrasts were masked by the [3-back – crosshair] contrast; only the voxels that were active in the [3-back – crosshair] contrast were examined to test whether they were also significantly activated for the [3-back – 0-back] contrast. Finally, the individual's motion parameters were entered as regressors.

2.4.3 Group level processing

Statistical processing for contrasts for group analyses was carried out using FLAME (fMRIB's Local Analysis of Mixed Effects) stage 1. Z statistic images were thresholded using clusters determined by $Z>1.96$ and a corrected cluster significance threshold of $p = .05$. Time-series statistical analysis was carried out using FILM with local autocorrelation correction, as fMRI data are auto-correlated temporally (Woolrich, 2001).

FEAT results were interrogated using Featquery. Results of the F test yielded peak and subpeak coordinates within thresholded clusters that were significant for main effects or interactions. Locations (and corresponding Brodmann areas) of all peaks and subpeaks were determined using Talairach Daemon Atlases. In addition, spherical ROIs of 3mm were created around the voxels of interest. Voxels of interest were defined as all peaks in significant clusters,

as well as subpeaks that were in our ROIs (i.e. Brodmann's areas 9 and 46 for the DLPFC and Brodmann's areas 32 for the ACC). Mean % signal change within each spherical mask (of peaks and relevant subpeaks) was calculated using Featquery.

2.5 Statistical analyses

There were four levels of statistical analyses, each corresponding to the four aims of the study. These are detailed in the following sections.

2.5.1 Behavioral analysis

In order to evaluate whether survivors differ from healthy controls in terms of behavioral performance, two different ANOVAs were conducted, using a 2 (group: survivors vs. control) x 2 (time: beginning vs. end) mixed design. Here, group was the between subjects factor, while time was the repeated-measure factor. Assumptions of ANOVA (e.g. normality of data, equal population variances) were tested before proceeding with statistical analyses. Based on the population, it was possible that assumptions of ANOVA may not be met (e.g. nonnormality of data and unequal population variances). The ANOVA test is a robust statistical test across a variety of nonnormal distributions, especially when sample sizes are equal (even if population variances are unequal). As such, controls were selected such that the sample sizes for groups are equal.

Although the main purpose of the study was to examine the practice effects associated with general survivorship of a brain tumor, there remain questions about the contributions that certain treatments have on the performance and overall learning curve on the task. As such, survivors with specific tumor types (i.e. medulloblastomas vs. low-grade astrocytomas) were selected for further analysis. In addition, only the survivors with tumors in their posterior fossa were selected to control for tumor location.

Medically, the two survivor groups differ in treatment regimen, as the medulloblastoma tumor pathology necessitates an aggressive treatment regimen that includes radiation (often to the craniospinal axis, with a boost to the posterior fossa), extensive chemotherapy, as well as surgery. In contrast, low grade astrocytomas are often treated with surgery with no further treatments. In addition, medulloblastoma survivors often have more health-related complications that result from their treatments (e.g. endocrine dysfunction). Due to these factors, the medulloblastoma group was expected to perform worse on the n-back task when compared to the astrocytoma group and the controls.

We chose to investigate neurological risk factors in this way (rather than dividing the group by radiation vs. no radiation) as we believed that the information from these analyses would be more clinically relevant; the results would provide a better understanding of the neuropsychological effects that accompany long-term survivorship in a certain tumor type, the treatment regimen and other resulting complications that frequently follow the tumor pathology. To ensure that the frequency of the treatment-related factors (i.e. radiation treatment, chemotherapy treatment, presence of hormone deficiency, seizure medication or hydrocephalus) was truly different between the two survivor groups, several independent sample t-tests were conducted, using Bonferroni corrections. It should be noted that there were only 9 medulloblastoma survivors and 9 low-grade astrocytoma survivors; as such, effect sizes rather than significance levels were explored.

Post-hoc t-tests tests were performed to identify the directions and magnitudes of main effects and significant interactions. The learning rates in the groups at different loads were identified by examining whether performance changes occurred in any direction from before the

task to after the task; in these cases, the graphs of interactions (with means and standard errors) were utilized to probe the nature of the learning patterns.

2.5.2 Functional neuroimaging differences

Groupwise analyses were conducted with an F test (2 x 2 mixed ANOVA for between subjects effect of group [survivors vs. controls], and within subjects effect of time [beginning vs. end]). Performance on the 3-back was de-meaned within each group and added as a regressor to the general linear model. This model yielded regions of the brain that emerged as significant for main effects of time and group, as well as interactions of group*time after controlling for behavioral performance.

2.5.3 Brain behavior relationships

Mean percent signal change in the areas of interest (i.e. all peaks and subpeaks in ROIs) was correlated with reaction times on the 3-back using bivariate Pearson correlations. As accuracy was entered into the GLM as a covariate, we did not expect significant correlations between percent change in these regions and accuracy.

2.5.4 Conjunction analysis

Mean activations in the survivor group for the [3-back – 0-back] contrast were compared to controls' mean activations for the same contrast; results of the analysis determined whether both groups activated the same regions in the brain. For more details on the model used and the concepts, procedures and assumptions underlying the model, refer to Price and Friston (1997).

3 Results

3.1 Behavioral Analysis: 3-back performance

Two 2 (group: survivors vs. controls) x 2 (time: average of the first two runs versus average of the last two runs) mixed-design ANOVAs were conducted. Two dependent variables were tested: accuracy and reaction time for the 3-back condition. The following tests were conducted to ensure that the dependent variables did not violate ANOVA test assumptions, including Levene's test (for homogeneity of variance), Mauchly's test (assumption of sphericity) and the Kolmogorov-Smirnov test (normality). Histograms of the dependent variables were created for each group to visually examine whether there was significant skew. In addition, for significant omnibus findings, we conducted post-hoc tests using the Bonferroni correction to ensure that family-wise error rates were controlled.

The first mixed ANOVA was conducted to determine whether there was an effect of group or time on the accuracy of the 3-back task. Here, d' was used as an index of accuracy, which incorporated the ratio of hits, false alarms, misses and correct negatives into one metric. This variable did not violate repeated-measures ANOVA assumptions. Overall, there was no significant main effect of group or time, nor was there a significant group by time interaction ($p > .05$).

The second mixed ANOVA evaluated whether there was an effect of group or time on the reaction times on the 3-back task. Histograms of the reaction time distributions for both groups indicated that the skew was within acceptable limits and that means were unlikely to be influenced heavily by very low or very fast reaction times. There was a significant main effect of time on reaction time for correct responses, $F(1, 68) = 8.73$, $p < .05$, partial $\eta^2 = .11$. Contrasts revealed that overall, reaction times at the beginning of the task ($M = 833.34$, $SE = 26.79$) was

higher than reaction times at the end of the task (M = 795.86, SE =23.15, $p < .05$). This indicates that for the 3-back task, when averaging across both groups, participants responded more quickly at the end of the task. There was no significant main effect of group ($p > .05$). In addition, there was a trending interaction effect between time and group $F(1,68) = 3.06$, $p = .085$, partial η^2 =.04. Qualitatively, the graph of the accuracy based on time and group revealed a cross-interaction, where survivors showed a small change in reaction times from the beginning of the task (M = 827.22, SE = 37.89) to the end of the task (M = 811.92, SE = 32.74). Reaction times for the control participants, however, evidenced a larger decrease from the beginning of the task (M = 839.47, SE = 37.89) to the end of the task (M = 779.80, SE = 32.74). These results suggest that survivors do not experience a substantial change in their reaction time as the task progresses in time whereas controls may experience a slightly larger change in reaction time between the beginning and the end of the task. Refer to Figure 2 for a graphical representation of performance on the 3-back over time.

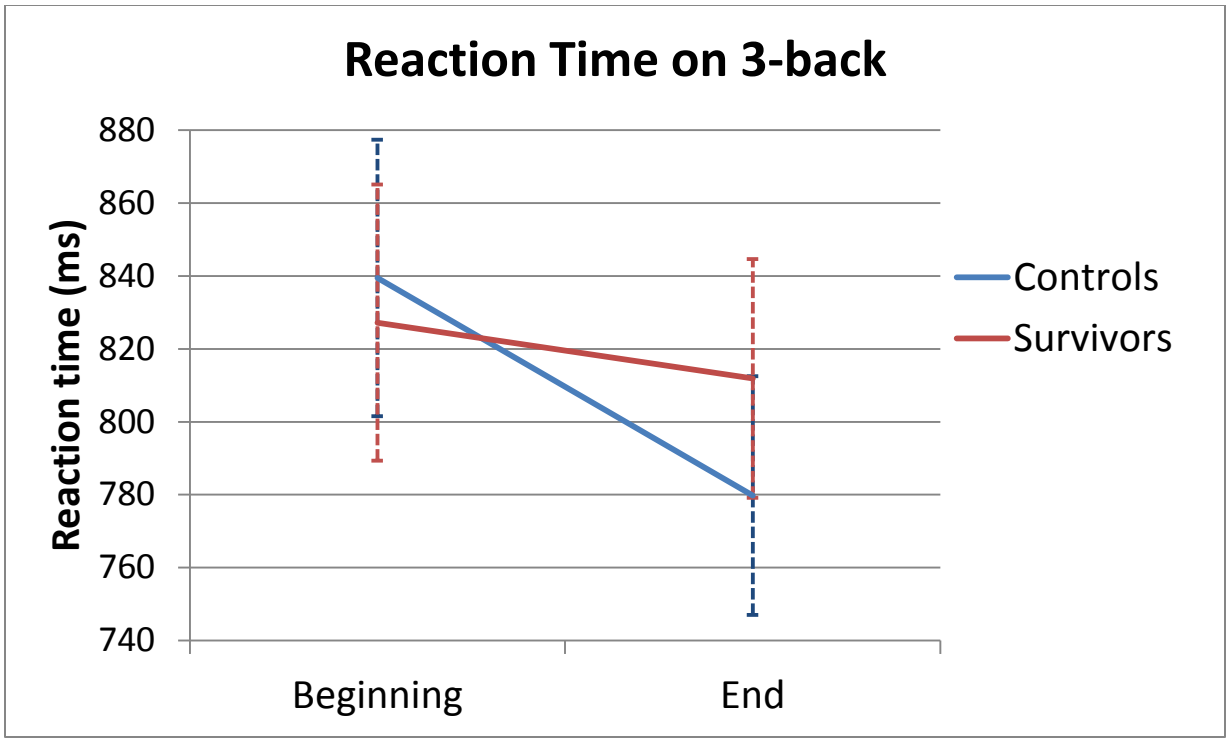

Figure 2 Reaction times on 3-back

3-back performance over time specific to group

3.2 Medulloblastomas vs. low-grade astrocytomas

A separate analysis was conducted to examine the practice effects associated with specific tumor types and the neuropsychological effects that accompany long-term survivorship of a specific tumor type.

First, chi-square tests indicated that the frequency of treatment types did indeed differ between the two groups. These analyses showed that the medulloblastoma survivor group as a whole had more survivors that experienced radiation (χ^2 (1, N = 18) = 10.90), chemotherapy (χ^2 (1, N = 18) = 18.00) and endocrine dysfunction (χ^2 (1, N = 18) = 5.57) relative to the low-grade astrocytoma group ($p < .05$ for each).

For the behavioral analysis of performance on the working memory task, two 3 (group: medulloblastomas vs. low grade astrocytomas vs. controls) x 2 (time: average of the first two runs versus average of the last two runs) mixed-design ANOVAs were conducted, where group was the between-subjects factor and time was the repeated-measures factor. Two dependent variables were tested: accuracy and reaction time.

The first mixed ANOVA was conducted to determine whether there was an effect of group or time on the accuracy of the 3-back task. Here, d' was used as an index of accuracy, which incorporated the ratio of hits, false alarms, misses and correct negatives into one metric. This variable did violate repeated-measures ANOVA assumptions for normality. However, since evidence suggests that the F-statistic is relatively unaffected violations of normality (especially when group sizes are equal), we utilized the F-statistic for the analyses. Overall, there was no significant main effect of group or time, nor was there a significant group by time interaction ($p > .05$).

The second mixed ANOVA evaluated whether there was an effect of group or time on the reaction times on the 3-back task. This variable did not violate repeated-measures ANOVA assumptions. There was a significant main effect of group on reaction times, $F(2, 24) = 4.37$, $p < .05$, partial $\eta^2 = .27$. Contrasts revealed that overall, medulloblastoma survivors ($M = 948.43$, $SE = 63.75$) had higher reaction times than the astrocytoma survivors ($M = 694.86$, $SE = 63.75$). The controls ($M = 751.02$, $SE = 63.75$) and astrocytoma survivor groups were not significantly different with respect to reaction time ($p > .05$). This indicates that for the 3-back task, averaging across the entire task, medulloblastoma survivors took longer to respond correctly compared to low grade astrocytoma survivors and controls. There was no significant main effect of time ($p > .05$).

There was also a trending interaction effect between time and group, $F(2,24) = 3.29$, $p = .055$, partial $\eta^2 = .22$. Qualitative observations of the two-way interaction of group and time revealed that medulloblastoma survivors seemed to experience slight (nonsignificant) increases in reaction times from the beginning of the task ($M = 921.87$, $SE = 66.95$) to the end of the task ($M = 975.00$, $SE = 64.68$). In control participants, however, reaction times evidenced a (nonsignificant) decrease from the beginning of the task (M = 783.91, SE = 66.95) to the end of the task (M = 718.13, SE = 64.68). In contrast, the low grade astrocytoma survivor group did not seem to experience any changes in reaction time performance from the beginning of the task (M = 697.74, SE = 66.95) to the end of the task (M = 691.97, SE = 64.68). These results suggest that differences may indeed exist based on different types of treatment regimens. For a graphical representation of performance on the 3-back over time specific to each group, refer to Figure 3.

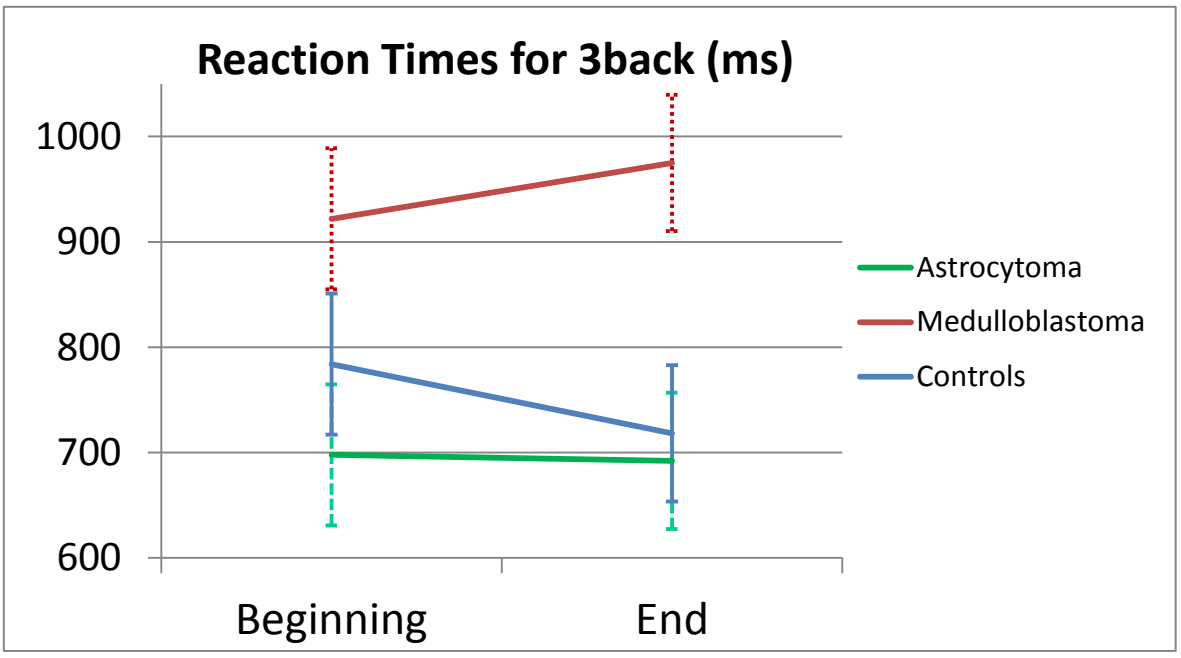

Figure 3 Medulloblastoma vs astrocytoma behavioral performance

Reaction times for medulloblastoma survivors, astrocytoma survivors and controls over time on the 3-back task

It is important to note that although the Shapiro-Wilk's tests for deviations from normality were nonsignificant for each group's reaction time, there was significant skew in the reaction time distribution for the two survivor groups. Given that asymmetrical distributions with tails for high reaction times may skew the mean such that it is not an appropriate central measure of the distribution, we also evaluated the medians of the distributions to examine whether the groups were still significantly different with respect to reaction time. At the beginning of the task, the low grade astrocytoma group (Median = 637.43) was still faster than the medulloblastoma group (Median = 870.90), and the differences in reaction times between the two groups' medians were remarkably similar to the differences between the means. The same was true of the median performance between the two groups at the end of the task, with the low-grade astrocytoma group (Median = 674.27) performing more quickly than the medulloblastoma group (Median = 951.38). Finally, the effects of time within each group showed the same pattern when evaluating medians as well as means. Specifically, control participants still showed an increase in their reaction time from the beginning to the end ($Median_{beg}$ = 804.4, $Median_{end}$ = 711.04), while the medulloblastoma survivors evidenced an increase in their reaction times over time ($Median_{beg}$ = 870.90, $Median_{end}$ = 951.38). In sum, examination of the median reaction times in each group supports the results found by using means as a central measure of the distribution.

Finally, we considered the possibility that differences in reaction times at the beginning of the task may be explaining the differences between the three groups (not the treatment and health related factors). As such, we conducted an ANCOVA to test whether reaction times at the end of the task were significantly different between groups after controlling for the variability in reaction times at the beginning of the task. Results of the ANCOVA indicated that the effect of

group was still significant, $F(2, 23) = 4.482$, $p < .023$, partial $\eta^2 = .28$. Examination of the post-hoc t-tests indicated that the control participants performed significantly better than medulloblastoma survivors at the end of the task after controlling for beginning task performance (Mean difference = 140.07, SE = 46.95). The adjusted reaction time means for each group did indeed show a gradation in performance, with controls performing the fastest ($M_{adjusted}$ = 732.75, SE = 31.86), medulloblastoma survivors performing the slowest ($M_{adjusted}$ = 779.53, SE = 33.91), and the low-grade astrocytoma survivors performing in between the two ($M_{adjusted}$ = 779.53, SE = 33.37).

Based on all of these analyses, it is clear that the medulloblastoma group evidences the longest reaction times and is significantly different from the control group. In contrast, the low-grade astrocytoma survivors do not differ significantly from the control group. As such, it seems that behavioral profiles on a working memory task do indeed differ by tumor type.

3.2.1 3-back behavioral subset analysis

Although the behavioral analysis included the performance of all individuals who were scanned, many of the same individuals had artifact and significant motion that precluded their inclusion in the fMRI analysis. Specifically, 16 survivors were excluded from the fMRI analysis due to excessive motion and artifact (indicating a remaining 20 survivors who were included in the fMRI analysis). The same sets of 2x2 ANOVA analyses were performed for the 20 individuals who were selected for fMRI analysis (n=20) for 3-back performance. For both dependent variables (i.e. accuracy and reaction time), there were no significant main effects or significant interactions. Both control and survivor groups in this subset had similar performances and also did not show improvement in speed or accuracy behavioral performance over time. These results differed from the behavioral results of the entire sample, and warranted an analysis

of the differences in the subsample that were included in the fMRI analysis versus those who were excluded based on artifact and excessive motion.

Previous research has found that discarding data from subjects who exhibit head movement during fMRI may bias sampling away from subjects with lower cognitive ability (Wylie et al., 2012). Based on this research, we tested the differences between the two groups (acceptable fMRI vs. not acceptable fMRI) with independent samples one-tailed t-tests and predicted that the acceptable fMRI group would represent a higher functioning group. For this analysis, we tested whether the groups differed by cognitive ability (verbal IQ, perceptual IQ), adaptive functioning (SIBR), age, and treatment factors (NPS, time between diagnosis and exam).

Time between diagnosis and the exam was significantly different between the two groups, with the acceptable fMRI group closer to their diagnosis date ($M_{years\ between\ diagnosis\ and\ exam}$ = 14.3, SD = 5.39) than the not acceptable fMRI group (M = 18.49, SD = 5.82, t(34) = 2.21, p = .017. In addition, the acceptable fMRI group was significantly younger than the not acceptable fMRI group, t(34) = 2.11, p = .021. There were no significant differences in the degree of neurological risk. One-tailed t-tests were significant for higher verbal IQ in the acceptable fMRI group relative to the not acceptable fMRI group, t(33) = -1.74, p = .046. There were no significant differences for perceptual IQ between the two groups. Finally, on a measure of adaptive and independent living skills, the acceptable fMRI group had significantly higher independent living skills when compared to the not acceptable fMRI group. Means, standard deviations and effect sizes of the two groups are indicated in Table 2. It is worthy of note that although these analyses and significant levels do not survive stringent Bonferroni corrections, an examination of the effect sizes indicate a medium to large effect for the variables that were

significantly different. As such, these analyses suggest that the group that did not exhibit head movement or have artifact and thus were included in the analysis represents a higher functioning group.

Table 2 Differences between acceptable vs acceptable fMRI group

	Acceptable fMRI group n = 20		Not Acceptable fMRI group n = 16			
	Mean	SD	Mean	SD	t (one-tailed)	Cohen's d
Age (years)	23.10	4.14	26.31	5.00	2.11*	-.70
Time between diagnosis and exam (years)	14.3	5.39	18.49	5.82	2.21*	-.75
Degree of neurological risk (NPS score)	5.8	2.1	6.1	2.5	.34	-.13
Verbal IQ (Scaled Score)	102	18	93	13	-1.74*	.57
Performance IQ (Scaled Score)	104	13	100	22	-.73	.22
Adaptive/Independent Living Skills	110	28	88	25	-2.46*	.83

Note. * indicates significant of $p < .05$

3.3 3-back BOLD signal changes and signal patterns

An F-contrast was conducted to identify the main effects of group and time, as well as the interactions between group and practice in the [3back - 0back] contrast after using accuracy as a covariate. The regions significantly affected by practice were localized to the left hemisphere: the left prefrontal cortex (BA 8) and left motor planning regions (BA 6) were involved. For a detailed list of peaks and subpeaks and their corresponding locations, refer to Table 3. For a pictorial representation of the clusters that were significant for the effect of time, refer to Figure 4. In addition, we evaluated the % change value in the peak cluster (i.e. the left middle frontal gyrus) for each individual at the beginning and end of the task. Both the survivor group and control group evidenced remarkably similar levels of activations at the beginning and end of the task. For both groups, this region was significantly activated at the beginning of the task.

Conversely, at the end of the task, this region was no longer significantly activated, indicating a decreased recruitment of this region as the task progressed.

Table 3 Peak and subpeak clusters for the main effect of practice

Region (BA)	Z-value	Coordinates (X, Y, Z)
Left middle frontal gyrus	6.72	-46, 12, 48
Left middle frontal gyrus (6)	5.67	-42, 10, 54
Left superior frontal gyrus (6)	4.45	-4, 28, 62
Left middle frontal gyrus (8)	4.28	-34, 20, 54
Left middle frontal gyrus (8)	4.26	-34, 20, 58
Left middle frontal gyrus (6)	4.07	-14, 20, 62

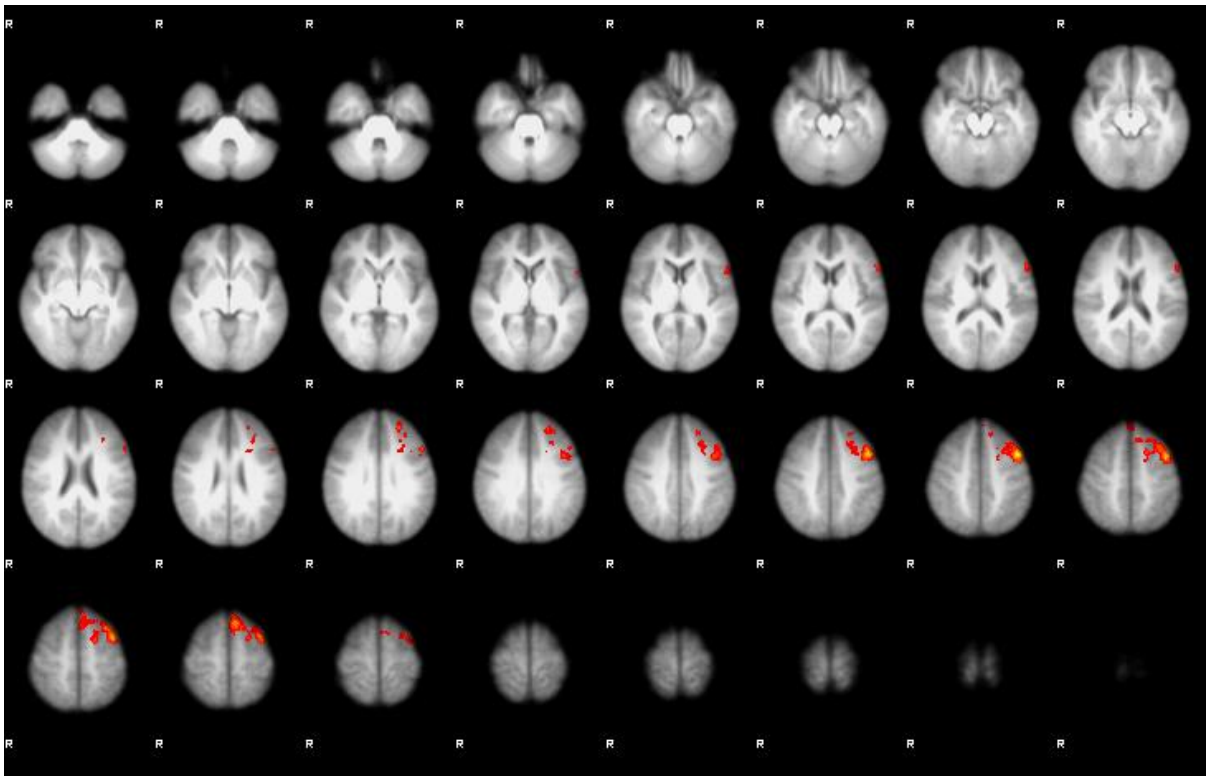

Figure 4 Brain regions significant for the main effect of practice
[3-back – 0-back] contrast

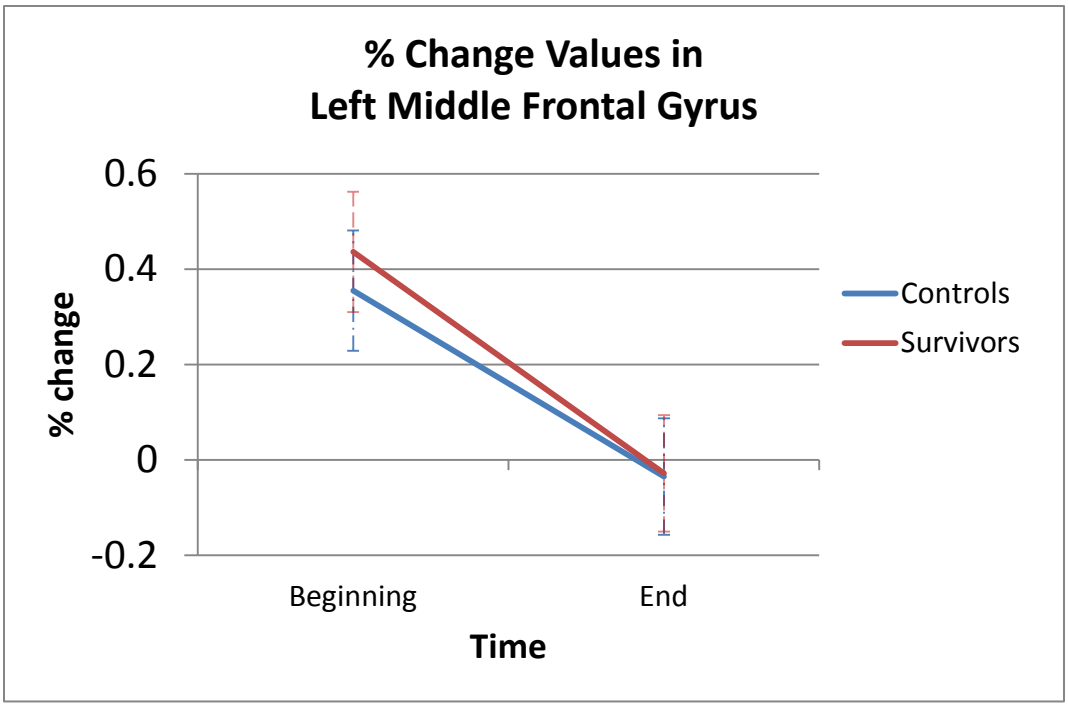

Figure 5 Percent signal change in left middle frontal gyrus

Percent signal change for survivors and controls in a region significant for the main effect of practice

Group main effects were present and analyzed with respect to directionality with further t-tests to assess the regions of the brain where activations were higher in survivors or higher in controls. Overall, the survivor group had greater levels of recruitment than controls in the following regions: right and left precuneus (BA 7, 19), left and right prefrontal cortex (BA 8, 9, 10, 46), and left motor planning region (BA 6). Significant clusters can be seen in Figure 6. There were also several brain regions where controls had higher levels of activity when compared to survivors, including: the left precuneus, left inferior temporal gyrus and left temporal occipital fusiform cortex. Locations of the peak and subpeak MNI coordinates in the clusters significant for the main effect of group are listed in Table 4.

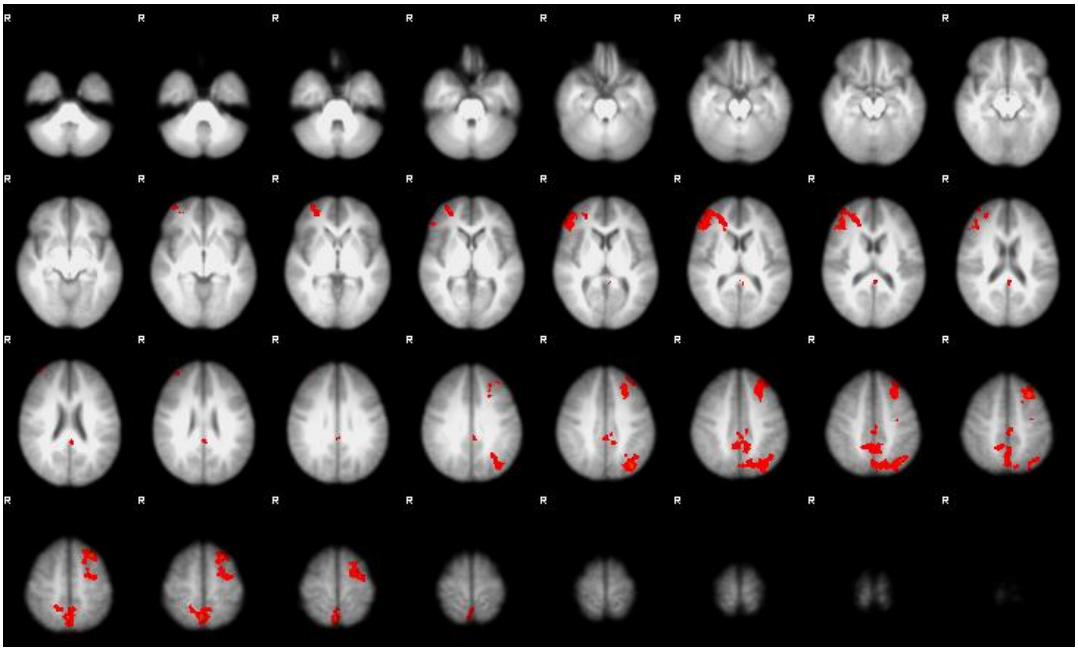

Figure 6 Regions where activations were higher in survivors than controls

[3-back – 0-back] contrast

Table 4 Peak and subpeaks for regions significant for the main effect of group

Locations and MNI coordinates for peak and subpeak clusters for the main effect of group, [3-back – 0-back] contrast

Survivors > Controls			Controls > Survivors		
Region (BA)	Z-value	Coordinates (X, Y, Z)	Region (BA)	Z-value	Coordinates (X, Y, Z)
L precuneus (19)	4.94	-34, -72, 40	L precuneus	4.47	-20, -54, 8
L precuneus (19)	4.81	-34, -76, 40	L temporal occipital fusiform cortex (37)	4.33	-34, -48, -12
L precuneus (19)	4.67	-36, -66, 48	L inferior temporal gyrus	4.04	-22, -66, -10
L precuneus (7)	4.47	-2, -72, 50			
L middle frontal gyrus (8)	5.54	-26, 22, 58			
L superior frontal gyrus (8)	5.52	-30, 24, 52			
L middle frontal gyrus (6)	4.58	-30, -4, 64			
L middle frontal gyrus (8)	4.43	-26, 28, 42			
L middle frontal gyrus (6)	4.33	-20, -2, 64			
L middle frontal gyrus (9)	4.31	-36, 38, 40			
R precuneus	5.51	4, -60, 60			
R precuneous	5.29	4, -66, 64			
R middle frontal gyrus (10)	4.19	40, 54, 16			
R middle frontal gyrus	4.17	46, 50, 10			
R inferior frontal gyrus (46)	4.02	52, 36, 8			
R superior frontal gyrus (10)	3.8	30, 50, 2			
R middle frontal gyrus (46)	3.7	42, 36 ,14			

Percent signal change values of the [3-back – 0-back] contrast were also calculated in peak coordinates and subpeaks in the regions of interest. These values were then tested with one-sample t-tests to identify whether the peak was significantly activated. For detailed means and standard deviations and indications of activations, refer to Table 5. These analyses indicated that survivors activated regions that were not significantly activated by controls (e.g. right precuneous, left and right middle frontal gyri). In addition, survivors activated regions that

controls significantly activated, but to higher degrees (e.g. left middle frontal gyrus, right middle frontal gyrus, left superior frontal gyrus). Significantly, regions in the dorsolateral prefrontal cortex were recruited to a higher extent in survivors relative to controls, even when controlling for behavioral performance.

Table 5 Percent signal change in regions significant for main effect of time

Percent signal change levels in peaks and subpeaks significant in the main effect of time, [3-back – 0-back] contrast

	Control (n = 20)		Survivor (n = 20)	
Location	Beginning Mean (SD)	End Mean (SD)	Beginning Mean (SD)	End Mean (SD)
Left Middle Frontal Gyrus	.36 (.51) †	-.03 (.48)	.44 (.61) †	-.03 (.60)
Right Precuneous	.13 (.49)	.20 (.47)	.52 (.43) †	.61 (.65) †
Left superior frontal gyrus	.45 (.92) †	.02 (.47)	.73 (1.04) †	.42 (.56) †
Left Middle frontal gyrus (BA 9 subpeak)	-.08 (.77)	.02 (.67)	.45 (.96) †	.43 (1.27)
Right Middle frontal gyrus	.30 (.55) †	.22 (.48)	.42 (.51) †	.36 (.76) †
Right Inferior frontal gyrus (BA 46 subpeak)	-.12 (.35)	-.11 (.33)	.14 (.51)	.16 (.41)
Right Middle frontal gyrus (BA 46 subpeak)	.00 (.22)	.10 (.43)	.38 (.37) †	.24 (.42) †

Note. † indicates significant activation above zero (one-sample t-test)

No areas were implicated in the group by practice interaction, indicating that there are no differences in activation slopes between the control and survivor groups.

3.4 Correlations

Bivariate correlations were tested between behavioral performance and percent signal change values in peak and subpeak spheres. The activation levels in these specific regions were not significantly associated with reaction time ($p > .05$).

Although the level of activations in the peak and subpeak sphere clusters did not correlate with accuracy, we were interested to see whether other regions in the brain would be significantly associated with performance. As such, accuracy on the 3-back task was demeaned and entered as a regressor in the GLM to identify regions in which activations and accuracy was significantly correlated in survivors (n = 20). Interestingly, at the beginning of the task, there were no regions of the brain that were positively correlated with accuracy (that is, where increased activation corresponded with better performance. However, there were a number of anterior and posterior regions where activity level was *negatively* correlated with performance. An examination of the cluster locations indicated that the DLPFC is included in these regions; higher levels of activity in regions of the DLPFC at the beginning of the task thus corresponded with poorer performance on the task. The same analysis was run for the functional activity at the end of the task. Results showed that a wider network was negatively associated with accuracy at the end of the task. Brain areas that were negatively correlated with accuracy at the beginning and end of the task are represented in Figure 7A and 7B, respectively.

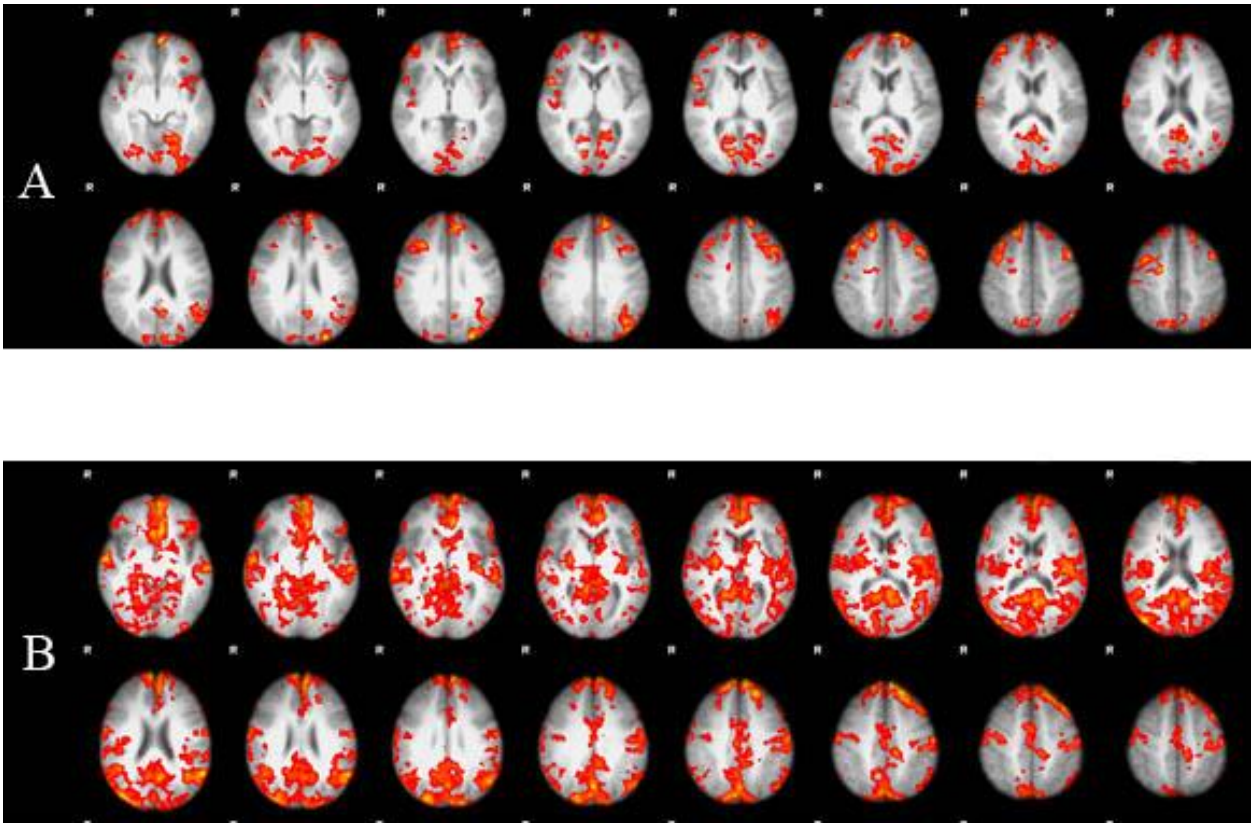

Figure 7 Conjunction regions correlated with accuracy

A. Brain regions in survivors that are negatively correlated with accuracy at the beginning of the task for the [3-back – 0-back] contrast. B. Brain regions in survivors that are negatively correlated with accuracy at the end of the task for the [3-back – 0-back] contrast.

3.5 Conjunction Analyses

Conjunction analyses were conducted to test which areas of the brain were activated to similar degrees between the two groups. At the end of the task, similar degrees of activation between the two groups were identified in the bilateral fronto-parietal consistent with the working memory network. Peak coordinates that have been identified in a meta-analysis of functional neuroimaging studies of the n-back (Owen et al., 2005) were also activated in the conjunction analysis of the present study. These regions included the lateral premotor cortex, medial premotor cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, frontal pole, medial posterior parietal cortex, inferior parietal lobule, and the cerebellum. Consistent

with our hypothesis, both groups appear to be recruiting the same fronto-parietal working memory network to complete the task. Refer to Figure 8 to view the brain regions that were similarly activated between both survivor and control groups.

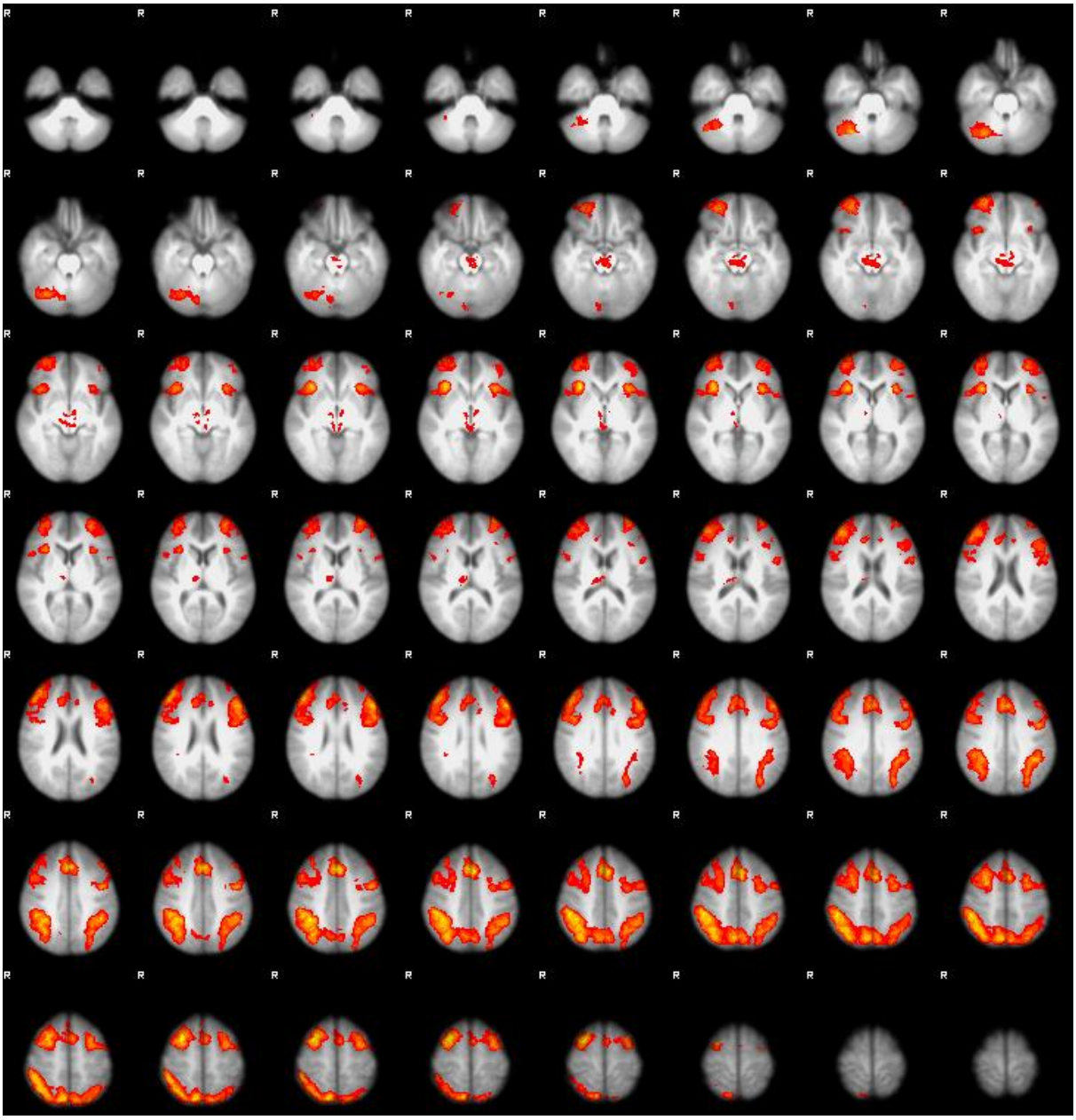

Figure 8 Conjunction analysis for survivor and control groups

Conjunction analysis for [3-back – 0-back] contrast at the end of the task

4 Discussion

Four main results emerged from this study. (a) Behaviorally, there were trending differences in the effects of practice between the survivor group and control group. (b) Survivors and controls largely activated the same bilateral fronto-parietal working memory networks throughout the entirety of the task. (c) There were qualitative and quantitative differences in the brain regions that survivors recruited relative to controls. Specifically, there were bilateral regions in the prefrontal and parietal cortices (including the dorsolateral prefrontal cortex) that were activated at higher levels in survivors even when controlling for accuracy. (d) Effects of practice were present in left prefrontal regions, with both survivor and control groups showing decreases in activation as the task progressed.

These results and their implications will be discussed in detail in the following sections and organized with respect to the original aims and hypotheses.

4.1 Aim 1: Behavioral differences

Consistent with the original hypotheses, an overall main effect of practice was found, with improvements in performance occurring over time. In addition, there was a trending interaction for group by practice, suggesting that survivors and controls evidence different patterns of performance change with time. This finding suggests that differences in behavioral measures of working memory may exist between groups with respect to cognitive skill learning. Significantly, there was no main effect of group overall, suggesting that subtle differences in skill learning between groups may be masked when analyzing performances that are collapsed across the entire time frame of a cognitive measure.

A corollary of the first aim involved determining whether differences in treatment and various other complex health factors would result in different behavioral profiles on a working

memory task over time. Indeed, there were clear overall group differences. When comparing medulloblastoma survivors and low grade astrocytoma survivors, medulloblastoma survivors (who underwent radiation, chemotherapy and also had endocrine dysfunction) performed worse than low grade astrocytoma survivors both at the beginning and at the end of the task. In contrast, the behavioral performance of low grade astrocytoma survivors (who only underwent neurosurgery for brain tumor treatment) did not differ from the performance of controls. These findings suggest that behavioral profiles on working memory tasks are indeed related to specific tumor types (associated with different treatments and comorbid health factors).

4.2 Aim 2: Functional neuroimaging differences

It is important to note that of the 36 total survivors who were part of the behavioral analysis in Aim 1, only 20 of these individuals had good quality imaging data. Results showed that the subset of survivors with good quality imaging data were on average younger adults, had higher verbal intelligence, and increased adaptive functioning when compared to those who were excluded from the imaging analysis based on motion and artifact. These results present the possibility that as technology and medicine advances such that a broader array of survivors are able to be scanned, larger effect sizes may result when comparing the functional activation between survivors and controls. Even so, it is important to stress that the neuroimaging findings of the current study may only apply to the survivors who are functioning more highly.

4.2.1 Effects of Practice

Although the changes in functional activation over time were hypothesized to be different between the survivor and control group select regions of interest, no regions emerged as significant for a group by time interaction. Instead, there were a number of areas that were significant for the main effect of practice after controlling for performance on the task.

Significant clusters were localized to the left prefrontal cortex in the middle and superior temporal gyri. Analysis of percent signal change activation in the peak voxel that emerged as significant in the [3-back – 0-back] contrast indicated that both survivor and control groups activated these regions similarly at the beginning of the task. In contrast, at the end of the task, there was no longer any significant activation in the region in either group. This pattern corresponds to a decrease in activity in left prefrontal regions as the task progresses, even after controlling for performance.

It was hypothesized that changes in the activity in the dorsolateral prefrontal cortex and the anterior cingulate cortex from the beginning to the end of the task would differ between the survivor and control groups. This was due to the proposed roles of these regions; the DLPFC and ACC have been implicated as areas essential for top-down attentional control. This attentional control is particularly necessary when the task is novel and requires more cognitive resources. Once the task has been practiced for a period of time and becomes less novel, there is decreased need for effortful attentional processing. As such, it was expected that the activations in these two regions would decline over time and that the level to which the activations would decrease over time would differ by group.

Based on the results of the current study, the DLPFC continues to be recruited at the beginning and end of a twenty minute task, with no evidence of significant decline over time in either group. These findings suggest that the cognitive task used as an indicator of working memory in the present study (i.e. the 3-back task) may be too difficult due to its high load. Given the persistent activation at the end of the task, it is likely that continued top-down control and attention is required for the task. Indeed, a number of research studies have indicated that the DLPFC is recruited in a load-dependent manner, with higher working memory loads

corresponding to higher levels of activity in this region (Linden, 2007). Previous practice effects studies comparing brain activations in a neurologically compromised group versus a neurologically healthy control group have used lower loads of the n-back tasks (Medaglia et al., 2012). Additionally, the aforementioned study reported significant effects of practice in the DLPFC for the 1-back task but not the 2-back task, which had trending levels of significance for practice effects. As such, it is possible that the increased load and difficulty of the 3-back task demands the same level of cognitive control from the beginning to the end in both groups and thus did not emerge as an area of significance for the main effect of practice.

Prominent theories of the working memory network suggest that the DLPFC is involved in the selection of a motor response, rather than for the maintenance and rehearsal of information (Pochon et al., 2001; Curtis & D'Esposito, 2003). Event-related designs of working memory tasks that explore time-dependent processes indicate that areas that are posterior to the dorsolateral prefrontal cortex (e.g. posterior parietal and premotor regions) are involved in the maintenance and rehearsal of items to be remembered in the short-term. Internal representations of the items are thought to be 'held' and maintained in these regions. Research also supports that these parietal and premotor areas are activated at the first level of working memory processing when there is little demand for executive processing; it is only when the load or complexity of the task is increased that the DLPFC is recruited (Pochon et al., 2001). A model by Curtis and D'Esposito (2003) suggests that the DLPFC is involved in directing and supervising the cognitive processes occurring in the posterior parietal and premotor regions in order to selectively attend to the relevant stimuli in the environment.

Indeed, these same premotor regions in the middle and superior frontal gyrus were significant for the effects of practice in this study. That is, participants were able to perform at

the same level at the end of the task without significant recruitment of these regions. Clearly, although the working memory task itself continued to require significant activation in the DLPFC at the end due to its difficulty and need for continued scaffolding support, the areas under the direct supervision of the DLPFC evidenced signs of decreased activation even over the course of a twenty minute task. Notably, Curtis and D'Esposito (2003) posit that Broca's area is also an area under the supervisory control of the DLPFC; in a verbal identity n-back task, subvocal strategies may be implemented to help with the task. Given that Broca's area is thought to also be under the top-down control of the DLPFC, we expected that this area may also evidence signs of decreased activation over time. Indeed, although Broca's area did not emerge as a subpeak when analyzing the significant clusters, the thresholded cluster of the main effect of practice overlapped with Brodmann's area 44. This overlap suggests that Broca's area is indeed an area significant for the effect of practice. Overall, this provides support for the model that areas under top-down control by the DLPFC are becoming more practiced, even though the difficulty of the working memory task may demand continued recruitment of the DLPFC itself.

It is also notable that the percent change in bold signal in peak clusters for the areas significant for practice indicated a *decrease* in activation with time. There was no evidence for increased activation in these clusters with time. Decreases in BOLD signal compounded with lack of behavioral change suggest that these are truly effects of practice, rather than fatigue. Fatigue would be the case if BOLD signal increase had been accompanied by poorer performance. Consistent with previous studies on short-term practice effects on cognitive tasks (Kelly & Garavan, 2005), our results indicated *only* decreases in activation, even when there was no significant change in accuracy (partial η^2 =.04) or reaction time (partial η^2 =.03). These

results suggest that less activation in these regions is required to complete these tasks as they become more learned and practiced.

4.2.2 Effects of Group

There were also a number of regions that were significant for the main effect of group (averaging across time). Clusters in the bilateral prefrontal and parietal cortices were activated to higher degrees in the survivor group relative to the control group. Examination of the percent signal change values of these clusters indicated that these differences were both qualitative and quantitative in nature. Qualitative differences existed in brain regions where survivors were significantly activating while controls were not significantly activating those regions. Quantitative differences existed in regions where both controls and survivors significantly activated regions but the survivor group had significantly *higher* activations when compared to controls. These findings indicate that the survivor group on average requires a wider network than controls to perform at the same rate. In addition, the survivor group overall require higher levels of activation in the fronto-parietal working memory network to perform similarly to controls. Significantly, clusters within the DLPFC had higher BOLD signal activity in survivors relative to controls for the entirety of the task, suggesting that the survivor group requires more top-down processing and attentional control to perform at the same level as controls behaviorally.

Interestingly, the pattern of qualitative and quantitative differences between the two groups reflects developmental changes that occur in the brain. Cross-sectional research evaluating working memory activations in children, adolescents and adults broadly show that adults use the ‘tightest’ networks of all three groups and have the most localized recruitment of necessary regions for a task (Scherf, Sweeney & Luna, 2006). The study concluded that children

seem to rely on regions that play a much smaller role in the adult network, suggesting that a biological process of efficiency in brain networks occurs with age. As the brain tumor and all associated treatments are occurring in survivors when they are children, these critical biological and developmental processes are being disrupted. As such, even when survivors have grown into adulthood, their functional activity still differs from the activity of a neurologically healthy adult of the same age.

4.2.3 Complementary Roles of Anterior Cingulate and Prefrontal Cortices

The initial hypothesis for the imaging portion of the study also included the anterior cingulate cortex as an area that would emerge as part of the network necessary for both groups. An examination of the thresholded clusters in the conjunction analysis did indeed show that the most anterior portion of the ACC was activated similarly in both groups. However, the ACC did not emerge as significant for main effects of group or practice. A study by Milham et al. (2002) indicates that the ACC and the DLPFC may play complementary roles in top-down attentional processes. This study examined the patterns of activations in these two regions as time passed and found that activity in the DLPFC increased just as activity in the ACC waned and dropped sharply. Specifically, the ACC showed a significant amount of activation within the first two cycles of the task (corresponding to the first minute of the task), whereas BOLD levels in the DLPFC rose and remained high over the course of the entire task. Given that the current study conceptualized the ‘beginning’ of the task as the average of the first eight minutes, it remains a possibility that any significant activity in the ACC was masked by collapsing the activity over the entire eight minutes, far after the activity in the ACC has waned.

4.3 Aim 3 – Brain behavior relationships

Percent signal change in peak clusters were not correlated to reaction time, as previously hypothesized. It is possible that the block design of the current study may have made it difficult to identify specific brain and behavior relationships.

A post-hoc test was thus conducted to examine whether any brain regions were significantly associated with accuracy on the task. Results showed that higher levels of activation in anterior regions (including the DLPFC) and certain posterior regions were associated with poorer performance at the beginning of the task. Results also showed that these negative correlations between activations and performance were present in *more* areas at the end of the task. A possible explanation for this finding is that the individuals who fail to show effects of practice (and thus remain significantly activated) are also the ones who are performing more poorly at the end of the task. In contrast, the survivors who do exhibit decreases in their levels of activations decline from the beginning to the end of the task are the ones who perform better at the end of the task. It is important to note that this analysis was not part of the original planned methodology and thus should be interpreted with caution. In addition, as only twenty people were part of this analysis, it is possible that these findings may be driven by one or two poor performers. As such, brain behavior relationships and possible differences in these relationships based on the level of practice that one has had with the task remain an area for further exploration in future studies.

4.4 Aim 4 – Conjunction Analysis

The final aim of the study hypothesized that a conjunction analysis of the functional activations in both survivors and controls would implicate regions consistent with the fronto-parietal network for working memory. Consistent with this prediction and previous meta-

analyses of neuroimaging studies identifying regions that are most commonly activated across different n-back studies, both the survivor and control groups similarly activated the lateral premotor peak, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, frontal pole, medial posterior parietal lobe, inferior parietal lobule and the thalamus. These results indicate that both groups were activating and using the same bilateral fronto-parietal networks to support their performance on a working memory task.

4.5 Limitations and Strengths

Limitations of this study include selection bias. Both survivor and control groups were self-selected. In the case of our survivor group, it is possible that our sample was biased towards higher functioning individuals who have the time to devote to the study and the means to transport themselves to the study site. It is also possible that the sample was comprised mainly of survivors who had a number of cognitive impairments that they wished to be documented. Another limitation related to the sample is that the group was very heterogeneous with regard to tumor type, tumor location, adjuvant treatments and health related factors. However, steps were taken to minimize the concern that all of the findings were being driven by poor performers. Firstly, performance was entered as a covariate into the imaging model, indicating that each of the results presented accounted for the variability in accuracy on the task. Secondly, the within-effects approach in the model demands that changes due to practice are calculated *within* the context of that individual's specific medical history. Another limitation was the nature of the imaging model; as FSL does not have a mixed ANOVA model built into the program, each person's imaging data for the 'beginning' and 'end' were entered as two separate dependent variable inputs into the model. As such, a fixed effects design was utilized, indicating that the results from this study are not generalizable to the general population and are thus limited to the

current sample. Finally, the methodology of the study utilized the [3-back – 0-back] contrast to generate regions of the brain associated with working memory. However, it should be noted that there are ambiguities regarding the vigilance contrast condition. It is entirely possible that changes over time may be reflective of changes in vigilance (0-back) rather than working memory changes (3-back). As such, it will be important to examine the 0-back condition as compared to a true baseline to state with more certainty that changes over time stated by this study are reflective of changes due to a working memory task.

However, there are also a number of strengths to the study. Specifically, this research study used theory-driven aims and hypotheses and only probed subpeaks that emerged as significant in the regions of analyses. There are also very few studies that evaluate functional activity in survivors of brain tumors, especially in survivors who are between one to two decades past their initial diagnosis. Of the few existing functional neuroimaging studies of pediatric brain tumor survivors, one did not employ a control group (Wolfe et al., 2013) and the others examined survivors when they were children (Robinson et al., 2014). In addition, this study is the first of its kind to examine the effects of practice in a pediatric brain tumor survivor sample. Finally, by using performance measures as covariates in the analyses, we can state with more certainty that more prefrontal and parietal regions of the brain are utilized to higher degrees in the survivor group in order to perform at the same rate as controls. The finding that these neurobiological differences persist years after initial diagnosis speaks to the long lasting effects that occur due to a neurological insult during key developmental years. Finally, this type of analysis examined a process that is usually disregarded in neuropsychological tests – cognitive tests typically last on the order of minutes (if not seconds), and practice effects are typically treated as confounding variables that ‘muddy’ up the data. Studying this very process, however,

is clearly a valuable enterprise, as examining practice effects provides 1) important theoretical contributions regarding the bases of how brains repair and recover following damage, and 2) clinically meaningful information with regards to how continued practice on a task affects the performance in a clinical population.

4.6 Conclusions and Future Directions

In summary, this study suggests that the DLPFC is a central point of difference between survivor and control groups; this area is activated at a higher level in the survivor group due to survivors' need for increased attentional control and top-down processing. This study also indicates that regions under top-down control of the DLPFC (i.e. premotor cortex, Broca's area) show effects of practice even without signs of behavioral improvement. Based on this framework, it will be important to examine lower loads in future studies (i.e. 2-back or 1-back) to test whether DLPFC activity truly decreases as working memory task becomes less novel and more practiced

Another direction for future studies may involve employing an event-related design to investigate each stage involved in working memory (e.g. encoding, maintenance, rehearsal, preparation for motor response). Event-related designs may also elucidate whether certain stages of working memory are particularly affected in survivors of pediatric brain tumors. In addition, specific brain-behavior relationships may be easier to investigate in event-related designs.

Finally, the behavioral portion of the current study identified different cognitive profiles for different tumor types, with medulloblastoma survivors performing the worst out of all three groups throughout the entire task. The neuroimaging analysis lacked the power to explore questions regarding how tumor type, tumor location and treatment related factors affect functional activity in the brain. In addition, the study showed that lower functioning survivor

groups may be systematically precluded from neuroimaging analyses due to the presence of artifact and significant motion. With increased recruitment and advances in technology and medicine, it may be possible in the future to explore how specific neurological risk factors are associated with different outcomes.

References

Anderson, C. A., Wilkening, G. N., Filley, C. M., Reardon, M. S., & Kleinschmidt-DeMasters, B. K. (1997). Neurobehavioral outcome in pediatric craniopharyngioma. *Pediatric Neurosurgery, 26,* 255-260.

Anderson, F. S., & Kunin-Batson, A. S. (2009). Neurocognitive late effects of chemotherapy in children: the past 10 years of research on brain structure and function. *Pediatric Blood and Cancer, 52*(2), 159-164. doi: 10.1002/pbc.21700

Aukema, E. J., Caan, M. W., Oudhuis, N., Majoie, C. B., Vos, F. M., Reneman, L., . . . Schouten-van Meeteren, A. Y. (2009). White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. *International Journal of Radiation Oncology, 74*(3), 837-843. doi: 10.1016/j.ijrobp.2008.08.060

Bechtel, N., Kobel, M., Penner, I. K., Specht, K., Klarhofer, M., Scheffler, K., Opwis, K., Schmitt-Mechelke, T., Capone, A., & Weber, P. (2012). Attention-deficit/hyperactivity disorder in childhood epilepsy: A neuropsychological and functional imaging study. *Epilepsia, 53*(2), 325-333.

Butler, R. W., & Copeland, D. R. (2002). Attentional processes and their remediation in children treated for cancer: A literature review and the development of a therapeutic approach. *Journal of the International Neuropsychological Society, 8,* 115-124. doi: 10.1017.S1355617701020112

Central Brain Tumor Registry of the United States. (2012). *Primary brain and central nervous system tumors diagnosed in the United States in 2004-2008.* Chicago, IL: Author

Chein, J. M., & Schneider, W. (2005). Neuroimaging studies of practice-related change: fMRI and meta-analytic evidence of a domain-general control network for learning. *Cognitive Brain Research, 25*(3), 607-623. doi: 10.1016/j.cogbrainres.2005.08.013

Curtis, C. E., D'Esposito, E. (2003). Persistent activity in the prefrontal cortex during working memory. *TRENDS in Cognitive Sciences, 7*(9), 415-423.

de Ruiter, M. A., van Mourik, R., Schouten-van Meeteren, A. Y., Grootenhuis, M. A., & Oosterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. *Developmental Medicine & Child Neurology*, *55*(5), 408-417. doi: 10.1111/dmcn.12020

Edelstein, K., Spiegler, B. J., Fung, S., Panzarella, T., Mabbott, D. J., Jewitt, N., . . . Hodgson, D. C. (2011). Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. *Neuro-Oncology, 13*(5), 536-545. doi: 10.1093/neuonc/nor015

First, M.B., Gibbon M, Spitzer R.L., Williams, J.W., & Benjamin L.S.: Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc., 1997.

Fry, A. F., & Hale, S. (2000). Relationships among processing speed, working memory, and fluid intelligence. *Biological Psychology, 54*, 1-34.

Garavan, H., Kelley, D., Rosen, A., Rao, S. M., & Stein, E. A. (2000). Practice-related functional activation changes in a working memory task. *Microscopy Research and Technique, 51*, 54-63.

Gathercole, S. E., & Alloway, T. P. (2004). Working memory and classroom learning. *Professional Association for Teachers of Students with Specific Learning Difficulties, 17*, 2-12.

Gragert, M. N., & Ris, M. D. (2011). Neuropsychological late effects and rehabilitation following pediatric brain tumor. *Journal of Pediatric Rehabilitation Medicine, 4*(1), 47-58. doi: 10.3233/PRM-2011-0153

Haatveit, B. C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., & Andreassen, O. A. (2010). The validity of d prime as a working memory index: Results from the "Bergen n-back task". *Journal of Clinical and Experimental Neuropsychology, 32*(8), 871-880.

Hardy, K. K., Bonner, M. J., Willard, V. W., Watral, M. A., & Gururangan, S. (2008). Hydrocephalus as a possible additional contributor to cognitive outcome in survivors of pediatric medulloblastoma. *Psychooncology, 17*(11), 1157-1161. doi: 10.1002/pon.1349

Jaeggi, S.M., Buschkuehl, M., Perrig, W.J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory, 18*(4), 394-412.

Jansma, J. M., Ramsey, N.F., Coppola, R., & Kahn, R.S. (2000). Specific versus nonspecific brain activity in a parametric N-back task. *NeuroImage, 12*(6), 688-697.

Jansma, J. M., Ramsey, N. F., Slagter, H. A., Kahn, R. S. (2001). Functional anatomical correlates of controlled and automatic processing. *Journal of Cognitive Neuroscience, 13*(6), 730-743.

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage, 62*, 782-790.

Kelaghan, J., Myers, M. H., Mulvihill, J. J., Byrne, J., Connelly, R. R., Austin, B. P., . . . Holmes, F. F. (1988). Educational achievement of long-term survivors of childhood and adolescent cancer. *Medical and Pediatric Oncology, 36,* 320-326.

Kelly, A. M., & Garavan, H. (2005). Human functional neuroimaging of brain changes associated with practice. *Cereb Cortex, 15*(8), 1089-1102. doi: 10.1093/cercor/bhi005

King, T. Z., & Smith, K. M. (2012, February). *Functional MRI activation to increased working memory demands among long-term survivors of childhood brain tumors*. Poster session presented to the 41st Annual International Neuropsychological Society Conference, Waikoloa, HI.

Koch, K., Wagner, G., Schachtzabel, C., Schultz, C., Sauer, H., & Schlosser, R. G. (2010). Association between learning capabilities and practice-related activation changes in schizophrenia. *Schizophrenia Bulletin, 36*(3), 486-495. doi: 10.1093/schbul/sbq028

Landau, S. M., Garavan, H., Schumacher, E. H., & D'Esposito, M. (2007). Regional specificity and practice: Dynamic changes in object and spatial working memory. *Brain Research, 11(8),* 78-89.

Landau, S. M., Schumacher, E. H., Garavan, H., Druzgal, T. J., & D'Esposito, M. (2004). A functional MRI study of the influence of practice on component processes of working memory. *NeuroImage, 22*(1), 211-221. doi: 10.1016/j.neuroimage.2004.01.003

Lannering, B., Marky, I., Lundberg, A., & Olsson, E. (1998). Long-term sequelae after pediatric brain tumors: Their effect on disability and quality of life. *Medical and Pediatric Oncology, 18,* 304-310.

Linden, D. E. (2007). The working memory networks of the human brain. *Neuroscientist, 13*(3), 257-267.

Lis, S., Apostolopoulos, J., Kirsch, P., & Gallhofer, B. (2011). Sensory and motor encoding strategies in n-back tasks: A simulation of schizophrenic working memory deficits in healthy subjects. *Neuropsychobiology, 63,* 138-146.

Macedoni-Luksic, M., Jereb, B., & Todorovski, L. (2003). Long-term sequelae in children treated for brain tumors: impairments, disability and handicap. *Pediatric Hematology and Oncology, 20*(2), 89-101.

McClelland, M. M., & Cameron, C. E. (2011). Self-regulation and academic achievement in elementary school children. *New Directions for Child and Adolescent Development, 133,* 29-44.

Medaglia, J. D., Chiou, K. S., Slocomb, J., Fitzpatrick, N. M., Wardecker, B. M., Ramanathan, D., . . . Hillary, F. G. (2012). The less BOLD, the wiser: Support for the latent resource hypothesis after traumatic brain injury. *Human Brain Mapping, 33,* 979-993.

Milham, M. P., Banich, M. T., Claus, E. D., & Cohen, N. J. (2003). Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control. *NeuroImage, 18,* 483-493. doi:10.1016/S1053-8119(02)00050-2

Mostow, E. N., Byrne, J., Connelly, R. R., & Mulvihill, J. J. (1991). Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *Journal of Clinical Oncology, 9*(4), 592-599.

Moyer, K. H., Willard, V. W., Gross, A. M., Netson, K. L., Ashford, J. M., Kahalley, L. S., . . . Conklin, H. M. (2012). The impact of attention on social functioning in survivors of pediatric acute lymphoblastic leukemia and brain tumors. *Pediatric Blood & Cancer, 59*(7), 1290-1295. doi: 10.1002/pbc.24256

Mulhern, R. K., Kepner, J. L., Thomas, P. R., Armstrong, F. D., Friedman, H. S., & Kun, L. E. (1998). Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive concentional or reduced-dose craniospinal irradiation: A pediatric oncology group study. *Journal of Clinical Oncology, 16*, 1723-1728.

Mulhern, R. K., Reddick, W. E., Palmer, S. L., Glass, J. O., Elkin, T. D., Kun, L. E., . . . Gajjar, A. (1999). Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Annals of Neurology, 46*, 834-941.

Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E., & Kun, L. E. (2004). Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncology, 5,* 399-408.

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*, 46-59.

Palacios, E. M., Sala-Llonch, R., Junque, C., Roig, T., Tormos, J. M., Bargallo, N., & Vendrell, P. (2012). White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology*, *78*, 852-859.

Palmer, S. L. (2008). Neurodevelopmental impact on children treated for medulloblastoma: a review and proposed conceptual model. *Developmental Disability Research Reviews, 14*(3), 203-210. doi: 10.1002/ddrr.32

Palmer, S. L., Goloubeva, L., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L. E., . . . Mulhern, R. K. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. *Journal of Clinical Oncology*, *19*(8), 2302-2308.

Perna, R., Loughan, A. R., & Talka, K. (2012). Executive functioning and adaptive living skills after acquired brain injury. *Applied Neuropsychology: Adult, 19*(4), 263-271.

Pochon, J., Levy, R., Poline, J., Crozier, S., Lehericy, S., Pillon, B., Deweer, B., Bihan, D., Dubois, B. (2001). The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. *Cerebral Cortex, 11*, 260-266.

Pogorzala, M., Styczynski, J., Kurylak, A., Debski, R., Wojtkiewicz, M., & Wysocki, M. (2010). Health-related quality of life among paediatric survivors of primary brain tumours and acute leukaemia. *Quality of Life Research, 19*(2), 191-198. doi: 10.1007/s11136-009-9580-1

Porter, K.R., McCarthy, B.J., Freels, S., Kim, Y., & Davis, F.G. (2010). Prevalence estimates for primary brain tumors in the US by age, gender, behavior, and histology. *Neuro-Oncology, 12*(6), 520-527.

Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: A new approach to brain activation experiments. *NeuroImage, 5,* 261-270.

Radcliffe, J., Bennett, D., Kazak, A. E., Foley, B., & Phillips, P. C. (1996). Adjustment in childhood brain tumor survival: Child, mother, and teacher report. *Journal of Pediatric Psychology, 21*(4), 529-539.

Reddick, W. E., Glass, J. O., Palmer, S. L., Wu, S., Gajjar, A., Langston, J., . . . Mulhern, R. K. (2005). Atypical white matter volume development in children following craniospinal irradiation. *Neuro-Oncology, 7*, 12-19. doi: 10.1215/S1152851704000079

Reddick, W. E., White, H. A., Glass, J. O., Wheeler, G. C., Thompson, S. J., Gajjar, A., . . . Mulhern, R. K. (2003). Developmental model relating white matter volume to

neurocognitive deficits in pediatric brain tumor survivors. *Cancer, 97*(10), 2512-2519. doi: 10.1002/cncr.11355

Ris, M. D., & Noll, R.B. (1994). Long-term neurobehavioral outcome in pediatric brain-tumor partients: Review and methodological critique. *Journal of Clinical and Experimental Neuropsychology, 16*(1), 21-42.

Robinson, K. E., Kuttesch, J. F., Champion, J. E., Andreotti, C. F., Hipp, D. W., Bettis, A., . . . Compas, B. E. (2010). A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatric Blood & Cancer, 55*(3), 525-531. doi: 10.1002/pbc.22568

Robinson, K. E., Pearson, M. M., Cannistraci, C. J., Anderson, A. W., Kuttesch, J. F., Wymer, K., Smith, S. E., & Compas, B. E. (2014). Neuroimaging of executive function in survivors of pediatric brain tumors and healthy controls. *Neuropsychology, 28*(5), 791-800. doi: 0894-4105/14/

Robinson, K. E., Pearson, M. M., Cannistraci, C. J., Anderson, A. W., Kuttesch, J. F., Wymer, K., Smith, S. E., Park, S., & Compas, B. E. (2014). Functional neuroimaging of working memory in survivors of childhood brain tumors and healthy children: Associations with coping and psychosocial outcomes. *Child Neuropsychology.* doi: 10.1080/09297049.2014.924492

Robison, L. L., Green, D. M., Hudson, M., Meadows, A. T., Mertens, A. C., Packer, R. J., . . . Zeltzer, L. K. (2005). Long-term outcomes of adult survivors of childhood cancer. *Cancer, 104*(11 Suppl), 2557-2564. doi: 10.1002/cncr.21249

Saury, J. M., & Emanuelson, I. (2011). Cognitive consequences of the treatment of medulloblastoma among children. *Pediatric Neurology, 44*(1), 21-30. doi: 10.1016/j.pediatrneurol.2010.07.004

Sayala, S., Sala, J. B., & Courtney, S. M. (2006). Increased neural efficiency with repeated performance of a working memory task is information-type dependent. *Cerebral Cortex,16*(5), 609-617.

Schatz, J., Kramer, J. H., Ablin, A., & Matthay, K. K. (2000). Processing speed, working memory, and IQ: A developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology, 14*(2), 189-200. doi: 10.I037//0894-4105.14.2.189

Scherf, K. S., Sweeney, J. A., & Luna, B. (2006). *Journal of Cognitive Neuroscience, 18*(7), 1045-1058.

Schlosser, R., Koch, K., Wagner, G., Schultz, C., Robel, M., Schachtzabel, C., . . . Sauer, H. (2009). Intensive practice of a cognitive task is associated with enhanced functional integration in schizophrenia. *Psycholical Medicine, 39*(11), 1809-1819. doi: 10.1017/S0033291709005820

Seaver, E., Geyer, R., Sulzbacher, S., Warner, M., Batzel, L., Milstein, J., & Berger, M. (1994). Psychosocial adjustment in long-term survivors of childhood medulloblastoma and ependymoma treated with craniospinal irradiation. *Pediatric Neurosurgery, 20*, 248-253.

Shan, Z. Y., Liu, J. Z., Glass, J. O., Gajjar, A., Li, C. S., & Reddick, W. E. (2006). Quantitative morphologic evaluation of white matter in survivors of childhood medulloblastoma. *Magnetic Resonance Imaging, 24*(8), 1015-1022. doi: 10.1016/j.mri.2006.04.015

Shucard, J. L., Lee, W. H., Safford, A. S., & Shucard, D. W. (2011). The relationship between processing speed and working memory demand in systemic lupus erythematosus: evidence from a visual n-back task. *Neuropsychology, 25(*1), 45-32.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., Bannister, M., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*(S1), 208-219.

Spiegler, B. J., Bouffet, E., Greenberg, M. L., Rutka, J. T., & Mabbott, D. J. (2004). Change in neurocognitive functioning after treatment with cranial radiation in childhood. *Journal of Clinical Oncology, 22*(4), 706-713. doi: 10.1200/JCO.2004.05.186

Sweet, L. H., Rao, S. M. Primeau, M., Durgerian, S., & Cohen, R. A. (2005). Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human Brain Mapping, 27,* 28-36.

Taylor, L. A., Reeves, C., McCart, M. R., Bushardt, R. L., Jensen, S. A., Elkin, T. D., . . . Boll, T. (2007). A preliminary investigation of cognitive late effects and the impact of disease versus treatment among pediatric brain tumor patients. *Children's Healthcare, 36*(4), 373-384.

Whitton, A. C., Rhhydderch, H., Furlong, W., Feeny, D., & Barr, R. D. (1997). Self-reported comprehensive health status of adult brain tumor patients using the health utilities index. *Cancer, 80*(2), 258-265.

Wolfe, K. R., Madan-Swain, A., Hunter, G. R., Reddy, A. T., Banos, J., & Kana, R. K. (2013). An fMRI investigation of working memory and its relationship with cardiorespiratory

fitness in pediatric posterior fossa tumor survivors who received cranial radiation therapy. *Pediatric Blood & Cancer, 60*(4), 669-675. doi: 10.1002/pbc.24331

Wolfe, K. R., Madan-Swain, A., & Kana, R. K. (2012). Executive dysfunction in pediatric posterior fossa tumor survivors: a systematic literature review of neurocognitive deficits and interventions. *Developmental Neuropsychology, 37*(2), 153-175. doi: 10.1080/87565641.2011.632462

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., & Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage, 45,* 173-186.

Wylie, G. R., Genova, H., DeLuca, J., Chiaravalloti, N., & Sumowski, J. F. (2014). Functional magnetic resonance imaging movers and shakers: does subject-movement cause sampling bias? *Human Brain Mapping, 35*(1), 1-13. doi: 10.1002/hbm.22150

Zebrack, B. J., Gurney, J. G., Oeffinger, K., Whitton, J., Packer, R. J., Mertens, A., . . . Zeltzer, L. K. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *Journal of Clinical Oncology, 22*(6), 999-1006. doi: 10.1200/JCO.2004.06.148

Zhang, Y., Zou, P., Mulhern, R. K., Butler, R. W., Laningham, F. H., & Ogg, R. J. (2008). Brain structural abnormalities in survivors of pediatric posterior fossa brain tumors: a voxel-based morphometry study using free-form deformation. *NeuroImage, 42*(1), 218-229. doi:10.1016/j.neuroimage.2008.04.181