THE EFFECTS OF RADIATION TO THE HIPPOCAMPUS AND SUBVENTRICULAR ZONE ON VERBAL MEMORY AND EXECUTIVE FUNCTION

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Kara M. Fitzgerald

December, 2012

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Abstract

As cancer treatments improve survival time for patients with brain tumors, increased importance has been placed on maintaining quality of life for longer periods of time. Cognition is an important aspect of quality of life that can be affected both by tumor effects as well as treatment-related effects. Research has recently begun to investigate interventions for reducing these effects, particularly with radiation, as it typically used to treat these patients. In an effort to reduce radiation treatment-related effects, radiation treatment planning can be contoured to avoid various structures known to be especially sensitive to the effects of radiation or those structures central to various cognitive processes. Given the growing tendency to avoid structures of special import during radiation therapy, the present study investigated the role of radiation dose to the hippocampus in changes in verbal memory and likewise the role of radiation dose to the subventricular zone (SVZ) in changes in executive function. Radiation to the hippocampus was found to be related to various indices of verbal memory. Radiation to the subventricular zone was related to learning acquisition, the rate at which a list of words was learned. Radiation to the left hippocampus was not related to any indices of executive functioning. A relationship was observed between radiation to the SVZ and one index of executive functioning. Implications, limitations, and future directions are discussed.

Table of Contents

Cancer is a disease that has plagued people for innumerable generations. Historical records of this affliction dates back even to ancient societies. As information as to the etiology and biology of cancer steadily increases, treatments have improved as well. Treatments are increasing the likelihood of remission and improving length of survival. Thus while a primary goal in cancer treatment continues to be prolonging survival, preserving quality of life has become an additional goal (Glantz & Conlee, 2008). Maintaining a high quality of life may involve minimizing pain and other disease-related effects, preserving functional status, and reducing treatment related effects (Roman & Sperduto, 1995; Li et al., 2008). Preserving function is necessarily related to the organ system involved in the disease and treatment. With respect to primary brain cancer, function takes the form of cognition, which is critical to maintaining quality of life.

What is Cancer

Generally speaking, cancer is a group of diseases wherein cells display unchecked growth and division, as well as an independence from typical programmed cell-death processes. These cells can also travel via fluid systems in the body and affect other areas of the body, or metastasize (Hill & Tannock, 1992).

Tumor Histology

The primary concern of the proposed study is tumors of the central nervous system, which include an array of different histologies, or tissues of origin, the most common type of which are gliomas. Gliomas are intracranial tumors which typically arise from glial cells, and less frequently from other cell types. These tumors are typically located supratentorially, without basal ganglia or brain stem involvement (Herrmann, 1990).

Gliomas can be categorized into four grades dependent on characteristics of tissue and appearance on CT scan. Grade I and II gliomas, or low grade gliomas, comprise between 15 – 20% of all gliomas (Taphoorn & Niel, 2008). In terms of histology, they may be classified as astrocytomas, oligodendrogliomas, ependymomas, or mixed gliomas. Importantly, low grade gliomas, particularly oligodendrogliomas, may have genetic loss in chromosomes 1p and 19q, which play an important role in determining treatment (Taphoorn & Niel, 2008). Typically, in terms of clinical presentation, these individuals experience fewer neurological side effects, than those individuals suffering from a rapidly growing higher-grade tumor, while this is not always the case. The prognosis, in terms of median overall survival time, for these individuals, due to slow tumor progression among other factors, has been found to range from 5-10 years in some studies (Ashby & Shapiro, 2004). Median survival was even found to be 15 or more years by another study (Olson, et al., 2000).

Grade III and IV gliomas, or high grade gliomas, comprise approximately 60% of all primary brain tumors in the United States (Glantz & Conlee, 2008). Histologies include glioblastoma multiforme (GBM), gliosarcoma, anaplastic astrocytoma (AA), anaplastic oligodendroglioma, anaplastic ependymoma, and anaplastic mixed glioma. These are typically rapidly growing tumors, which can result in a spectrum of neurological side effects. These may include focal deficits, such as hemiparesis or hemianopsia; medical complications, such as myopathy, fatigue, or endocrine deficiencies; and cognitive impairments. The median survival for these individuals, due to rapid tumor progression, as well as additional neurological symptoms, has been found to be 14-16 months for individuals with GBM and 2-3 years for individuals with AA (Stupp et al., 2005).

However, there is great individual variability in actual survival, with studies reporting a 10 year survival for 25% of individuals with AA and 5 year survival for over 10% of individuals with GBM (Central Brain Tumor Registry of the United States, 2005; Stupp et al., 2009).

Cancer Treatment

Cancer treatment can embody a variety of forms. Often an initial step is a physical separation of tumor tissue from normal tissue, via surgery. However, because of the insidious nature of cancer, this is often insufficient as a sole treatment modality. The most typical additional means of treatment include chemotherapy and radiation therapy. While other treatments are used with specific types of cancers, they are not widely used across disease histology (Hill & Tannock, 1992).

While surgical or radiosurgical (i.e. the use of intense, focused radiation to ablate tissue with analogous results to surgery) interventions are by their very definition aimed at differentiating between cancerous and normal tissue, systemic treatments have historically not been very successful in this. Systemic treatments, such as chemotherapy or targeted, but pervasive treatments like radiation therapy, while succeeding in damaging cancerous cells, also damage normal healthy cells in the process (Hill & Tannock, 1992).

Radiation

In radiation therapy ionizing radiation is applied to tissue, ultimately leading to a cascade of cellular and intracellular reactions, which begin initially with the creation of ions from the tissue matter (Hill, 1992).

When interacting with matter, photon rays, the form of energy typically used in treatment, cause energy to be absorbed into the affected molecule of matter, which results in loss of a high-energy electron from its stable orbit around the atom. This ultimately leaves a positively charged molecule, or ion. Direct effects of radiation are further conferred as the photon continues to move through the matter. After the initial contact with matter, some of the energy of the photon is conferred to the electron of the affected molecule of matter, and the electron with its remaining energy is scattered in a random direction, where it will collide with and transfer a degree of energy to the electron of another molecule and be scattered again in another direction. This process continues at random until the photon and subsequent colliding electron's energy is null and it comes to a rest (Hill, 1992).

The energy transferred at each interaction is not the same and actually varies as a function of the velocity of the photon, such that the most energy is lost as the particle travels the most slowly. Energy loss of a photon is described in terms of the average amount energy lost over a set pathlength, or the linear energy transfer (LET).

While absorbed radiation dosages are measured in Gray (Gy), or the amount of energy absorbed by one unit of mass, one joule of energy from the ionizing radiation by one kilogram of matter (1 J/kg), this value does not directly speak to the biological effects of this ionizing radiation. Rather it is the "size and localized nature of the energy-deposition events...that is the reason for their efficacy in damaging biological systems." (Hill, 1992, p. 261).

Effects of Radiation

Immediate Effects

The biological effects of radiation therapy can be categorized as direct and indirect effects. Direct effects are those that occur as a result of direct energy absorption, whereas indirect effects involve transfer of energy from one molecule to another. Direct absorption of radiation creates an alteration of the cells into which it is absorbed, particularly to water molecules inside of the cells, given that cells are largely comprised of water. Thus, many of the indirect effects of radiation occur through interactions with water derived free radicals, like OH-, which may ultimately lead to altered cellular and tissue function in the ensuing days, and even years. (Hill, 1992). More specifically, these free radicals, initiate breaks in nearby DNA strands. Should the break occur in a single strand, the repair process is somewhat easier, as the intact strand can serve as a template by which to repair the other strand. However, if the break occurs in both strands, repair is more difficult, with higher probability of errors arising. DNA damage in the nervous system causes the protein kinase, ATM (ataxia telangiectasia mutated), to initiate an apoptotic process, thereby eliminating cells with genomic damage (Clancy, 2008; Lee & McKinnon, 2000, Lord & Ashworth, 2012).

Late Effects

Mechanisms for the late effects have been the source of much investigation and debate. The vascular hypothesis posits that vascular damage produced by the aforementioned cascade leads to ischemia, which then in turn leads to white matter necrosis. However, more recent evidence has suggested gray matter is relatively radioresistant. Biologically

speaking, it should be about equally susceptible to vascular changes. This suggests the mechanism posited by the vascular hypothesis is flawed and cannot be solely responsible for changes noted as a result of radiation (Shaw & Robbins, 2008). The parenchymal hypothesis posits that the damage produced by the previously mentioned cascade disproportionately affects oligodendrocytes, as compared to other cell types. Thus the loss of these myelin producing cells and their O-2A progenitor cells, leads to demyelination. However, research has shown this to be inconsistent with the late onset of white matter necrosis, as compared to relative immediacy of oligodendrocyte cell death, suggesting this mechanism is also flawed (Shaw & Robbins, 2008).

These classic views of radiation injury models are now felt to be overly simplistic, with more contemporary models focusing not only upon white matter cells and oligodendrocytes, as integral to the injury process, but also upon astrocytes, microglia, and neurons (Shaw & Robbins, 2008).

Astrocytes, particularly, play a crucial role in brain function, and thus may play a crucial role in brain injury. In the healthy brain, these cells function to secrete different cytokines, proteases, and growth factors, which regulate vasculature, neurons, and oligodendrocytes in their functioning, including cellular division (Shaw & Robbins, 2008). Recent findings have even suggested these cells direct hippocampal neurogenesis, by signaling stem cells to become neurons, rather than other cell fates (Muller et al., 1995; Song, Stevens, & Gage, 2002). Due to these functions, astrocytes play a particularly important role in responding to injury. This has been shown to include injury due to ionizing radiation. In general, astrocytes respond to injury by acute cellular swelling, or by a "chronic reactive gliosis (Pekny & Nilsson, 2005)." However, the exact

mechanism by which astrocytes contribute to CNS radiation injury is still unknown (Shaw & Robbins, 2008).

Microglia also play a role in responding to injury, as they are major mediators of neuroinflammation (Van Rossum & Hanisch, 2004) and respond to a vast array of harmful events to the CNS, in general and in response to radiation (Kalm et al., 2009). Evidence exists that in animal models microglia often can intensify the injury itself by creating reactive oxygen species (ROS), lipid metabolites, and hydrolytic enzymes, and potentially decreasing neurogenesis in the subventricular zone and in parts of the hippocampus in rat models (Shaw & Robbins, 2008). However, more recent evidence suggests that the effect of microglia on neurogenesis is more complicated in humans (Ekdahl, Kokaia, & Lindvall, 2009). These cells can both play a role in post-injury inflammation, as previously discussed, but have also been shown to be involved in neuroprotection via trophic factors (Shein et al., 2008). As microglia are affected by radiation, other damaged tissue will be less likely to be restored by these microglia related trophic factors, as a result (Kalm, Lannering, Bjork-Eriksson, & Blomgreri, 2009; Kalm et al., 2009). Neurons are also affected by radiation injury. As previously mentioned, radiation injury has been shown to decrease the potential for neurogenesis. Even low-doses of radiation, which would be considered sub-therapeutic, have been shown to increase programmed cell-death, decrease precursor cell proliferation, and decrease the likelihood of production of neuronal fated cells from stem cells. It is thought that this latter outcome is the result of microenvironmental effects of radiation. This thus reflects three sources of functional depletion of neuron population, particularly in areas of neurogenesis (Monje, et al., 2002; Monje & Palmer, 2003). Additionally, radiation results

in changes in neuronal gene expression, which holds the potential to alter the function of neuronal cells.

Overall, a contemporary view of the effects of radiation on the brain proposes that radiation causes acute cell death. In addition, it leads to a recovery/repair process involving cytokines, which leads to a secondary reaction of oxidative stress and chronic inflammation (Robbins & Zhao, 2004). Ultimately, this results in changes in progenitor cells, particularly in the hippocampus and subventricular zone, and changes in O2A cells, progenitors of oligodendrocytes, responsible for myelination (Dietrich, 2008).

Clinical Aspects of Radiation Therapy

Radiation tolerance can be defined as the ability of cells to withstand absorption of ionizing radiation without large effect or damage. It hinges upon a number of factors. For example, a higher total dose of radiation has been shown to be a risk factor for CNS injury, as has hypofractionation, or fewer daily fractions with higher doses per fraction. Additional risk factors for CNS injury are a dose per fraction greater than 180-200 cGy, host factors (other illnesses), and adjunctive therapies (chemotherapies) (Leibel & Sheline, 1991).

Radiation injury to the brain is typically described in terms of course and severity. Reactions can be classified according to their timeframe or course (Shaw & Robbin, 2008). Acute injury, or acute radiation encephalopathy, can begin within the first two weeks following initiation of radiation therapy. It is thought to be a result of vasogenic edema. Symptoms can include headache, fatigue, and an exacerbation of pre-existing

neurological symptoms. However, these effects can be quickly and effectively reversed with corticosteriods (Taphoorn & Klein, 2004).

Early-delayed radiation encephalopathy typically occurs 1-6 months following the completion of radiation therapy (Taphoorn & Klein, 2004). It is thought to be related to a disruption of myelin synthesis, due to radiation effects on oligodendroglial cells. Clinically, this involves increased fatigue and irritability, as well as a potential exacerbation of tumor-related effects (Shaw & Robbins, 2008). Additionally, cognitive symptoms may be noted, such as declines in short-term memory and attention. These deficits are typically thought to be transient, with evidence for a return to pre-radiation function within 12 months (Armstrong et al., 1993; Armstrong et al., 1995; Taphoorn & Klein, 2004; Vigliani et al., 1996).

Late-delayed radiation encephalopathy may occur up to several years following treatment. These effects are typically thought to be related to damage or changes to arteries of the brain, which decreases blood supply to the brain (Shaw & Robbins, 2008). Biologically, these effects may be the result of radiation necrosis that is localized to the treatment site or periventricular in nature. Alternatively, late-delayed effects may be a result of diffuse leukoencephalopathy and atrophy. These late-delayed effects involve a host of neurological symptoms and often near-global cognitive declines and are not reversible, though treatments are currently under investigation (Taphoorn & Klein, 2004).

Cognitive Effects of Radiation Therapy

The clinical and cognitive symptoms attributable to the radiation necrosis associated with early and delayed late effects are thought to result from direct tissue damage or the

indirect effects on adjacent tissue. Decreased white matter integrity, as well as reduced cell proliferation, including neurogenesis, in the hippocampus, result in decreased repopulation of hippocampal cells. Similar processes affect the functionality of the subventricular region, which, in a healthy brain, provides support, in the form of astrocytes, oligodendrocytes, and potentially neurons, to brain areas experiencing injury, are thought to underlie radiation therapy-related changes in cognition (Dietrich et al., 2008; Romankob et al., 2004).

There has been much support for the notion that radiation to areas capable of neurogenesis decreases the integrity of these areas, in part by decreasing neurogenesis. As it has been posited that some cognitive functions rely upon neurogenesis in these areas, radiation-induced decreases in neurogenesis are thought to underlie changes in cognition (Monje & Palmer, 2003). The hippocampus is known to be one area of the brain capable of neurogenesis. The hippocampus is located in the medial temporal lobe towards the midline of the brain and is composed of two gyri: Ammon's horn and the dentate gyrus (DG). The DG consists largely of granule cells, while Ammon's horn is consists primarily of pyramidal cells, which are divided into four discrete groups (CA1, CA2, CA3, and CA4) (Kolb & Wishaw, 2003). The DG is the structure in the hippocampus that serves as site of neurogenesis and consists of granular and subgranular layers. Progenitor cells remaining in the area from embroygenesis are responsible for the formation of the area of germination in the subgranular layer. Neuronal precursors from the subgranular layer migrate to the granular layer, where they differentiate into granule neurons and are incorporated into the structure, thus allowing for the plasticity of hippocampal functioning (Cayre, Canoll, & Goldman, 2009).

The subventricular zone (SVZ) is an additional area known to contain neural stem cells. This area in rodents is characterized by a layer of ependymal cells, which separate the subependymal layer from the ventricles. Astrocytes in this region have processes that receive inputs both from the cerebrospinal fluid (CSF) of the ventricles, as well as nearby blood vessels. With this input, astrocytes play a role in coordinating proliferation, differentiation, as well as migration. In the adult rodent, neuron precursor cells migrate along the rostral migratory stream (RMS) to the olfactory bulb (Cayre, Canoll, & Goldman, 2009). However, other evidence has suggested that in both rodent and human brains neuronal precursors from this region may migrate more diversely in response to injury, diverting from the rostral stream toward injured tissue in the surrounding cortex (Zhang, Zhang, & Chopp, 2005).It has been suggested that the SVZ plays an important role in cell replacement, both of neurons and glia, for extended time periods following injury (Chen et al., 2004). However, the SVZ, and its restorative capacity, is also subject to injury itself from a variety of sources including chemical and radiation -related injury (Romankob et al., 2004). A reduction in SVZ functionality would thus reduce the ability of the rest of the brain to recover from injury as well, causing reductions in functionality for other affected brain regions as well. Given the relative close proximity of the frontal lobes to the anterior SVZ, it stands to reason that the frontal lobes, if injured, may evidence a decrease in functionality, as a result of injury, which is less likely to be attenuated by help with response to injury from the SVZ.

The effects of radiation-induced damage to neural stem cells on neurobehavioral function, particularly memory, have been borne out in animal models (Hodges et al, 1998; Peissner et al., 1999). Much of the research exploring the cognitive sequelae of

radiation therapy has been conducted within the pediatric population, as radiation has historically and continues to be preferential component of treatment for many forms of childhood cancer (Ris, 2007). In the pediatric population, it has been well established that there is a dose-response relationship, such that the greater the amount of radiation administered to the brain, the greater the cognitive effects. Thus whole-brain radiotherapy has been demonstrated to be relatively more harmful (Ris & Noll, 1994). Additionally, it has been demonstrated that declines in IQ may occur, to a magnitude of 25-30 points in some cases (Ris & Noll, 1994; Merchant, et al., 2005). A more current review of the extant literature has gone on to describe losses such as the aforementioned drop in IQ, as well as decreases in school performance, as secondary. In this sense, it has been posited that declines in more "core" processes underlie these phenomena. The "core" domains in which declines occur as a result of radiation therapy have been identified as executive functions, attention, and processing speed (Mulhern & Palmer, 2003).

More limited research has illustrated the effects of cranial radiation on cognition in adult patients (Roman & Sperduto, 1995). Reductions in attention and short-term memory capabilities have been reported following radiation therapy in adults (Vigliani et al., 1996). More frequent learning and memory problems within four months of treatment have also been noted in patients with brain metastases treated with radiosurgery and whole brain radiation as compared to radiosurgery alone (Chang et al, 2009). Similarly, findings of memory impairment were noted in the majority of patients treated with radiation for tumors located at the base of the skull. A smaller portion additionally evidenced visual-motor speed, and executive function difficulties. Total dose of radiation was found to be related to neurocognitive symptoms, rather than brain volume irradiated

(Meyers et al., 2000). Additional studies have indicated that these effects on memory and attention may be expected in the first one to six months following radiation therapy and often resolve by the twelfth month following completion of radiation therapy in lower grade primary brain tumor patients treated with focal RT (Armstrong et al, 1995). Sun et al. (2010) found that prophylactic cranial irradiation in individuals with small-cell lung cancer was associated was associated with significant verbal memory declines at one year after RT and was associated with increased risk of later developing chronic neurotoxicity when treated to a total dose of 36 Gy, which decreased at lower levels, in the Radiation Therapy Oncology Group (RTOG) trial 0212 (Wolfson et al., 2011). A dose dependent relationship was also noted between RT and neurocognitive function, thought to be mediated by cerebral blood flow and metabolism (Hahn et al., 2009). Other complications arising from radiotherapy, like late-delayed effects, are irreversible and have been shown to affect both attention and short-term memory in some individuals (Taphoorn & Klein, 2004). In an additional study, RTOG 0214, some of the adverse effects of whole brain radiation therapy (WBRT) on cognition were abated in patients who also received adjuvant Motexafin Gadolinium. Additionally, this study displayed an interesting dissociation between measures of memory and measures of executive function and motor speed. For memory function, less decline was noted in individuals who experienced partial response to treatment (i.e. unprogressed). However, individuals displaying partial response to treatment experienced an improvement in executive tasks, while those experiencing progression declined (Meyers et al., 2004). This may indiciate a discrepancy between differential effects of disease and treatment effects on memory and

executive function, such that executive function is more affected by disease, rather than treatment effects, while memory appear susceptible to both.

More recent research has utilized improvements in the specificity of radiation therapy delivery to determine the dose of radiation directed to various regions of interest. Initial findings regarding change in neurocognitive functioning associated with radiation therapy, indicated that a dose of 40% of the bilateral hippocampi receiving greater than 7.3 Gy was predictive of a decline in verbal memory (Gondi et al., 2012).

Radiation contouring

Given the known effects of radiation therapy on cognition and other brain function, the importance of intervention has been recognized. Because of the relative inability to effectively "repair" damage to the central nervous system, prevention of radiation injury has received more attention in the extant literature (Ris, 2007). Advances in radiation therapy techniques have allowed for radiation directed at the brain (and other parts of the body) to be focused to hit various structures selectively. This has allowed for radiation oncologists to specialize treatment such that the highest doses of radiation are being absorbed by the area affected by the tumor/s, as well as at-risk areas for disease recurrence, with relatively less radiation being absorbed by adjacent areas, which are at some risk for being affected by infiltrative cells. A relatively smaller amount of radiation is directed to be absorbed by areas that lie further away from the site of the tumor. Additionally, this type of contouring can allow radiation to avoid structures of the brain thought to be at little risk of tumor infiltration or those which display particular toxicity to radiation, like those active in neurogenesis (Gutierrez et al., 2007). The hippocampus

is one such structure, because it is an unlikely site of tumor recurrence for metastatic disease and is known to be involved in memory (Ghia et al., 2007; Gondi et al., 2010.)

Cognition

Memory

One of the cognitive functions that has the potential to be affected by radiation in a way which could adversely affect quality of life is memory. One's ability to remember generally speaking is essential to many of the roles fulfilled in maintaining daily function. While there are many forms of memory, the most obviously affected by neurological injury typically is explicit memory - or "conscious, intentional recollection of previous experiences" (Kolb & Wishaw, 2003). Explicit memory is thought to be processed in a "top-down" manner, wherein data input is conceptually considered and potentially reorganized for storage. Because this is a relatively active process, recall may be dependent upon the way in which the data is conceptually broken down and stored. Because of the processing done at the conceptual level during encoding, or putting into memory, these same concepts used to organize may serve as internal cues, facilitating spontaneous recall (Craik & Lockhart, 1972; Demb et al., 1995).

In terms of the neural circuitry involved in explicit memory, Petri and Mishkin (1994) proposed a model involving structures largely based in the temporal lobe. In this circuit, information is thought to pass from the midbrain to cortical systems, including passage through the medial thalamus, and temporal lobe, such as the hippocampus, amygdala, and entorhinal cortex, with further and potentially recursive processing occurring via the prefrontal cortex.

Further study has revealed the medial temporal lobes (MTLs) to be considered important in the process of memory. MTLs consist of the hippocampal complex (hippocampus, dentate gyrus, subiculum) and the surrounding neocortex (entorhinal cortex, parahippocampal gyrus, and perirhinal cortex). Relational Binding Theory, as discussed by Shimamura (2002), states that the medial temporal lobes are critical for integrating new information with pre-existing memories, which are believed to be stored in the cortex. In this way the MTLs are believed to be crucial for initial learning, also known as encoding or feature-binding. Additionally, the MTLs are thought to help strengthen connections between or consolidate information, particularly if the information is repeated. Additionally, Relational Binding Theory holds that the MTLs are necessary for retrieval or reactivation of information that is recently learned, but not for well-rehearsed information, which would rely upon cortical-cortical activation (Shimamura, 2002). This assertion has been corroborated with evidence from biochemical models of memory as well (Izquierdo & Medina, 1997).

The role of the hippocampus in memory has been the subject of much empirical work as well, with a number of studies suggesting a role of the hippocampus in memory, both in the form of animal models and case studies In terms of animal models, rats with damage to the MTLs performed worse, as compared to intact counterparts, on a task of radial maze learning, insofar as they would return to the paths in the maze along which they had already been, and thus had already received their food incentive. Similarly, rats with MTL damage performed worse, when compared to intact counterparts, on the Morris Search Task. In this task, rats were placed in a pool of murky water, in which there was a platform obscured by the water, so that rats would have to swim until locating the

platform. Normal controls would learn the location and then find it more efficiently in subsequent trials, whereas rats with MTL damage did not show such learning (Heilman & Valenstein, 2003).

Empirical work exploring the role of the hippocampus in human memory has largely focused on case studies. In the case study of patient R.B., damage sustained to area CA1 of the hippocampus secondary to an anoxic episode produced anterograde amnesia, but not retrograde amnesia. This suggested that the area CA1 is important in the formation of, but it is not the site of storage for, memories, which are believed to be in the associated cortex. One of the more influential of works of this nature is the series of studies conducted by Squire (1982, 2001). In studying patients with retrograde amnesia, it was demonstrated that the larger the portion of hippocampal damage, the greater the temporal span of the retrograde amnesia. Additionally, patients who had damage to structures surrounding the hippocampus experienced an even greater temporal span of loss, which was not experienced by those for whom only the hippocampus was damaged. Squire et al. (1982, 2001) concluded from these findings that the hippocampus is important to memory during and after the learning process for a relatively short period of time, whereas other cortical areas are responsible for memory which extends further back in time. As can be noted, for theories such as these, while the hippocampus is just one of many structures involved in memory, it is thought to be a crucial component (Kolb & Wishaw, 2003; Izquierdo & Medina, 1997; Winocour & Moscovitch, 2011).

Another function of the hippocampus may be to consolidate, or make permanent, new memories, before they are transferred for storage elsewhere in the brain. While this would fit with the tendency to lose memory for peri – traumatic brain injury (TBI) events

with amnesia, it would be difficult to account for occasional amnestic cases wherein memory loss extends back long periods of time (Kolb & Wishaw, 2003). Other theories hold that the hippocampus serves as a cataloging or tagging system for memories, pairing the memory with the context in which it was learned or with other attributes (Henke et al., 1997). Other structures that are considered integral to the process of memory include the temporal cortex, the amygdala, the perirhinal cortex, and the diencephalon, each playing a unique role (Tulving & Markowitsch, 1998). The amygdala is also thought to play a role in memory for events that have emotional significance and this has been borne out in animal models (Paton et al., 2006). Lesions to the right temporal cortex produce relatively greater difficulties with memory for nonverbal material, whereas lesions to the left temporal cortex lead to verbal memory, such as list learning, word pairs, and story memory (Kolb & Wishaw, 2003).

The asymmetrical contributions of the prefrontal cortices are discussed in the hemispheric encoding/retrieval asymmetry (HERA) model. This model states that the left prefrontal cortex is more involved in the encoding rather than retrieving of both semantic and episodic information. Additionally, it states that the right prefrontal cortex is more involved in memory retrieval (Habib, Nyberg, & Tulving, 2003).

Further studies regarding cortical involvement in memory have found that diffuse damage can also lead to memory impairments. For example, neurological populations, such as those with dementia, provide much evidence towards this end (Murre, Graham, & Hodges, 2000). Patterns of change in memory performance coupled with structural or histological change have revealed relationships between various areas of the cortex and amnestic symptoms. For example, the medial temporal cortex is associated with

anterograde amnesia, or loss of memory for new information, whereas damage to other temporal structures or the frontal areas is related to retrograde amnesia, or difficulty with memory for past events (Kolb & Wishaw, 2003).

Overall, many structures have been implicated as potentially important in various aspects of memory. While the specific role of the hippocampus remains not fully clear, it is evident that this structure is involved in memory and is crucial for some aspects of memory function.

Executive Function

Another cognitive function which bears noticeable impact upon daily life and functioning is that of executive function. It is noted to be the most complex of cognitive abilities and allows us to respond to and adapt to new information. These abilities can have a profound effect on behavior, and have been found to be good predictors of everyday functioning, particularly in terms of activities of daily living (ADLs) (Cahn-Weiner, Boyle, & Malloy, 2002; Johnson, Lui, & Yaffe, 2007). However, it has been noted that changes in this domain are difficult to measure and changes may not be captured in a standard evaluation (Lezak, 2012). This may be due in part to testing typically occurring with structured tasks in a structured environment and in its truest sense, executive functioning is the ability to create and adequately apply structure to a new situation.

The skills or behaviors encompassed in the domain of executive functions can be characterized as volition, planning and decision making, purposive actions, and self-regulation. Volition can be characterized as the skill of identifying wants or needs, and then developing motivation and intention to meet those wants and needs. Planning and

decision making is then the next sequential step in this domain and involves prospective thinking, perspective taking, and abstraction. Goals and methods must be first generated, then assessed for practicality and feasibility, and information must be incorporated into goals as the situation progresses. This requires a capacity for sustained attention, as well as the ability to inhibit impulsive action. Purposive action, is the ability to translate plans and intentions into action in a planned way, and the initiation of said action, particularly for unfamiliar tasks, which cannot benefit from automaticity. Finally, self-regulation involves the ability to monitor performance, thus maintaining efficient and goal-directed actions, while changing or altering those that are not deemed effective or efficient as per the goal (Lezak, 2012). A disruption in any one of these processes can cause changes in functionality.

In terms of brain - behavior relationships, executive functions have been found to be dependent upon frontal lobes. However, changes in executive function can occur as a result of injury to many additional areas of the brain, as the variety of complicated abilities subsumed under the label executive functions is vast (Godefroy, 2003).

Present Study

The present study investigated the role of radiation therapy, absorbed by specific brain regions of interest, in a primary brain cancer population, on changes in verbal memory and executive function. Specific regions of interest include the hippocampus and the subventricular zone, given their capacity to repopulate cells of the hippocampus and surrounding cortex, respectively. It is hypothesized that greater radiation exposure to the hippocampus will be associated with greater decline in verbal memory performance

following radiation therapy from pre-treatment baseline performance. Additionally, in its ability to provide support to damage in surrounding areas, including the frontal lobes, it is hypothesized that greater radiation exposure to the SVZ will be associated with greater decline in executive function following radiation therapy from pre-treatment baseline performance. A double dissociation is expected, such that radiation to the hippocampus is expected to be related changes in memory, but not executive function, and radiation to the SVZ is expected to be related to changes in executive function, but not memory.

Method

Participants

Retrospective clinical data was used and obtained with permission from the M.D. Anderson Cancer Center and under the approval of institutional-review boards of the M.D. Anderson and the University of Houston. Participants consisted of primary brain cancer patients who both underwent neuropsychological testing and received radiation treatment at the M. D. Anderson Cancer Center. To be eligible for participation, individuals were required to be 18 years of age or older, to have had neuropsychological testing prior completing radiation therapy, as well as follow-up neuropsychological testing on at least one additional time point following radiation treatment. It was required that this second time point occur at a minimum of 9 months following radiation treatment. An additional inclusion criterion for being involved in the study was having a diagnosis of primary brain cancer. Primary tumor histologies consisted of glioblastoma multiforme, astrocytic astrocytoma, oligodendroglioma, low-grade glioma, and mixed histology. Primary tumor locations were required to be located in cortical and insular regions.

Cases with evidence of tumor progression were not included in the analyses, as this may have a confounding effect on the neuropsychological results. Existence of progression was determined based upon review of the treating clinicians chart notes including all visits in the record for one month following the date of the neuropsychological evaluation in question. In cases in which the occurrence of progression was listed as "questionable"

per radiographic data, conclusions were derived from follow-up scans and clinical evaluations serving as the determinant.

Clinical variables of interest include medications at times 1 and 2, including depressants (benzodiazepines), SSRIs, steroids, stimulants, analgesics, anti-emetics, and cardiovascular active medications. Also explored was the number of anticonvulsants, as well as concomitant medical and psychological diagnoses at times 1 and 2 (i.e. depression, anxiety, and cardiovascular diagnoses). Time since radiation, or the interval between completion of radiation therapy and second neuropsychological evaluation, was also a variable of interest, as the relationship between radiation and cognition has been shown to have a temporal component. As there existed variability in the interval between surgery and neuropsychological testing, surgery interval was also a variable of interest. It was organized into three levels, those who received neuropsychological testing before surgery, those who received neuropsychological testing less than two weeks following surgery, and those who received neuropsychological testing greater than or equal to two weeks following surgery.

Radiation Dosimetry

Radiation treatment was required to have been completed at M. D. Anderson Cancer Center. Radiation therapy was completed using Intensity Modulated Radiation Therapy (IMRT) or 3-Dimensional Conformal Radiation Therapy (3DCRT). Dosimetric treatment planning was completed using the Pinnacle Treatment Planning System version 9. Using MR/CT fused images regions of interest were contoured. Hippocampal contouring was completed using the atlas and guidelines used in RTOG 0933 (Gondi, 2010), a trial of

hippocampal-sparing WBRT. Test-retest reliability and inter-rater reliability was assessed, using Pearson Correlations, on a set of 10 of the cases not included in the sample and are presented in Table 1 Additionally, degree of volumetric overlap between inter-rater and intra-rater tracings is presented in Table 2, using Dice Coefficients. These were calculated according to the following formula (Dice, 1945):

$$S = 2(A \cap B)/(|A| + |B|)$$

From the contoured treatment plans, dose volume histograms were extracted, to statistically determine the dose of radiation per volume that each region of interest received. From this various radiation variables can be obtained, including mean dose, maximal dose, and volumetric doses, or the dose received by x% of the structure for percentages from –5-100. Regions of interest included the left and right hippocampi and left and right subventricular zones (SVZs).

Neuropsychological Assessment

Neuropsychological data used was obtained from medical records of routine neuropsychological evaluations, provided to participants as a part of their routine medical care.

Hopkins Verbal Learning Test-Revised

Memory was measured using data obtained from the Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001). In the administration of this task, a standardized word list, consisting of twelve words, in three semantic categories, is presented to patients in three consecutive trials. There are six alternate forms of this task, such that

patients are only administered the same list every seventh evaluation. The patient is asked to recall as many of the words in any order following each trial. Recall for each of the three trials constitutes the learning acquisition, or their ability to increasingly benefit from repetition of the word list. This is represented by recall for the higher of trial 2 or 3, less initial recall (trial 1). Total recall is derived from the sum of recall for each of the three trials. Following a 20-minute delay, delayed free recall is assessed in an uncued format. Percent retention is calculated by dividing the highest number of words recalled in any of the first three trials, by the number of words recalled in the delay trial. Cued recognition is assessed following delayed recall. The patient is asked to state whether each of 24 words were present on the original list. Recognition discriminability index is calculated by subtracting false positives errors from true positive words identified. Total learning, learning acquisition, delayed recall, percent retention, and recognition discriminability index are particular variables of interest and were derived from scores on this measure. Data were normed on the basis of age using the normative data provided in Benedict et al. (1998).

Trail Making Test (TMT)

This task was originally developed for use in the Army Individual Test Battery and was later included as part of the Halstead-Reitan Battery (Reitan & Wolfson, 1985). The two-part test is now widely used as a stand-alone measure. The first test, Part A (TMT A), consists of twenty-five encircled numbers (1-25), which are pseudo-randomly distributed across a page. The individual is asked to draw lines connecting the numbers in ascending order. The second test, Part B (TMT B), consists of 13 encircled numbers (1-13) and 12 letters (A-L), pseudo-randomly distributed across a page. The individual is asked to draw

lines connecting numbers and letters in ascending order, while alternating between number and letter. The score on each test is the total time to completion in seconds (Tombaugh, 2003).

While TMT A maps on to cognitive processes such as processing and motor speed, TMT B necessarily involves both of these components, in addition to executive functioning required for switching sets (letters vs. numbers), and inhibiting the previously activated set (Tombaugh, 2003). Scores on these measures were normed using the age and education adjusted norms provided by Tombaugh (2003). Additionally, to provide a cleaner estimation of executive functioning, less affected by motor and processing speed constructs also tapped by the measure, various comparisons between TMT A and TMT B, including difference and ratio comparisons originally derived and normed by Drane et al. (2002). Thus variables of interest include normed time to complete TMT B (B), TMT difference (B-A), and TMT ratio (B/A).

Practice Effects

Given that test-retest data was used in the current study, practice effects are an important aspect to consider, Practice effects refer to an influence on test performance born from previous experience with taking the same or similar test, potentially involving procedural or semantic learning processes (Slick, 2006). Measures with large practice effects can cause difficulties in elucidating the nature of change in test score over time, as it yields another confound.

For HVLT, practice effects were found, with individuals taking the same form of the test over four sessions. However, minimal practice effects were found for individuals taking

alternate forms of the test (Benedict & Zgaljardic, 1998). For TMT, multiple studies have indicated small or no practice effects on this measure, particularly for longer test- retest intervals (Basso, et al., 1999). Similar results were found when test-retest dates ranged from 2-16 months and Dikmen et al. (1999) noted that the vast majority of individuals did not experience substantial practice effects. Thus, on the whole, neither of the primary neurocognitive measures should be unduly influenced by practice effects.

Statistical Analyses

The primary objective was to test the hypothesis that the amount of radiation absorbed by the hippocampus and subventricular zone would be negatively correlated with memory and executive function performance, respectively.

Exploratory analyses were conducted, which investigated which of the many potential volumetric radiation dose variables (dose received by X% of the ROI, where X is a constant) is the most predictive of memory performance, as a result of dose. The same analyses were conducted to determine which of the radiation variables were most predictive of executive function performance. Additional radiation variables included mean dose, max dose, modal dose, as well as weighted radiation dose variables for each ROI. To capture a theoretical overall dose effect to each structure, weighted radiation dose variables were calculated according to the formula below, where ROIa Vol5 represents the dose received by 5% of the ROI, ROIa V10 represents the dose received by 10% of the structure, and so forth. From the weighted variable a bilateral hippocampal weighted variable will be calculated by adding the RHC and LHC weighted variables.

Weighted ROIa = (ROIa V5 x volume ROIa) + (ROIa V10 x volume ROIa) + ... + (ROIa V65 x volume ROIa).

Additionally, repeated measures ANOVAs comparing memory scores between groups based on presence, number of agents, and number of cycles of chemotherapy, and additional medical condition groups were used to determine the appropriateness of including additional potential covariates. Clinical factors which are known to affect radiation tolerance, such as additional medical conditions, and additional treatments, were explored as covariates/factors. Finally, additional medications which are CNS-active, including anxiolytics, antidepressants, anticonvulsants, and stimulants, were explored as covariates/factors. Based on the known temporal nature of radiation effects, length of time between completion of radiation and second neuropsychological evaluation was explored as a covariate.

Repeated measures ANOVAs were also conducted to determine if differences existed, in change in neuropsychological outcome scores of interest, across three surgical groups: those who underwent neuropsychological testing prior to surgery, those who underwent between surgery and testing was greater. For neuropsychological variables for which significant differences were found regression analyses were completed using a subset of the data (i.e. cases with a post-resection interval of greater two weeks).

Hierarchical regressions were calculated with the neuropsychological outcome score from the second evaluation serving as the dependent measure. The pretreatment test performance was force entered in to the equation, followed by a step containing chemotherapy variables and time since radiation entered in a stepwise fashion, another

step containing previously determined medication variables entered in a stepwise fashion, and then a step containing previously determined radiation variables of interest entered in a stepwise fashion.

As the aim of the present study is to examine the contribution of radiation to various ROIs to change in cognition, neuropsychological outcome data will also be explored in terms of Reliable Change (RC). RC seeks to determine if changes in test scores across time points within an individual are sufficient in size to be unlikely to be due to chance. This necessarily requires that the change be greater in magnitude than what would be expected given known standard deviation (sd), as well as known test-retest reliability of the measure or metric (Jacobson et al., 1984; Christensen & Mendoza, 1986). More specifically, a standard error of change SEΔ can be calculated using the following formulae, using the standard error of measurement (SEM):

$$SEM = sd\sqrt{(1 - r^2)}$$

$$SE\Delta = \sqrt{2(SEM)^2}$$

The SEΔ can be used to determine cut-off RC values for a chosen confidence interval (CI). Thus, for a CI of 95%, if the SEΔ is multiplied by 1.96, the resultant value would represent any change greater in absolute value is unlikely to be due to chance 95% of the time. Similarly, to identify the cut-off value for a CI of 90%, the SEΔ would need to be multiplied by 1.645. This is thought to represent clinical significance (Jacobson & Truax, 1991).

RC values for CI of both 90 and 95% are listed in Table 3. RC values for memory variables were based on sd and test-retest reliabilities reported by Benedict et al, (1998) and RC values for TMTB was based on sd and test-retest reliabilities reported by Levine et al. (2004). For B – A and B/A, due to a lack of existing data on test-retest reliability, RC values were calculated as a function of relationship of each metric to TMTB. Two linear regressions were run with B – A and B/A predicting TMTA respectively. Each regression yielded significant results and RC values for B – A and B/A were derived from the respective regression equations and the previously computed RC value for TMTB.

It can thus be determined for if change in outcome score, for each metric, is clinically significant. This output can then be organized into three RC groups: clinically significant decline, no clinically significant change, and clinically significant improvement.

Univariate ANOVAs will be run to determine if there is a significant difference between groups for any of the initially correlated radiation variables. Logistic regressions or ANOVAs will be completed using significant predictors from the regression analyses, as well as for those associated with a significant difference between RC groups.

Results

A total of 36 participants were identified from the sample, which met aforementioned exclusion and inclusion criteria. The demographic data of these participants are listed in Table 4.

All participants had formal diagnoses of a primary brain cancer and all underwent a full course of radiation therapy and had two neuropsychological evaluations at M.D. Anderson Cancer Center. Sixty-one percent of the sample (n = 22) underwent surgical resection prior to neuropsychological evaluation. For those who underwent surgical resection before neuropsychological evaluation, the number of weeks between the two events ranged from 0.4 to 18.9 (M = 4.20, SD = 4.05). The interval between surgery and neuropsychological resection was greater than or equal to two weeks for eighteen percent (n = 4) of the subsample who underwent resection prior to evaluation. Sixty-one percent of the total sample (n = 22) had no concomitant medical or psychiatric diagnoses. Twenty-five percent of the total sample had concomitant cardiovascular diagnoses (i.e., hypertension, hyperlipidemia, atrial fibrilation, and congestive heart failure) with hypertension being the most common diagnosis (19%, n = 7). Three percent of the sample had a diagnosis of obstructive sleep apnea (n = 1), polycystic ovary disease (n = 1), or latent tuberculosis (n = 1). Eleven percent of the sample (n = 4) had a concomitant diagnosis of Major Depressive Disorder, per the medical record, or an anxiety disorder of unspecified type, though the specific diagnosis was not available. Three percent of the sample developed non-epileptic seizures (n = 1), per the medical record, or a pulmonary embolism during the course of treatment (n = 1).

At the time of the initial neuropsychological evaluation, nineteen percent of the sample (*n* = 7) were not on any anticonvulsant medications, sixty-seven percent of the sample (*n* = 24) were on a single anticonvulsant agent, and fourteen percent (*n* = 5) were on two anticonvulsant agents. At the time of the follow-up evaluation, sixteen percent of the sample (*n* = 6) were not on any anticonvulsant medications, sixty-one percent of the sample (*n* = 22) were on a single anticonvulsant agent, and fourteen percent (*n* = 5) were on two anticonvulsant agents.

Fourteen percent of the sample (*n* = 5) was prescribed anxiolytic medications at the time of the initial evaluation, and eight percent (*n* = 3) at the time of the follow-up evaluation. Eight percent (*n* = 2) was prescribed selective serotonin reuptake inhibitor (the only anti-depressant used in the sample) medications at the time of the initial evaluation, and twenty-two percent (*n* = 8) at the time of the follow-up evaluation. Thirty-three percent of the sample (*n* = 12) was prescribed steroids at the time of the initial evaluation and none at follow-up. None of the sample was prescribed stimulants at the time of the initial evaluation, and fourteen percent of the sample (*n* = 5) at the time of the follow-up evaluation. Seventeen percent of the sample (*n* = 6) was prescribed pain medications at the time of the initial evaluation, and eleven percent (*n* = 4) at the time of the follow-up evaluation. Eight percent of the sample (*n* = 3) was prescribed anti-emetic medications at the time of the initial evaluation, and nineteen percent (*n* = 7) at the time of the follow-up evaluation. Twenty-eight percent of the sample (*n* = 10) was prescribed cardiovascular active medications at the time of the initial and follow-up evaluations. Further clinical characteristics of the participants are described in Table 5.

Descriptive statistics for each of the outcome variables are provided in Table 6. The administration of the memory measure was noted to be non-standardized for 28% of the total sample (n = 10), secondary to the preference of the attending clinician. In this non-standardized administration, a recognition trial was given immediately following the initial three learning trials. Given this, normative data would be invalid for this 28% of the sample for delayed recall, recognition discriminability index, and percent retention and thus these variables were analyzed with the subset of the population for whom memory test administration was standard (n = 26). As the non-standard practice did not occur until after the three initial learning trials, the variables initial recall, total recall, and learning acquisition were analyzed using the entire sample. Because the non-standard administration occurred pseudo-randomly among patients, and was not based upon any disease, treatment or demographic characteristics, these groups should be fairly equivalent. Disease and demographic characteristics of these two groups are presented in Tables 7 and 8.

Repeated measures ANOVAs were run on each of the standardized memory variables (total learning, initial recall, learning acquisition, delayed recall, percent retention, and recognition discriminability index) and each of the executive function variables (B, B – A, and B/A) to determine if there were significant differences in performance among the surgery groups. Significant differences were not found in any of the analyses and results can be found in Table 9. Repeated measures ANOVAs were run on each of the standardized memory variables (total learning, initial recall, learning acquisition, delayed recall, percent retention, and recognition discriminability index) and executive function variables (B, B – A, and B/A) to determine if there were significant differences in

performance associated with the aforementioned medication variable groups, as both these factors are known to have a potential effect on radiation tolerance.

Total learning was found to be significantly different across evaluations between steroids at time 1 compared to those who were not, $F(1, 17) = 7.94$, $p < .05$. Performance in Initial Learning was found to be significantly different across time evaluations between those who were prescribed depressant medications at time 2 and those not, $F(1, 9) = 5.63$, $p < .05$, as well as those prescribed SSRIs at time 2 and those not, $F(1, 9) = 6.62$, $p < .03$. No significant differences were found in Learning Acquisition, Percent Retention, or Delayed Recall performance across times for any medications at time 1 or 2. Recognition discriminability index was found to be significantly different across evaluations between those who were prescribed pain medications at time 1 and those not, $F(1, 11) = 13.45$, $p < .005$, as well as those prescribed cardiovascular active medications at time 1 and those not, $F(1, 11) = 7.68$, $p < .05$. TMTB performance was found to be significantly different across evaluations between number of anticonvulsant at time 2, $F(2, 10) = 97.70$, $p < .001$, prescription of depressants at time 2, $F(1, 10) = 126.44$, $p < .001$, prescription of SSRIs at time 2, $F(1, 10) = 119.11$, $p < .001$, number of anticonvulsants at time 1, $F(2, 17) = 6.75$, $p < .01$, prescription of depressants at time 1, $F(1, 17) = 12.27$, $p < .01$, and prescription of SSRIs at time 2, $F(1, 17) = 119.11$, $p < .01$. B – A performance was found to be significantly different across evaluations between number of anticonvulsants at time 2, $F(2, 10) = 24.35$, $p < .001$, prescription of depressants at time 2, $F(1, 10) = 27.02$, $p < .001$, prescription of SSRIs at time 2, $F(1, 10) = 25.50$, $p < .001$, prescription of depressants at time 1, $F(1, 17) = 11.55$, $p < .01$, and prescription of SSRIs at time 1, $F(1, 17) = 9.98$, $p < .01$. B/A performance was found to be significantly different across

evaluations between number of anticonvulsants at time 2, $F(2, 10) = 4.31$, $p < .05$, and prescription of pain medications at time 1, $F(1, 17) = 4.48$, $p < .05$. Significant results are presented in Table 10.

Radiation variables of interest

To determine if amount radiation absorbed by ROIs might have contributed to changes in cognitive functioning within the domains of memory and executive functioning, radiation dosimetry was calculated. Radiation characteristics are described in Table 11. Volumetric variables were calculated at intervals of 5, representing dose of radiation absorbed by 5-65% of ROIs, represented as V5-V65.

Exploratory analyses of the relationships between memory variables and the full set of volumetric radiation variables revealed significant correlations for V5, and V25-V40 of the right hippocampus (RHC), V30-55 of the left hippocampus (LHC), V60 of the right subventricular zone (RSVZ) and V50-60 of the left subventricular zone (LSVZ). These are listed in Table 12. Exploratory analyses of the relationships between executive function variables and the full set of volumetric radiation variables revealed significant correlations for V5 and V10 of the RHC, V5 and V10 of the LHC, total volume of the RSVZ and LSVZ, and V25-V40 of the LSVZ. These are listed in Table 13.

Impact of radiation on changes in memory

To determine if the dose of radiation to ROIs was associated with decline in verbal memory performance, analyses were conducted with the radiation variables yielding significant correlations, as well as mean, minimum, maximum, and weighted dose to the ROIs, on verbal memory indices. Hierarchical regression analyses were used to evaluate

whether these radiation variables could predict neuropsychological scores at post-radiation, over and above previous test performance as a predictor. Colinearity between predictors, and directionality of relationship between predictor and outcome variables was explored via zero order correlations. This was of particular interest in cases where in the relationship between outcome and predictor was directionally opposed to what was predicted, or for cases wherein directionality of two related predictors was opposed for the same outcome variable. Beta weights indicated directional relationships opposed to the zero order correlations, were the determined to be the result of multicolinearity with additional predictors in the equation. Zero order correlations for significant predictors can be found in Tables 14-19.Regression results can be found in Tables 20-25.For total learning, the dose received to 55% of the LHC (V55 LHC) was found to account for a significant proportion of the variance in total learning at time 2 after controlling for performance at time 1, $R^2 = .54$, $F(2, 25) = 14.61$, $p < .001$. This is consistent with zero order correlation for dose being negatively related to performance.

For initial learning, number of cycles of chemotherapy at time 2 accounted for a significant proportion of the variance in initial learning at time 2 after controlling for performance at time 1, $R^2 = .65$, $F(2, 23) = 21.08$, $p < .001$, This is consistent with zero order correlations, number of cycles being positively related to performance.

For learning acquisition, a six-variable model was found to best account for variance in learning at time 2 after controlling for learning at time 1, $R^2 = .83$, $F(6, 19) = 15.85$, $p <.001$. Standardized beta weights were -0.16 for learning acquisition at time 1, -0.49 for number of cycles of chemotherapy at time 2, -0.94 for minimum dose to the LHC, 0.91 for minimum dose to the LSVZ, 0.55 for dose to 55% of the LSVZ, and -0.44 for the

mean dose to the LSVZ. Directionality of beta weights is largely consistent with zero order correlations. A negative relationship between dose to the hippocampus and performance was noted. However, positive relationship between all LSVZ variables and outcome was noted for zero order correlations, indicating that the negative relationship found in the regression is likely spurious.

For delayed recall, dose to 50% of the LHC accounted for a significant proportion of the variance in initial learning at time 2 after controlling for performance at time 1, $R^2 = .54$, $F(2, 16) = 9.49$, $p<.005$. A negative relationship between dose and performance was observed, consistent with zero order correlations.

For percent retention, a three-variable model was found to best account for variance in percent retention at time 2 after controlling for delayed recall at time 1, $R^2 = .59$, $F(3, 14) = 6.73$, $p < .05$. Standardized beta weights were 0.54 for percent retention at time 1, -0.67 for dose to 50% of the LHC, and 0.63 for dose to 60% of the LHC. Zero order correlations revealed negative relationships between dose and performance for both predictor variables, indicating the positive relationship found in the regression between dose to 60 % of the LHC and performance is likely artificial.

For recognition discriminability index, a seven-variable model was found to best account for variance in recognition memory at time 2 after controlling for delayed recall at time 1, $R^2 = .95$, $F(7, 11) = 32.85$, $p<.001$. Standardized beta weights were 0.43 for recognition memory at time 1, -1.15 for weighted dose to the LHC, 0.63 for dose to 60% of the LHC, 1.14 for maximum dose to the LHC, -0.68 for dose to 50% of the LHC, 0.89 for dose to 45% of the RHC, and -0.69 for mean dose to the RHC. Zero order correlations revealed

negative relationships between dose to the LHC and performance for all dose variables except dose to 60% of the LHC, which is consistent with regression findings for this variable. Given a negative zero order correlation between maximum dose to the LHC, the positive relationship found in the regression is likely artificial. Positive zero order correlations were found between dose to the RHC and performance for both dose variables, indicating that the negative relationship observed in the regression is likely artificial.

Impact of radiation on changes in executive function

To determine if the dose of radiation to ROIs would affect changes in performance in executive function, analyses were conducted with the radiation variables bearing significant correlations, as well as mean, minimum, maximum, and weighted dose of the ROIs, on verbal memory indices. Hierarchical regression analyses were used to evaluate whether these radiation variables could predict neuropsychological scores at post-radiation, over and above previous test performance as a predictor. Colinearity between predictors, and directionality of relationship between predictor and outcome variables was explored via zero order correlations. This was of particular interest in cases where in the relationship between outcome and predictor was directionally opposed to what was predicted, or for cases wherein directionality of two related predictors was opposed for the same outcome variable. Beta weights indicated directional relationships opposed to the zero order correlations, were the determined to be the result of multicolinearity with additional predictors in the equation. Zero order correlations for significant predictors can be found in Tables 26-28.

Regression results are presented in Tables 29 – 31. For time to complete TMT B, SSRI use at time 2 was found to account for a significant proportion of variance in time to complete TMT B at time 2 after controlling for performance at time one, $R^2 = .61$, $F(2, 18) = 16.37$, $p < .001$. A negative relationship between dose and standardized performance was observed, consistent with zero order correlations.

Similarly, for B – A SSRI use at time 2 was found to account for a significant proportion of variance in B – A at time 2 after controlling this metric at time one, $R^2 = .46$, $F(2, 18) = 9.38$, $p < .005$. A positive relationship between dose and unstandardized performance was observed, consistent with zero order correlations.

For B/A, a five-variable model was found to best account for variance in B/A at time 2 after controlling for this metric at time 1, $R^2 = .76$, $F(5, 22) = 13.74$, $p < .001$. Standardized beta weights were 0.04 for B/A at time 1, 0.94 for time elapsed since radiation, -0.63 for number of cycles of chemotherapy, 0.73 for minimum dose to the LSVZ, and -0.29 for weighted dose to the LSVZ. Zero order correlations revealed positive relationships between both LSVZ dose variables and performance for both predictor variables, indicating the negative relationship found in the regression between weighted dose and performance is likely artificial. Directionality for other beta weights is consistent with zero order correlations.

Overall results for linear regression models for all neuropsychological variables and all significant predictors can be found in Table 32. A similar summary table of results, after accounting for variables with high multicolinearity, can be found in Table 33.

As a majority of participants had a left frontal primary tumor focus, difference in neuropsychological outcome scores between those with a left frontal tumor focus and those with tumor focus in other locations. Results are presented in Table 34. Only B – A was found to differ significantly as a function of presence of left frontal tumor. This suggests that left frontal tumor presence is not solely driving the aforementioned relationships, with the exception of B – A.

Dose - Decline Relationships

Radiation results were additionally examined in terms of dose, as the aforementioned results indicate dose at a particular volume is related to cognitive function. However, it does not provide assessment of specific doses at these aforementioned volumes which increase the likelihood of a decrease in cognitive functioning. As can be seen in Figure 1, the relationship between dose to 55% of the left hippocampus and total learning does not appear to be linear. However, as there are not an equal number of data points for every radiation dose increment, with some cases having only a single data point, this may be unduly affected by outliers. To reduce this, average outcome score for each 10 Gy interval is displayed in Figure 2. The relationship here too appears to be affected by outliers. Thus for this variable, a dose value at which decline is likely cannot be reliably determined. Figure 3 depicts the relationship between dose to 50% of the left hippocampus and delayed recall. Inspection of the trendline suggests that a score of a standard deviation and a half below average in delayed recall is associated with a dose of 50 Gy or more to 50% of the left hippocampus. This is consistent with inspection of the trendline for average outcome score per 10 Gy interval, in Figure 4. Figure 5 depicts the relationship between dose to 50% of the left hippocampus and percent retention.

Inspection of the trendline suggests that a score of a standard deviation and a half below average is associated with a dose of 55 Gy or more to 50% of the left hippocampus. This is more evident in Figure 6, which depicts the relationship of average outcome score per 10 Gy interval and outcome score. Figure 7 depicts the relationship between dose to 50% of the left hippocampus and recognition discriminability index, with a third order polynomial trendline. However, as there is not an equal number of data points for every radiation dose increment, with some cases having only a single data point, this may be unduly affected by outliers. Figure 8 depicts the relationship between average outcome score per 10 Gy and radiation. The relationship here too appears to be affected by outliers. Thus for this variable, a dose value at which decline is likely cannot be reliably determined.

Reliable Change Results

Univariate ANOVAs were run on each of the RC-transformed variables, to determine if there were significant differences in performance between surgery intervals, and RC category (declined, stable, or improved) for each outcome measure. No significant differences were found for any of these sets of analyses.

Examination of cases per RC category yields small frequencies of cases that experienced decline. More specifically, 0-6 cases experienced decline across memory variables, and 3-5 cases experienced decline across executive function variables. This indicates there is not sufficient power to conduct the intended analyses on Reliable Change.

Alternatively, data are described in Table 35, which lists RC category per surgery confound category. It is evident that the majority of individuals across variables and

across surgery confound categories remained stable in their performance from a reliable change perspective. The number of individuals who experienced decline greater in scope than what would be predicted from psychometric approximation of fluctuations in test performance, in memory outcome variables, ranged from 0-5, for those who underwent neuropsychological testing prior to surgery. The number of individuals who experienced decline greater in scope than what would be expected, in executive outcome variables, ranged from 0-3, for those who underwent neuropsychological testing prior to surgery. The number of individuals who experienced decline greater in scope than what would be expected, in memory outcome variables, ranged from 0-1, for those who underwent neuropsychological testing less than two weeks after surgery. The number of individuals who experienced decline greater in scope than what would be expected, in executive outcome variables, ranged from 0-2, for those who underwent neuropsychological testing less than two weeks after surgery. The number of individuals who experienced decline greater in scope than what would be expected, in memory outcome variables, ranged from 0-1, for those who underwent neuropsychological testing greater than two weeks after surgery. The number of individuals who experienced decline greater in scope than what would be expected, in executive outcome variables, ranged from 0-1, for those who underwent neuropsychological testing greater than two weeks after surgery.

Discussion

The current study investigated the role of therapeutic radiation to the hippocampus and SVZ on changes in verbal memory and executive function. Findings from this study provide partial support of the hypothesis that changes in verbal memory would be related to amount of radiation to the hippocampus. More specifically, it was observed that the radiation to the left hippocampus predicted changes in total learning, delayed recall, learning acquisition, delayed recall, percent retention, and recognition discriminability index. Radiation to the right hippocampus was found to predict changes in recognition discriminability index. However, a double dissociation was not observed, as radiation to the SVZ was found to account for changes in verbal memory as well. More specifically, radiation to the left SVZ was found to predict learning acquisition. Amount of radiation to 50-55 % of the left hippocampus is negatively related to verbal memory at time two, including total learning, delayed recall, percent retention, and recognition discriminability index, while dose to 60% of the left hippocampus is positively related to recognition discriminability index. Dose to the right hippocampus was found to be positively related to recognition performance at time 2.

The negative relationship between dose to the left hippocampus and memory is consistent with expectations and provides support for the role of the hippocampus in memory, as well as the ability of radiation to disrupt this function. The higher the dose of radiation to the hippocampus is related to a greater likelihood of injury to the structure or cells within (Hill, 1992; Shaw & Robbins, 2008). This then would increase the likelihood of disruption of function of this structure, namely memory (Heilman & Valenstein, 2003; Shimamura, 2002). The positive relationship between dose to 60% of the left

hippocampus and recognition index discriminability and the positive relationship between dose to the right hippocampus and recognition memory cannot be explained in this manner, as they run antithetically to expectations, based solely on the aforementioned rationale. The positive relationship between dose to the right hippocampus and recognition memory, at first glance, is inconsistent with expectations. A higher dose of radiation was expected to be related to poorer, not better, performance on measures of memory. It is possible, however, that this finding represents a more direct effect of disease. Given the specificity with which radiation can be directed to particular structures, the tumor cavity and surrounding tissues typically receive a relatively higher dose of radiation than other more distal tissue (Hill, 1992). Thus, a positive relationship between dose to a structure and performance may indicate that performance is affected positively by absence of tumor in another region, creating a secondary relationship between radiation dose and performance. In this sense, findings may represent that recognition memory positively related to absence of tumor focus in the left hippocampus, or other brain regions related to this cognitive function.

Radiation to the SVZ was found to account for variance in executive functioning, above and beyond previous performance, only in terms of TMT ratio. More specifically, minimum and dose to 55% of radiation to the left SVZ was found to be positively related to TMT ratio. Radiation to the hippocampus did not predict change in any metrics of executive function. The positive relationship noted between radiation to the SVZ and outcome on ratio scores is in keeping with expectations. A decrease in functionality of the SVZ, secondary to radiation, has been suggested to result in a lessened ability to assist other damaged brain regions in injury response and repair (Chen et al., 2004;

Romankob, et al., 2004; Zhang, Zhang, & Chopp, 2005). Thus increased radiation to the SVZ would be expected to be related to increased injury and thus increased dysfunction to the surrounding tissue, including the frontal lobes. Additionally, a higher TMT ratio score reflects greater executive dysfunction.

Additional variables of interest were found to significantly predict cognitive functioning as well. More specifically, number of cycles of chemotherapy was found to predict change in initial learning, learning acquisition and TMT ratio. This result is in keeping with the association between chemotherapy and memory complaints, as well as more general cognitive dysfunction, in a variety of histological samples (Dietrich, Monje, Wefel, & Meyers, 2008; Kayl, Wefel, & Meyers, 2006; Meyers, 2000; Wefel, et al., 2004). Additionally, it is in keeping with the notion that chemotherapy is a risk factor for decreased radiation tolerance (Leibel & Sheline, 1991).

Prescription of SSRIs at time 2 was found to predict change in TMT B and TMT difference. While animal research by Majlessi and Naghdi (2002) has indicated a relationship between SSRIs and decreased spatial memory, review of the literature in the human population reveals more variable findings for the influence of SSRIs. While a review indicates relatively minimal effects of SSRIs, particularly when compared to other CNS-active agents, effects of SSRIs on cognition in certain subgroups is more variable (Dumont, De Visser, Cohen, &, Van Gerven, 2005). Increased perception of memory difficulties were noted in individuals with significant psychiatric symptoms on SSRIs (Wadsworth et al., 2005). Increased memory difficulties, among other symptoms, has been noted in some cases of use of anticholinergics in an elderly population, though not in cases of close medication managment (Harik et al., 2008; Sadavoy, 2004). Further, in

cases of effective treatment of depressive symptomatology with SSRIs, cognitive effects have been shown to remit (Brooks & Hoblyn, 2007).

Given the host of confounding factors, potentially influencing the relationship between SSRIs and cognition, it is important to consider that the relationship between prescription of SSRIs and change in TMT B and TMT difference is possibly mediated by depression or depressive symptomatology, for which SSRIs would typically be prescribed. The relationship between depression and psychomotor slowing has been borne out in the literature (Austin, et.al., 1999; Sobin & Sackeim, 1997). Additionally, a relationship between executive dysfunction and depression has been suggested, while contradictory findings exist regarding whether this effect is evident on TMT B (Grant et al., 2001; Harvey et al., 2004).

Time since radiation was found to predict TMT ratio. This may reflect a resolution of early – delayed cognitive effects of radiation, which is still possible during the 9-12 months following completion of radiation therapy (Taphoorn & Klein, 2004; Vigliani et al., 1996).

As radiation to the SVZ was found to account for changes in some aspects of verbal memory, the hypothesized double dissociation between the relationship between verbal memory and the hippocampus, and the relationship between executive function and the SVZ was not observed. However, a single dissociation was observed for the relationship of the SVZ and executive function was observed.

Insofar as a relationship was found between the SVZ and memory was observed, the results are consistent with the notion that many cognitive functions are not easily

dissociable. Indeed, the "higher" cognitive processes are not necessarily discrete entities, though often studied and discussed as such (Heilman & Valenstein, 2003; Luria, 1966). For example, attention necessarily underlies many other cognitive processes, such as memory. If one is not engaging in a minimum level of attention the to-be-remembered items, encoding will be adversely impacted, as will retention and recall. Attention and awareness have been repeatedly shown to be necessary for even fairly simple forms of memory, such as a two-cue discrimination eye blink conditioning task (Disterhoft, et al., 2002).

In the case of the study at hand, the relationship of the hippocampi and verbal memory has been well documented (Squire, 1992). The relationship between the SVZ and some aspects of verbal memory may be explained by the nature of the memory task itself. Strategies for approaching a word-memory task may differ. Some individuals may approach this in a relatively unstrategic manner, resulting in responses conforming to recency and primacy effects. Other individuals may rehearse certain subsets of words, resulting in different patterns (Wagner, 2002). Given that words on the list are from three semantic categories, some individuals may use this information to cluster responses semantically, decreasing demands on memory. Given improved recall and the notion that the three semantic clusters may serve as internal cues, this strategy may increase the likelihood of recall following a delay. Individuals may also use other mnemonic strategies to aid in remembering. The ability to determine and deploy strategies on this task could be considered to fall within the realm of executive function (Demb et al., 1995). The relationship between radiation to the SVZ and learning acquisition is concordant with this inference, as executive abilities likely come into play in adjusting

strategy to maximize total learning. However, directionality is the opposite of what would be predicted from a direct relationship. Thus, similar to the positive relationship between radiation to the right hippocampus and memory, the positive relationship between radiation to the SVZ and TMT ratio may indicate that performance is affected positively by absence of tumor in another region.

Laterality differences are also noted in the results, both for memory and executive function. With respect to memory, support for the HERA model is provided by the results. Radiation to the left hippocampus was found to predict changes in memory across multiple memory metrics, while radiation to the right hippocampus was found to significantly predict change in recognition discriminabilty index. This thus reflects the presumed greater role of the hemisphere in encoding, and provides some support for the posited greater role of the right hemisphere in retrieval (Habib, Nyberg, & Tulving, 2003). An additional possible explanation for findings in the right hippocampus may stem from the relationship between radiation to the left and right hippocampi being related, such that a higher degree of radiation to one is associated with a higher degree of radiation to the contralateral structure. This would be in keeping with findings suggesting radiation to the bilateral hippocampi significantly predicting changes in cognition (Gondi et al., 2012).

With respect to lateralized findings in the SVZ, significant findings were found for radiation to the left SVZ alone, while radiation to the right SVZ was not found to be a significant predictor of measured aspects of cognition. Localization of function to the left SVZ would be one explanation for the lateralized findings. Evidence in laterality within the prefrontal cortex, which provides input to the frontal lobes, suggest that damage to the

left dorsolateral prefrontal cortex, as compared to other brain regions, is related to decreased set-switching on a fluency task (Troyer et al., 1998). TMT was initially conceptualized as a left-lateralized task, but this has not been consistently shown (Wheeler & Reitan, 1963; Heilbronner et al., 1991). As set-switching is necessary for TMT B, TMT ratio reflects set-switching ability as well. Thus lateral findings in the left SVZ are consistent with this. However, another possible explanation may stem from the fact that a majority of primary tumor locations in the sample were left frontal, while analyses indicate that tumor location is not driving these differences alone. This asymmetry in the data may reflect tumor/disease burden in this region and its relationship to cognition. It may further reflect a complex interaction between disease effects, treatment effects, and the lessened ability of the damaged SVZ to aid in the repair of the affected tissue. However, as tumor location and amount of radiation to that location are necessarily related, these effects are difficult to parse.

Additionally, as previously mentioned, positive findings for a relationship between radiation to the left SVZ and learning acquisition is possibly reflective of absence of tumor in another region of the brain, such as the right frontal lobe. There is some suggestion that the right prefrontal cortex is differentially more involved in processing information at a holistic level, while the left prefrontal cortex is differentially more involved in processing at a specific and individual level (Huey et al., 2006). The holistic integration of information may be captured by aspects of learning, particularly if learning strategies are applied. Learning strategies, as previously mentioned, involve using semantic and other types of clustering, lessening memory demands, while utilizing the recognition of holistic relationships between to-be-remembered items.

Despite negative findings for a double dissociation, the current study does provide support of the hypothesis that radiation to the SVZ is related to changes in executive functioning and that radiation to the hippocampus is related to changes in verbal memory. Approximate maximum dose that can be absorbed without substantial risk of decreased memory function was noted to be between 50-60 Gy to the 50-55 % of the left hippocampus, though the relationship was not as strongly noted for certain variables.

This finding also provides further support for the role of the hippocampus in the process of memory and the role of the SVZ in executive function. Additionally, these findings provide some support for the practice of hippocampal avoidance during radiation treatment, particularly in cases in which there is a low probability of disease in this area.

Limitations

As previously discussed, limitations in measuring cognitive skills exist in the often non-dissociable nature of the skills themselves. Further, error exists in neuropsychological measures in their ability to accurately measure what they are used to measure, secondary to difficulty dissociating cognitive processes. In addition, error is introduced secondary to the process of measurement itself, with increasing amounts of error associated with subcomponents of each of these measures. In particular, learning acquisition is necessarily confounded by initial learning, such that a low learning acquisition may indicate little overall learning, or it may indicate a ceiling or near ceiling effect, if a high number of words was recalled on the initial learning trial.

Further, TMT B reflects only a portion the cognitive skills that could be considered to be executive functions. It taps into set-shifting and perhaps vigilance, but does not as much

reflect other executive skills. It is thus possible that the role of the SVZ would have been differently borne out with other aspects of executive function.

An additional limitation arose from the clinical nature of the data. As the data were collected as part of routine clinical care and not as a part of a standardized research protocol, great variation exists in concomitant medical and psychiatric diagnoses. There is additional variability in the timing of surgical resection, and the interval between surgical resection and evaluation. While significant differences were not found in performance when comparing these factors, a more standardized timeline would reduce potential confounds of effects of surgery on cognitive performance.

The small sample size did not allow for thorough exploration of some of the sources of variability, namely to determine variables predictive of direction of change from a reliable change standpoint. This would have allowed for a more thorough positing as to critical values of radiation to the ROIs.

The standard battery administered did not contain measures of effort, or symptom validity, nor do the measures used for analyses have imbedded indices of effort. Effort may be a significant factor in this population, given the often near temporal proximity of surgery to neuropsychological evaluation. Additionally, pain and illness has been associated with reduced effort on neuropsychological testing (Hart, Martelli, & Zasler, 2000). Thus it is unclear as to whether adequate effort was provided on the measures analyzed and as such effort may be a confounding.

Additional limitations of the study include the fact that the SVZ was not divided into anterior and posterior subsections. Division of this structure would have allowed for

separate analyses of the anterior section, which because of its relative proximity to the frontal lobes, as compared to the posterior section of the SVZ, has a theoretical basis for being more strongly associated with executive function. Thus, analysis of the whole structure may have diluted findings of association between the anterior SVZ and executive function.

Future Directions

As the role of radiation to the brain in changes in cognitive functioning is still a relatively unexplored issue, many empirical questions remain. Ideally, future studies may explore this issue in a prospective manner, such that intervals between surgery and initial assessment, as well as radiation and second assessment, could be relatively standardized. A prospective design would also allow for pre- and post-radiation imaging to be completed, which would allow for changes in volume of the ROIs to be investigated as a factor as well.

The role of radiation to both hippocampi, through calculating composite hippocampi dose volume histograms, would be an interesting variable to investigate, particularly as this has yielded significant results in predicting cognition in recent work (Gondi et al., 2012).

The roles of effort, depression, and anxiety in performance on cognitive measures have been well-established. Further, depression, as well as other psychological symptoms, is common comorbidities in illnesses such as cancer, increasing the likelihood that this may bear impact upon cognition in this population (McDaniel et al., 1995). Future research may also investigate the role of effort and mood in the relationship between radiation and changes in cognitive functioning.

Further, given the occurrence of directionally paradoxical findings, which are believed to potentially represent absence of tumor in another critical location, additional disease characteristics would be interesting sources of variance to consider in future research. One such variable of interest would be the gross tumor volume (GTV), which may provide a proxy for disease/treatment burden, and thus influence changes in cognitive functioning.

References

Austin, M.P., Mitchell, P., & Goodwin, G.M. (2001). Cognitive deficits in depression: Possible Implications for functional neuropathology. *British Journal of Psychiatry, 178*, 200-206.

Armstrong, C.L., Ruffer, J., Corn, B.W., DeVries, K., Mollman, J. (1995). Biphasic patterns of memory deficits following moderate-dose partial-brain irradiation: neuropsychological outcome and proposed mechanisms. *Journal of Clinical Oncology, 13*, 2263-2271.

Ashby, L.S., Shapiro, W.R. (2004). Low-grade glioma: supratentorial astrocytoma, oligodendroglioma, and oligoastrocytoma in adults. *Current Neurology and Neuroscience Reports, 4*, 211-217.

Basso, M.R., Bornstein, R.A., & Lang, J.M. (1999). Practice effects on commonly used measures of executive function across twelve months. *The Clinical Neuropsychologist, 13(3)*, 283-292.

Benedict, R. H. B., Schretlen, D., Groninger, L. Brandt, J. (1998). Hopkin's Verbal Learning Test-Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist, 12(1)*, 43-55.

Benedict, R.H.B., & Zgaljardic, D.J. (1998). Practice effects during repeated administrations of Memory with and without alternate forms. *Journal of Clinical and ExperimentalNeuropsychology, 20(3)*, 339-352.

Brandt, J., & Benedict, R.H.B. (2001). *Hopkins Verbal Learning Test-Revised*. Lutz, FL: Psychological Assessment Resources.

Brooks, J.O., & Hoblyn, J.C. (2007). Neurocognitive costs and benefits of psychotropic medications in older adults. *Journal of Geriatric Psychiatry and Neurology, 20*, 199-214.

Cahn-Weiner, D.A., Boyle, P.A., & Malloy, P.F. (2002).Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Neuropsychology, 9(3),* 187-191.

Carson, K.A. Grossman, S.A. Fisher, J.D. & Shaw, E.G. (2007). Prognostic factors for survival in adult patients with recurrent gliomas enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. *Journal of Clinical Oncology, 25*, 2601-2606.

Cayre, M., Canoll, P., Goldman J.E. (2009). Cell migration in the normal and pathological postnatal mammalian brain. *Progress in Neurobiology, 88*, 41-63.

Central Brain Tumor Registry of the United States (2005). *Primary Brain Tumors in the United States Statistical Report 1998-2002*, (pp. 8-50). Chicago, IL: Central Brain Tumor Registry of the United States.

Chang, E.L., Wefel, J.S., Hess, K.R., Allen, P.K., Lang, F.F., Kornguth, D., Arbuckle, R.B., Swint, J.M., Shiu, A.S., Maor, M.H., Meyers, C.A. (2009). Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus

whole-brain irradiation: a randomised controlled trial. *The Lancet Oncology, 10(11),* 1037-1044.

Chen, X.H., Iwata, A., Nonaka, M., Browne, K.D., Smith, D.H. (2003). Neurogenesis and glial proliferation persist for at least one year in the subventricular zone following brain trauma in rats. *Journal of Neurotrauma, 20(7),* 623-631.

Craik, F.I.M. & Lockhart, R.S.(1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior, 11,* 671-684.

Christensen, L. & Mendoza, J. L. (1986). A method of assessing change in a single subject: an alteration of the RC index. *Behavior Therapy 17,* 305-308.

Clancy, S. (2008). DNA damage & repair: mechanisms for maintaining DNA integrity. *NatureEducation, 1(1).* Retrieved from http://www.nature.com/scitable/topicpage/dna-damage-repair-mechanisms-for-maintaining-dna-344.

Demb, J.B., Desmond, J.E., Wagner, A.D., Chandan, J.V., Vaidya, C.J., Glover, G.H., & Gabrieli, J.D.E. (1995). Semantic encoding and retrieval in the left interior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *The Journal of Neuroscience, 15(9),* 5870-5878.

Dice, Lee R. (1945). Measures of the Amount of Ecologic Association Between Species. *Ecology, 26* (3), 297-302.

Dikmen, S.S., Machamer, J.E., Winn, H.R., & Temkin, N.R. (1995). Neuropyschological Outcome at 1-year post head injury. *Neuropsychology, 9,* 80-90.

Dietrich, J., Monje, M., Wefel, J., Meyers, C. (2008). Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *The Oncologist, 13,* 1285-1295.

Disterhoft, J.F. Carillo, M.C., Fortier, C.B., Gabrieli, J.D.E., Knuttinen, M. McGlinchey-Berroth, R., Preston, A., and Weiss, C. (2002) Impact of temporal lobe amnesia, aging, and Awareness on human eyeblink conditioning. In Squire, L.R. and Schacter, D.L. (Eds.), *Neuropsychology of Memory, Third edition* (pp. 204-214). New York: The Guildford Press.

Drane, D.L., Yuspeh, R.L., Huthwaite, J.S., Klingler, L.K. (2002). Demographic characteristics and normative observations for derived-trail making test indices. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 15(1),* 39-43.

Dumont, G.J.H., De Visser, S.J., Cohen, A.F., Van Gerven, J.M.A. (2005). Biomarkers for the Effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects, *British Journal of Clinical Pharmacology, 59(5),* 495-510.

Ekdahl, C.T., Kokaia, Z., Lindvall, O. (2009). Brain Inflammation and adult neurogenesis: the dual role of microglia. *Neuroscience, 158(3),* 1021-1029.

Ghia, A., Tome, W.A., Thomas, S., Cannon, G., Khuntia, D. Kuo, J.S., Mehta, M.P. (2007). Distribution of brain metastases in relation to the hippocampus:

implications for neurocognitive functional preservation. *International Journal of Radiation Oncology Biology Physics, 68*, 971-977.

Glantz, M.J. & Conlee, J.W. (2008) High-Grade Gliomas. In C.A. Meyers & J.R. Perry (Eds.) *Cognition and Cancer*, (pp. 142-155). New York: Cambridge University Press.

Gondi, V., Hermann, B.P., Mehta, M.P., Tome, W.A. (2012) Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *International Journal of Radiation Oncology Biology Physics, 83(4)*, 487-493.

Gondi, V., Tome, W.A., Marsh, J., Struck, A., Ghia, A., Turian, J.V., Bentzen, S.M., Kuo, J.S., Khuntia, D., Mehta, M.P. (2010). Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: Safety profile for RTOG 0933. *Radiotherapy Oncology*, *95*, 327-331.

Grant, M.M., Thase, M. E., & Sweeney, J.A. (2001). Cognitive disturbance in outpatient depressed younger adults: Evidence of modest impairment. *Biological Psychiatry, 50*, 35-43.

Gutierrez, A.N., Westerly, D.C., Tome, W.A., Jaradat, H.A., Mackie, T.R., Bentzen, S.M., Khuntia, D., Mehta, M.P. (2007). Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. *International Journal of Radiation Oncology Biology Physics, 69*, 589-597.

Habib, R., Nyberg, L., Tulving, E. (2003). Hemispheric asymmetries of memory: the HERA model revisited. *Trends in Cognitive Sciences, 7(6),* 241-245.

Hahn, C.A., Su-Min, Z., Raynor, R., Tisch, A., Light, K., Shafman, T., Wong, T., Kirkpatrick, J., Turkington, T., Hollis, D., & Marks, L.B. (2009). Dose-dependent effects of Radiation therapy on cerebral blood flow, metabolism, and neurocognitive dysfunction. *International Journal of Radiation Oncology Biology Physics, 73(4),* pp. 1082-1087.

Harik, L., Pica, A., Wright, S., Lee, J., & Bieliauskas, L. (2008). Cognitive deficits associated with anticholinergic therapy and drugs with anticholinergic properties in community dwelling Veterans. *Journal of the International Neuropsychological Society, 14*(Suppl S1), 106.

Hart, R.P, Martelli, M.F., & Zasler, N.D. (2000). Chronic pain and neuropsychological Functioning. Neuropsychology Review, 10(3), pp. 131-149.

Harvey, P.O., Le Bastard, G., Poshon, J.B., Levy, R., Allilaire, J.F., Dubois, B., & Fossati, P. (2004).Executive functions and updating of the contents of working memory in unipolar depression. *Journal of Psychiatric Research, 38,* 567-576.

Heilbronner, R.L., Henry, G.K., Buck, P., Adams, R.L., & Fogle, T. (1991) Lateralized brain damage and performance on Trail Making A and B, Digit Span Forward and Backward, and TPT memory and location. Archives of Clinical Neuropsychology, 6, 251-258.

Heilman, K.M., & Valenstein, E. (Eds.) (2003). *Clinical Psychology, Fourth Edition*. (pp. 1-14). New York: Oxford University Press.

Henke, K., Buck, A., Weber, & Wieser, H.G. Human hippocampus establishes associations in Memory. *Hippocampus, 7,* 249-256.

Herrmann, H.D. (1990). Tumors of the Central Nervous System. In D.K. Hossfield, C.D. Sherman, R.R. Love, F.X. Bosch (Eds.), *Manual of Clinical Oncology, Fifth Edition,* (pp. 319-336). New York: Springer-Verlag.

Hill, R.P. (1992). Cellular Basis of Radiotherapy. In I.F. Tannock & R.P. Hill (Eds.), *The Basic Science of Oncology,* (pp. 259-275). New York: Pergamon Press.

Hill, R.P. & Tannock, I.F. (1992). Introduction: Cancer as a Cellular Disease. In I.F. Tannock & R.P. Hill (Eds.), *The Basic Science of Oncology,* (pp. 259-275). New York: Pergamon Press.

Hodges, .H, Katzung, N., Sowinski, P., Hopewell, J.W., Wilkinson, J.H., Bywaters, T., Rezvani, M. (1998). Late behavioural and neuropathological effects of local brain irradiation in the rat. *Behavioural Brain Research, 91,* 99-114.

Huey E.D., Krueger, F., Grafman, J. (2006).Representations in the Human Prefrontal Cortex. *Current Directions in Psychological Science, 15(4),* 167-171.

Jacobson, N. S., Follette, W. C. & Revenstorf, D. (1984). Psychotherapy outcome research: methods for reporting variability and evaluating clinical significance. *Behavior Therapy, 15,* 336-352.

Jacobson, N. S. & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology 59(1),* 12-19.

Johnson, J.K., Lui, L.Y., & Yaffe, K. (2007). Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *The Journals of Gerontology: Series A, 62(10),* 1134-1141.

Kalm, M., Fukuda, A., Fukuda, H., Ohrfelt, A., Lannering, B., Bjork-Eriksson, T., Blennow, T., Marky, I., Blomgren, K. (2009) Transient inflammation in neurogenic regions after irradiation of the developing brain. *Radiation Research, 171(1),* 66-76.

Kalm, M., Lannering, B., Bjork-Eriksson, T., Blomgren, K. (2009). Irradiation-induced loss of microglia in the young brain. *Journal of Neuroimmunology, 206(1-2),* 70-75.

Kayl, A.E., Wefel, J.S., Meyers, C.A. (2006). Chemotherapy and Cognition: Effects, potential mechanisms, and management. *American Journal of Therapeutics, 13(4),* 362-369.

Kolb, B. & Whishaw, I.Q. (2003). *Fundamentals of Human Neuropsychology, Fifth Edition*. New York: Worth Publishers.

Lee, Y., & McKinnon, P.J. (2000). ATM dependent apoptosis in the nervous system. *Apoptosis, 5(6),* 523-529.

Leibel, S.A., Sheline, G.E. (1991). Tolerance of the brain and spinal cord to conventional irradiation. In Gutin, P., Liebel, S.A., Sheline, G.E. (Eds.) *Radiation Injury to the Nervous System* (pp.211-238). New York: Raven Press.

Levine, A.J., Miller, E.N., Becker, J.T., Selnes, O.A., Cohen, B.A. (2004). Normative date for determining significance of test-retest differences on eight common neuropsychological instruments. *The Clinical Neuropsychologist, 18,* 373-384.

Li, J., Bentzen, S.M., Li, J., Renschler, M., & Mehta, M.P (2008). Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *International Journal of Radiation Oncology Biology Physics, 71,* 64-70.

Lord, C.J., & Ashworth, A. (2012). The DNA damage response and cancer therapy. *Nature 481(19),* 287-294.

Luria, A.R. (1966). *Higher Cortical Functions in Man.* London: Basic Books. Majlessi, N. & Naghdi, N. (2002). Impaired spatial learning in the Morris water maze induced by serotonin reuptake inhibitors in rats. *Behavioural Pharmacology, 13(3),* 237-242.

McDaniel, J.S., Musselman, D.L., Porter, M.R., & Reed, D.A. (1995). Depression in patients with cancer: Diagnosis, biology, and treatment. *Archives of General Psychiatry, 52(2),* 89-99.

Merchant, T.E., Kiehna, E.N., Li, C., Xiong, X., Mulhern, R.K. (2005). Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with

localized ependymoma. *International Radiation Oncology Biology Physics, 63(5),* 1546-1554.

Meyers, C.A.(2000). Neurocognitive dysfunction in cancer patients. Oncology, 14(1), 75-79.

Meyers, C.A., Geara, F., Wong, P.F., Morrison, W.H. (2000). Neurocognitive effects of therapeutic irradiation for base of skull tumors. *Internatonal Journal of Radiation Oncology Biology Physics, 46(1),* 51-55.

Meyers, C.A., Smith, J.A., Bezjak, A., Mehta, M.P., Liebmann, J., Illidge, T., Kunkler, I., Caudrelier, J.M., Eisenberg, P.D., Meerwaldt, J., Siemers, R., Carri, C., Gaspar, L. E., Curran, W., Phan, S.C., Miller, R.A., & Renschler, M.F. (2004). Neurocognitive function and progression in patients with metastases treated with whole-brain radiation and Motexafin Gadolinium: Results of a randomized phase III trial. *Journal of Clinical Oncology, 22(1),* 157-165.

Monje, M.L., Mizumatsu, S., Fike, J.R., Palmer, T.D. (2002). Irradiation induces neural precursor-cell dysfunction. *Nature Medicine, 8(9),* 955-962.

Monje, M.L., & Palmer, T. (2003). Radiation injury and neurogenesis. *Current Opinion in Neurology, 16,* 129-134.

Mulhern, R.K. &Palmer, S.L. (2003). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer, 27, 177*-197.

Muller, H.W., Junghans, U., Kappler, J. (1995). Astroglial neurotrophic and neurite-promoting factors. *Pharmacological Therapy, 65,* 1-18.

Paton, J.J., Belova, M.A., Morrison, S.E., Salzman, C.D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature, 439(7078),* 865-870.

Pekny, M. & Nilsson, M. (2005). Astrocyte activation and reactive gliosis. *Glia, 50*, 427-434.

Petri, H.L., & Mishkin, M. (1994). Behaviorism, cognitivism, and the neuropsychology of memory. *American Scientist, 82*, 30-37.

Olson, J.D., Riedel, E., DeAngelis, L.M. (2000). Long-term outcome of low-grade oligodendroglioma and mixed glioma. *Neurology, 54*, 1442-1448.

Peissner, W., Kocher, M., Treuer, H., Gillardon, F. (1999). Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. *Brain Research Molecular Brain Research, 71*, 61-68.

Romankob, M.J., Rolac, R., Fikec, J.R., Szelee, F.G., Dizone, M.L.V., Felling, R.J., Brazelf, C.Y., Levison, S.W. (2004). Roles of the mammalian subventricular zone in cell replacement after brain injury. *Progress in Neurobiology, 74(2),* 77-99.

Ris, D.M. (2007). Lessons in pediatric neuropsycho-oncology: What we have learned since Johnny Gunther. *Journal of Pediatric Psychology, 32(9),* 1029-1037.

Ris. M. D., & Noll, R.B. (1994). Long-term neurobehavioral outcome in pediatric brain-tumor patients: Review and methodological critique. *Journal of Clinical and Experimental Neuropsychology, 16*, 21-24.

Robbins, M.E.C. & Zhao, W. (2004). Chronic oxidative stress and radiation-induced late normal tissue injury: a review. *International Journal of Radiation Biology, 80*, 251-259.

Roman, D.D., & Sperduto, P.W. (1995). Neuropsychological effects of cranial radiation: current knowledge and future directions. *International Journal of Radiation Oncology Biology Physics, 31*, 983-98.

Sadavoy, J. (2004). *Psychotropic drugs and the elderly*. New York: Norton & Company.

Shaw, E.G., & Robbins, M.E. (2008) Biological bases of radiation injury to the brain. In C.A. Meyers & J.R. Perry (Eds.) *Cognition and Cancer*, (pp. 142-155). New York: Cambridge University Press.

Shein, N.A., Grigoriadis, N., Horowitz, M., Umschwief, G., Alexandrovich, A.G., Simeonidou, C., Grigoriadis, S., Touloumi, O., Shohami, E. (2008). Microglial involvement in Neuroprotection following experimental traumatic brain injury in heat-acclimated mice. *Brain Research, 1244*, 132-141.

Sobin, C., & Sackeim, H.A. (1997). Psychomotor symptoms of depression. *American Journal of Psychiatry, 154*, 4-17.

Song, H., Stevens, C.F., & Gage, F.H. (2002). Astroglia induce neurogenesis from adult neural stem cells. *Nature*, *417*, 39-44.

Squire, L.R. (1982). The neuropsychology of human memory. *Neuroscience, 5*, 241-273.

Squire, L.R. (1992). Memory and the Hippocampus: A synthesis from findings with rats, Monkeys, and humans. *Psychological Review, 99(2),* 195-231.

Squire, L.R., Clark, R.E., Knowlton, B.J. (2001). Retrograde amensia. *Hippocampus, 11,* 50-55.

Slick, D.J. (2006). Psychometrics in neuropsychological assessment. In E. Strauss, E.M.S. Sherman, & O. Spreen (Eds.) *A Compendium of Neuropsychological Tests, Third Edition,* (pp. 3-43). New York: Oxford University Press.

Stupp R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., Belanger, K., Brandes, A.A., Marosi, C., Bogdahn, U., Curschmann, J., Janzer, R.C., Ludwin, S.K., Gorlia, T., Allgeier, A., Lacombe, D., Cairncross, J.G., Eisenhauer, E., Mirimanoff, R.O. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine, 352(10),* 987-996.

Stupp, R., Hegi, M.E., Mason, W.P., van den Bent, M.J., Taphoorn, M.J.B., Janzer, R.C., Ludwin, S.K., Allgeier, A., Fisher, B., & Belanger, K. (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet Oncology, 10(5),* 459-466.

Sun, A., Bae, K., Gore, E.M., Movsas, B., Wong, S.J., Meyers, C.A., Bonner, J.A., Schild, S.E., Gaspar, L.E., Bogart, J.A., Werner-Wasik, M., & Choy, H. (2010). Phase III Trial of Prophylactic cranial irradiation compared with observation in patients with locally advanced non – small – cell lung cancer: Neurocognitive and quality – of – life analysis. *Journal of Clinical Oncology, 29,* 279-286.

Taphoorn, M.J.B. & Klein, M. (2004). Cognitive deficits in adult patients with brain tumors. *The Lancet Neurology, 3,* 159-168.

Taphoorn, M.J.B. & Niel, C.G. (2008). Low-Grade Gliomas. In C.A. Meyers & J.R. Perry (Eds.) *Cognition and Cancer*, (pp. 142-155). New York: Cambridge University Press.

Tombaugh, T.N. (2003). Trail Making Test A and B: Normative data stratified by age and Education. *Archives of Clinical Neuropsychology, 19,* 203-214.

Troyer, A.K., Moscovitch, M., Winocur, G., Alexander, M.P., Stuss, D. (1998). Clustering and Switching on verbal fluency: the effects of focal frontal and temporal lobe lesions. *Neuropsychologia, 36(6),* 499-504.

Van Rossum, D., & Hanisch, U.K. (2004). Microglia. Metabolic Brain Disease, 19: 393-411.

Vigliani, M.C., Sichez, N., Poisson, M., Delattre, J.Y. (1996). A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. *International Journal of Radiation Oncology Biology Physics, 35*, 527-533.

Wadsworth, E.J., Moss, S.C., Simpson, S.A., & Smith, A.P. (2005). SSRIs and cognitive performance in a working sample. *Human Psychopharmacology, 20*, 561-572.

Wagner, A.D. (2002). Cognitive control and episodic memory. . In Squire, L.R. and Schacter, D.L. (Eds.), *Neuropsychology of Memory, Third edition* (pp. 204-214). New York: The Guildford Press.

Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., Meyers, C.A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma. *Cancer, 100(11),* 2292-2299.

Wheeler, L., & Reitan, R.M. (1963). Discriminant functions applied to the problem of predicting cerebral damage from behavioral tests: A cross-validation study. *Perceptual and Motor Skills, 16,* 681-701.

Winocour, G. & Moscovitch, M. (2011). Memory transformation and systems consolidation. *Journal of the International Neuropsychological Society, 17,* 1-15.

Wolfson, A.H., Bae, K., Komaki, R., Meyers, C., Movsas, B., Le Pechoux, C., Werner-Wasik, M., Videtic, G.M.M., Graces, Y.I., & Choy, H. (2011). Primary analysis of a phase II Randomized trial radiation therapy oncology group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *International Journal of Radiation Oncology Biology Physics, 81(1),* 77-84.

Zhang, R.L., Zhang, Z.G., Chopp, M. (2005). Neurogenesis in the adult ischemic brain: Generation, migration, survival, and restorative therapy. *Neuroscientist, 11,* 406-408.

Table 1

Inter and Intra Rater Reliability ($\rho_{x,y}$)

Characteristic	($\rho_{x,y}$)
Inter-rater Reliability	
Volume	.98
Minimum Radiation	.97
Maximum Radiation	.99
Mean Radiation	.99
Intra-rater Reliability	
Volume	.99
Minimum Radiation	.99
Maximum Radiation	.99
Mean Radiation	.99

Table 2

Inter and Intra Rater Dice Coefficients

Region of Interest	Mean(sd)	Median	Range
Intra-rater			
Total	0.80(0.07)	0.81	0.62 – 0.94
Right Ventricle	0.85(0.05)	0.85	0.74 – 0.91
Left Ventricle	0.84(0.07)	0.84	0.72 – 0.94
Right Hippocampus	0.76(0.05)	0.76	0.68 – 0.83
Left Hippocampus	0.77(0.07)	0.77	0.62 – 0.85
Inter-rater[a]			
Total	0.63(0.12)	0.65	0.27 – 0.83
Right Ventricle	0.67(0.09)	0.68	0.55 – 0.83
Left Ventricle	0.66(0.12)	0.65	0.52 – 0.83
Right Hippocampus	0.56(0.14)	0.64	0.27 – 0.69
Left Hippocampus	0.63(0.12)	0.68	0.40 – 0.72

[a]Inter-rater dice coefficients were calculated using the overlap of the three separate volumes, according to the following revised formula:

$$S = 3(A \cap B \cap C)/(|A| + |B| + |C|)$$

Table 3

Reliable Change Values

Variable	RCI(95%CI)	RCI cut-off	RCI(90%CI)	RCI cut-off
Hopkins Verbal Learning Test - R				
Total Learning	6.22	6	5.21	5
Trial 1	3.72	4	3.13	3
Learning	3.62	4	3.04	3
Delayed Recall	3.23	3	2.71	3
Percent Retention	28.14	28	23.62	24
Recognition	2.15	2	1.81	2
Trail Making Test				
Form A	14.26	14	11.96	12
Form B	31.35	31	26.32	26
Trails Difference (B-A)	34.05	34	29.11	29
Trails Ratio (B/A)	1.51		1.31	

Table 4

Patient Demographic Characteristics

Characteristic	No. of participants (%)[a] (N=36)
Age at Initial Testing	
Mean (SD)	42.37 (12.15)
Range	21.47-66.54
Years of Education	
Mean (SD)	15.56 (2.14)
Range	10-18
Gender	
Male	22 (61)
Handedness	
Right	35 (97)
Race	
African American/Black	1 (3)
Asian/Pacific Islander	2 (6)
Caucasian	30 (83)
Hispanic/Latino	3 (8)

[a] Due to rounding error, sum of percentages may not equal 100.

Table 5

Patient Clinical Characteristics

Characteristic	No. of participants (%)[a] (N=36)
Primary Tumor Focus	
Right Frontal	7 (19)
Left Frontal	12 (33)
Right Temporal	7 (19)
Left Temporal	8 (22)
Right Parietal	0 (0)
Left Parietal	2 (6)
Histology	
Low Grade	8(22)
Anaplastic Astrocytoma	17(47)
Glioblastoma Multiforme	11(31)
Chemotherapy[c] – Initial Testing	
No	32(89)
Chemotherapy[c] – Follow-up Testing	
No	10(27.8)
Surgery Prior to Initial Testing	
Yes	22 (61)
Interval – Surgery to Initial Testing (weeks)[b]	
Mean (SD)	4.20 (4.05)
Median	2.74
Range	0.43 - 18.92
Interval – Radiation to Follow-up Testing (months)	
Mean (SD)	17.61 (12.61)
Median	12.38
Range	9.1 – 58.67
Test – Retest Interval (months)	
Mean (SD)	19.19 (12.56)
Median	14.00
Range	9.00 – 61.00

[a] Due to rounding error, sum of percentages may not equal 100.
[b] $n = 22$
[c] $n = 35$

Table 6

Summary of Neuropsychological Scores at Time 1 and 2

	Time 1			Time 2		
Variable	M(sd)	Med	Range	M(sd)	Med	Range
HVLT-R						
Total Learning	22.28(7.08)	24	1 - 36	24.86(5.49)	25	12 - 35
Trial 1	5.5(2.37)	5	0 - 12	6.58(2.06)	6	2 - 11
Learning	3.68(1.85)	4	0 - 7	3.21(1.67)	3	1 - 7
Delayed Recall[a]	7.96(2.63)	8	0 - 12	8.35(3.79)	9	0 - 12
Percent Retention[a]	81.31(22.48)	90	0 - 100	79.72(29.31)	89	0 - 100
Recognition[a]	9.96(1.71)	10	6 - 12	10.73(1.34)	11	7 - 12
Trail Making Test						
Form B	83.17(59.19)	67	25 - 292	80.56(45.56)	71	26 - 234
(B-A)	52.66(48.76)	36	10 - 214	52.64(38.67)	46.5	8 - 183
(B/A)	2.70(1.15)	2.44	1.48 – 6.78	2.84(0.99)	2.60	

[a]Values based on standard memory administration (N = 26)

Table 7

Patient Demographic Characteristics by Memory Administration

Characteristic	Standard Administration No. of participants (%)[a] (N=26)	Nonstandard Administration No. of participants (%)[a] (N=10)
Age at Initial Testing		
Mean (SD)	41.48 (12.82)	43.00 (10.74)
Median	38.94	42.96
Range	20.90 – 65.45	26.92 – 60.09
Years of Education		
Mean (SD)	15.54 (1.99)	15.60 (2.63)
Median	16.00	16.00
Range	10 – 18	12 – 18
Gender		
Male	14 (54)	8 (80)
Handedness		
Right	25 (96)	10 (100)
Race		
African American/Black	1 (4)	0 (0)
Asian/Pacific Islander	0 (0)	2 (20)
Caucasian	22 (85)	8 (80)
Hispanic/Latino	3 (12)	0 (0)

[a] Due to rounding error, sum of percentages may not equal 100

Table 8

Patient Clinical Characteristics by Memory Administration

Characteristic	Standard Administration No. of participants (%)[a] (N=26)	Nonstandard Administration No. of participants (%)[a] (N=10)
Primary Tumor Focus		
Right Frontal	6 (23)	1 (10)
Left Frontal	10 (39)	2 (20)
Right Temporal	4 (15)	3 (30)
Left Temporal	6 (23)	2 (20)
Right Parietal	0 (0)	0 (0)
Left Parietal	0 (0)	2 (20)
Histology		
Low Grade	8 (22)	3 (30)
Anaplastic Astrocytoma	12 (46)	5 (50)
Glioblastoma Multiforme	9 (35)	2 (20)
Chemotherapy – Initial Testing		
No	22 (85)[b]	10 (100)[c]
Chemotherapy – Follow-up Testing		
No	9 (35)[b]	1 (10)[c]
Surgery Prior to Initial Testing		
Yes	13 (50)	9 (90)
Interval – Surgery to Initial Testing (weeks)		
Mean (SD)	5.04 (4.81)	2.97 (2.34)
Median	3.90	2.46
Range	1.16 – 18.92	0.43 – 8.23
Interval – Radiation to Follow-Up Testing (months)		
Mean (SD)	16.86 (12.14)	19.57 (14.27)
Median	12.07	13.20
Range	7.97 – 58.67	9.07 – 51.03
Test – Retest Interval (months)		
Mean (SD)	18.65 (12.21)	20.60 (14.00)
Median	13.00	14.5
Range	9.00 – 61.00	10.00 – 52.00

[a] Due to rounding error, sum of percentages may not equal 100
[b] n = 13
[c] n = 9

Table 9

Differences in neuropsychological outcome scores between surgical group

Independent Variable	df	*F*	*η*	*p*
Total Learning	2	0.24	0.15	0.79
Trial 1	2	0.13	0.01	0.88
Learning	2	0.59	0.04	0.56
Delay	2	1.69	0.09	0.20
Percent Retention	2	1.06	0.07	0.36
Recognition	2	1.78	0.13	0.19
TMTB	2	1.57	0.09	0.22
B-A	2	1.20	0.07	0.31
B/A	2	0.48	0.03	0.62

Table 10

Significant Effects of Medication on Change in Performance

Independent Variable	Medication	df	*F*	*η*	*p*
Total Learning	Steroids 1	1	7.94	0.32	0.01
Trial 1	Depressants 2	1	5.63	0.39	0.04
	SSRI 2	1	6.62	0.42	0.03
Recognition	Analgesics 1	1	13.45	0.55	0.004
	Cardiovascular Active 1	1	7.68	0.41	0.02
TMTB	No. Anticonvulsants 1	2	6.75	0.44	0.007
	No. Anticonvulsants 2	2	97.70	0.95	0.00
	SSRIs 1	1	9.37	0.36	0.007
	SSRIs 2	1	119.11	0.92	0.00
	Depressants 1	1	12.27	0.42	0.003
	Depressants 2	1	126.44	0.93	0.00
B-A	SSRIs 1	1	9.97	0.37	0.006
	SSRIs 2	1	25.50	0.72	0.00
	Depressants 1	1	11.55	0.41	0.003
	Depressants 2	1	27.02	0.73	0.00
	No. Anticonvulsants 2	2	24.34	0.83	0.00
B/A	No. Anticonvulsants 2	2	4.31	0.46	0.045
	Analgesics 1	1	4.48	0.21	0.049

Table 11

Radiation Characteristics

Region of Interest	Mean(SD)	Median	Range
Right Hippocampus			
Volume	3.26(1.17)	3.03	0.72 – 6.69
Minimum Dose	22.1(16.68)	16.26	0.84 – 55.89
Maximum Dose	39.89(19.10)	33.89	10.50 – 98.02
Mean Dose	30.39(18.34)	22.51	3.60 – 64.56
Weighted Dose	18.38(15.70)	13.31	0.85 – 73.90
V5	94.96(16.41)	100	19 – 100
V10	87.63(27.88)	100	4 – 100
V15	77.41(36.04)	100	0 – 100
V20	61.96(42.32)	84.60	0 – 100
V25	46.57(46.48)	22.75	0 – 100
V30	40.18(47.12)	3.56	0 – 100
V35	37.60(46.90)	0	0 – 100
V40	34.38(45.04)	0	0 – 100
V45	31.08(43.87)	0	0 – 100
V50	25.93(40.13)	0	0 – 100
V55	13.91(28.26)	0	0 – 100
V60	1.71(8.92)	0	0 – 53
V65	1.71(7.0)	0	0 – 42
Left Hippocampus			
Volume	3.37(1.00)	3.31	1.75 – 6.09
Minimum Dose	25(14.45)	24.48	0.80 – 52.85
Maximum Dose	46.86(14.94)	53.17	1.70 – 62.54
Mean Dose	38.01(15.39)	43.00	1.05 – 57.06
Weighted Dose	24.15(12.87)	22.57	0 – 58.99
V5	96.19(17.31)	100	0 – 100
V10	94.92(19.93)	100	0 – 100
V15	91.11(21.98)	100	0 – 100
V20	81.18(33.62)	100	0 – 100
V25	71.86(39.93)	98.78	0 – 100
V30	65.10(41.71)	91.69	0 – 100
V35	59.37(43.54)	85.02	0 – 100
V40	54.91(43.83)	72.94	0 – 100
V45	48.79(42.10)	46.96	0 – 100
V50	35.17(37.87)	22.27	0 – 100
V55	12.11(25.49)	0	0 – 82.32
V60	1.02(3.66)	0	0 – 20
V65	0	0	0 – 0

Table 11 (*Continued*)

Region of Interest	Mean(SD)	Median	Range
Right Subventricular Zone	38.04(10.59)	36.36	18.14 – 64.99
Minimum Dose	12.58(12.01)	10.31	0.30 – 52.53
Maximum Dose	51.90(15.63)	56.75	12.73 – 97.81
Mean Dose	32.32(16.30)	31.61	5.90 – 59.29
Weighted Dose	229.03(150.33)	233.55	22.30 – 606.31
V5	91.42(18.93)	100	39 – 100
V10	85.37(26.52)	100	16 – 100
V15	78.15(32.20)	96.15	0 – 100
V20	67.63(34.29)	84.14	0 – 100
V25	57.91(36.78)	63.99	0 – 100
V30	49.52(37.76)	46.50	0 – 100
V35	44.30(38.16)	36.81	0 – 100
V40	40.08(37.95)	29.25	0 – 100
V45	35.71(37.18)	21.44	0 – 100
V50	28.18(32.80)	13.32	0 – 100
V55	15.01(24.65)	1.08	0 – 100
V60	3.16(8.28)	0	0 – 38
V65	0.19(1.13)	0	0 – 7
Left Subventricular Zone			
Volume	35.94(9.72)	35.10	14.05 – 59.71
Minimum Dose	11.74(9.93)	11.25	0 – 37.85
Maximum Dose	37.03(13.51)	58.18	29.34 – 63.51
Mean Dose	37.03(13.51)	38.95	8.79 – 60.27
Weighted Dose	250.08(133.97)	248.41	40.96 – 699.43
V5	93.35(15.88)	100	34 – 100
V10	89.87(20.28)	100	27 – 100
V15	85.41(24.49)	99.30	21 – 100
V20	78.41(28.43)	95.12	14.97 – 100
V25	70.50(30.75)	83.58	6.58 – 100
V30	63.58(32.20)	75.97	0 – 100
V35	57.32(31.78)	63.45	0 – 100
V40	51.00(31.83)	55.32	0 – 99.90
V45	44.66(31.81)	45.93	0 – 99.60
V50	35.21(30.73)	26.95	0 – 99.06
V55	17.01(22.59)	5.26	0 – 95.14
V60	5.77(15.16)	0	0 – 78
V65	0	0	0 – 0

Table 12

Correlations between Memory and Radiation Variables

		Total Learning	Initial Recall	Learning Slope	Delayed Recall	Percent Retention	Recognition Discriminability Index
RHC	V5	0.03	0.12	-0.24	-0.12	-0.15	0.57**
	V25	0.21	0.17	0.11	0.09	0.10	0.48*
	V30	0.30	0.27	0.05	0.20	0.21	0.49**
	V35	0.24	0.26	0.03	0.24	0.63	0.42**
	V40	0.35*	0.33	-0.02	0.24	0.26	0.46**
LHC	V30	-0.39*	-0.35*	-0.17	0.36*	-0.39*	-0.35
	V35	-0.46**	-0.41*	-0.17	-0.42*	-0.44**	-0.40*
	V40	-0.50**	-0.44*	-0.16	-0.45**	-0.46**	-0.44*
	V45	-0.52**	-0.45**	-0.18	-0.50**	-0.52**	-0.44*
	V50	-0.46**	-0.40*	-0.18	-0.53**	-0.62**	-0.43*
	V55	-0.28	-0.25	-0.03	-0.30	-0.52**	-0.13
RSVZ	V60	0.02	-0.18	0.55**	0.02	0.01	0.23
LSVZ	V50	-0.26	-0.31	0.18	-0.30	-0.29	-0.40*
	V55	-0.19	-0.34	0.41*	-0.15	-0.18	-0.27
	V60	-0.05	-0.23	-0.44*	-0.11	-0.10	0.02

*$p < 0.05$, **$p < 0.01$

Table 13

Correlations between Executive Function and Radiation Variables

		TMT B	B - A	B/A
RHC	V5	0.02	-0.43**	-0.48**
	V10	0.04	-0.26	-0.39*
LHC	V5	-0.17	-0.22	-0.43**
	V10	-0.12	-0.18	-0.39
RSVZ	Volume	-0.14	-0.35*	-0.25
LSVZ	Volume	-0.22	-0.38	-0.13
	V25	0.15	0.34*	0.30
	V30	0.18	-0.36*	0.30
	V35	0.21	0.36	0.15
	V40	0.34*	0.34	0.26

*$p < 0.05$, **$p < 0.01$

Table 14

Zero Order Pearson Correlation Matrix for Significant Predictors of Total Learning

		1	2
1	Total Learning		
2	V55 LHC	-0.17	

Table 15

Zero Order Pearson Correlation Matrix for Significant Predictors of Trial 1

		1	2
1	Trial 1		
2	No. Cycles Chemo	0.42	

Table 16

Zero Order Pearson Correlation Matrix for Significant Predictors of Learning Acquisition

		1	2	3	4	5	6
1	Learning						
2	No. Cycles Chemo	-0.53					
3	Min Dose LHC	-0.38	-0.01				
4	Min Dose LSVZ	0.05	0.07	0.45			
5	V55 LSVZ	0.41	-0.08	0.03	0.45		
6	Mean Dose LSVZ	0.16	-0.02	0.35	0.77	0.63	

Table 17

Zero Order Pearson Correlation Matrix for Significant Predictors of Delayed Learning

		1	2
1	Delay		
2	V50 LHC	-0.43	

Table 18

Zero Order Pearson Correlation Matrix for Significant Predictors of Percent Retention

		1	2	3
1	Percent Retention			
2	V50 LHC	-0.66		
3	V60 LHC	-0.38	0.34	

Table 19

Zero Order Pearson Correlation Matrix for Significant Predictors of Recognition Discriminability Index

		1	2	3	4	5	6	7
1	Recognition							
2	Weighted LHC	-0.47						
3	V60 LHC	0.12	0.64					
4	Max Dose LHC	-0.26	0.45	0.31				
5	V50 LHC	-0.35	0.26	0.34	0.73			
6	V45 RHC	0.39	0.06	0.12	-0.35	-0.38		
7	Mean Dose RHC	0.45	0.08	0.13	-0.37	-0.46	0.93	

Table 20

Summary of Regression Analysis for Variables Predicting Total Learning Post XRT (***N*** = 36)

Variable	*B*	*SE B*	β
Step 1			
Total Learning Time 1	0.41	0.11	0.59**
Step 2			
Total Learning Time 1	0.47	0.10	0.67***
V55 Left Hippocampus	-0.03	0.01	-0.44**

Note. $R^2 = .35$ for Step 1; $\Delta R^2 = .19$
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 21

Summary of Regression Analysis for Variables Predicting Initial Learning Post XRT (***N*** = 36)

Variable	*B*	*SE B*	β
Step 1			
Initial Learning Time 1	0.57	0.11	0.73***
Step 2			
Initial Learning Time 1	0.55	0.10	0.72***
Number Chemo Cycles Time 2	0.09	0.04	0.33*

Note. $R^2 = .54$ for Step 1; $\Delta R^2 = .11$ for Step 2
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 22

Summary of Regression Analysis for Variables Predicting Learning Post XRT (*N* = 36)

Variable	*B*	*SE B*	β
Step 1			
Learning Time 1	-0.08	0.16	-0.11
Step 2			
Learning Time 1	-0.08	0.14	-0.11
Number Chemo Cycles Time 2	-0.07	0.03	-0.48*
Step 3			
Learning Time 1	-0.07	0.12	-0.10
Number Chemo Cycles Time 2	-0.06	0.02	-0.44*
Min Dose LHC	-0.03	0.01	-0.46**
Step 4			
Learning Time 1	-0.06	0.10	-0.08
Number Chemo Cycles Time 2	-0.71	0.02	-0.51***
Min Dose LHC	-0.07	0.01	-0.97***
Min Dose LSVZ	0.08	0.02	0.70**
Step 5			
Learning Time 1	-0.06	0.03	-0.36*
Number Chemo Cycles Time 2	-0.07	0.02	-0.48***
Min Dose LHC	-0.07	0.01	-0.97***
Min Dose LSVZ	0.07	0.02	0.65**
V55 LSVZ	0.02	0.01	0.34**
Step 6			
Learning Time 1	-0.12	0.08	-0.16
Number Chemo Cycles Time 2	-0.07	0.01	-0.49***
Min Dose LHC	-0.06	0.01	-0.94***
Min Dose LSVZ	0.10	0.02	0.91***
V55 LSVZ	0.03	0.01	0.55***
Mean Dose LSVZ	-0.03	0.01	-0.44*

Note. $R^2 = .02$ for Step 1; $\Delta R^2 = .24$ for Step 2; $\Delta R^2 = .21$ for Step 3; $\Delta R^2 = .22$ for Step 4; $\Delta R^2 = .11$ for Step 5; $\Delta R^2 = .05$ for Step 6

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 23

Summary of Regression Analysis for Variables Predicting Delayed Recall Post XRT (***N*** = 26)

Variable	*B*	*SE B*	β
Step 1			
Delayed Recall Time 1	0.46	0.27	0.39**
Step 2			
Delayed Recall Time 1	0.18	0.22	0.15
V50 LHC	-0.03	0.01	-0.67**

Note. $R^2 = .10$ for Step 1; $\Delta R^2 = .49$
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 24

Summary of Regression Analysis for Variables Predicting Percent Retention Post XRT (***N*** = 26)

Variable	*B*	*SE B*	β
Step 1			
Percent Retention Time 1	0.37	0.28	0.31
Step 2			
Percent Retention Time 1	0.09	0.25	-0.07
V50 LHC	-0.04	0.01	-0.62**
Step 2			
Percent Retention Time 1	0.63	0.32	0.54
V50 LHC	-0.04	0.01	-0.67**
V60 LHC	1.32	0.57	0.63*

Note. $R^2 = .10$ for Step 1; $\Delta R^2 = .33$ for Step 2; $\Delta R^2 = .16$ for Step 3
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 25

Summary of Regression Analysis for Variables Predicting Recognition Post XRT (***N*** = 26)

Variable	*B*	*SE B*	B
Step 1			
Recognition Time 1	0.19	0.15	0.30
Step 2			
Recognition Time 1	0.16	0.12	0.26
Weighted LHC	-0.04	0.01	-0.54*
Step 3			
Recognition Time 1	0.27	0.12	0.43*
Weighted LHC	-0.04	0.01	-0.67**
V60 LHC	0.40	0.17	0.46*
Step 4			
Recognition Time 1	0.27	0.11	0.43*
Weighted LHC	-0.08	0.02	-1.17**
V60 LHC	0.40	0.15	0.46*
Max Dose LHC	0.04	0.02	0.62*
Step 5			
Recognition Time 1	0.35	0.07	0.56***
Weighted LHC	-0.06	0.01	-0.95***
V60 LHC	0.53	0.11	0.62***
Max Dose LHC	0.05	0.01	0.88***
V50 LHC	-0.02	0.01	-0.67**
Step 6			
Recognition Time 1	0.31	0.07	0.50***
Weighted LHC	-0.07	0.01	-0.10***
V60 LHC	0.51	0.09	0.59***
Max Dose LHC	0.06	0.01	0.98***
V50 LHC	-0.01	0.01	-0.59**
V45 RHC	0.01	0.01	0.25*
Step 7			
Recognition Time 1	0.27	0.05	0.43***
Weighted LHC	-0.08	0.01	-1.15***
V60 LHC	0.55	0.07	0.63***
Max Dose LHC	0.07	0.01	1.14***
V50 LHC	-0.02	0.01	-0.68***
V45 RHC	0.02	0.01	0.89**
Mean Dose RHC	-0.04	0.01	-0.69**

Note. R^2 = .09 for Step 1; ΔR^2 = .29 for Step 2; ΔR^2 = .16 for Step 3; ΔR^2 = .14 for Step 4; ΔR^2 = .18 for Step 5; ΔR^2 = .05 for Step 6; ΔR^2 = .05 for Step 7

*p < 0.05, **p < 0.01, ***p < 0.001

Table 26

Zero Order Pearson Correlation Matrix for Significant Predictors of TMT B

		1	2
1	TMTB		
2	SSRI 2	-0.25	

Table 27

Zero Order Pearson Correlation Matrix for Significant Predictors of TMT Difference

		1	2
1	B-A		
2	SSRI 2	0.22	

Table 28

Zero Order Pearson Correlation Matrix for Significant Predictors of TMT Ratio

		1	2	3	4	5
1	B/A					
2	Time Since Rad	0.50				
3	No. Cycles Chemo	-0.23	0.39			
4	Min Dose LSVZ	0.19	-0.31	0.07		
5	Weighted LSVZ	0.02	-0.12	-0.11	0.65	

Table 29

Summary of Regression Analysis for Variables Predicting Trails B Post XRT (***N*** = 36)

Variable	*B*	*SE B*	β
Step 1			
Trails B Time 1	0.54	0.17	0.59**
Step 1			
Trails B Time 1	0.59	0.13	0.65***
SSRI Time 2	-4.97	1.27	-0.55***

Note. $R^2 = .35$ for Step 1; $\Delta R^2 = .30$ for Step 2
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 30

Summary of Regression Analysis for Variables Predicting Trails Difference Post XRT (***N*** = 36)

Variable	*B*	*SE B*	β
Step 1			
Trails Difference Time 1	0.40	0.17	0.47*
Step 2			
Trails Difference Time 1	0.49	0.14	0.57**
SSRI Time 2	60.27	18.47	0.55**

Note. $R^2 = .22$ for Step 1; $\Delta R^2 = .29$
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 31

Summary of Regression Analysis for Variables Predicting Trails Ratio Post XRT (***N*** = 36)

Variable	*B*	*SE B*	β
Step 1			
Trails Ratio Time 1	0.06	0.19	0.06
Step 2			
Trails Ratio Time 1	0.19	0.17	0.19
Time Since Radiation	0.26	0.08	0.55**
Step 3			
Trails Ratio Time 1	0.15	0.16	0.15
Time Since Radiation	0.33	0.08	0.70***
Number Chemo Cycles Time 2	-0.06	0.03	-0.42*
Step 4			
Trails Ratio Time 1	0.02	0.12	0.19
Time Since Radiation	0.43	0.06	0.92***
Number Chemo Cycles Time 2	-0.09	0.02	-0.59***
Min Dose LSVZ	0.07	0.02	0.58***
Step 5			
Trails Ratio Time 1	0.36	0.11	0.04
Time Since Radiation	0.44	0.06	0.94***
Number Chemo Cycles Time 2	-0.09	0.02	-0.63***
Min Dose LSVZ	0.08	0.02	0.73***
Weighted LSVZ	-0.01	0.01	-0.29*

Note. R^2 = .004 for Step 1; ΔR^2 = .28for Step 2; ΔR^2 = .15for Step 3; ΔR^2 = .27for Step 4; ΔR^2 = .06 for Step 5

*p < 0.05, **p < 0.01, ***p < 0.001

Table 32

Standardized Beta Weights from Significant Regression Results

	Total	Trial 1	Slope	Delay	Retention	Recognition	TMTB	B-A	B/A
LHC									
V50LHC				-0.67	-0.67	-0.68			
V55LHC	-0.44								
V60LHC					0.63	0.63			
MinLHC			-0.94						
MaxLHC						1.14			
WeightedLHC						-1.15			
RHC									
V45RHC						0.89			
MeanRHC						-0.69			
LSVZ									
WeightedLSVZ									-0.29
MeanLSVZ			-0.44						
MinLSVZ			0.91						0.73
V55LSVZ			0.55						
Other									
No Cycles 2		0.33	-0.49						-0.63
Time Since Rad									0.94
SSRI 2							-0.55	0.55	

Table 33

Standardized Beta Weights from Significant Regression Results after Controlling for Colinearity

	Total	Trial 1	Slope	Delay	Retention	Recognition	TMTB	B-A	B/A
LHC									
V50LHC				-0.67	-0.67	-0.68			
V55LHC	-0.44								
V60LHC						0.63			
MinLHC			-0.94						
MaxLHC									
WeightedLHC						-1.15			
RHC									
V45RHC						0.89			
MeanRHC									
LSVZ									
WeightedLSVZ									
MeanLSVZ									
MinLSVZ			0.91						0.73
V55LSVZ			0.55						
Other									
No Cycles 2		0.33	-0.49						-0.63
Time Since Rad									0.94
SSRI 2							-0.55	0.55	

Table 34

Neuropsychological Outcome Scores by Tumor Focus

Independent Variable	Left Frontal Tumor Focus (N = 12) M(sd)	Median	Other Tumor Focus (N = 23) M(sd)	Median
Total Learning	24.58(4.21)	24	25(6.14)	25
Trial 1	6.42(1.68)	6	6.67(2.29)	6
Learning	3.08(1.56)	3	3.29(1.77)	3
Delay	8.20(2.66)[a]	9[a]	8.44(4.44)[b]	10[b]
Percent Retention	84.90(21.48)[a]	95[a]	76.27(33.83)[b]	88[b]
Recognition	10.20(1.55)[a]	11[a]	11.06(1.12)[b]	11.50[b]
TMTB	72.69(27.53)	72	85.00(53.21)	70
B-A	46.00(21.55)	49	56.39(45.25)	45
B/A	2.82(0.96)	2.54	2.86(1.04)	2.67

*$p < 0.05$, **$p < 0.01$

[a]n = 16; [b]n = 10

Table 35

Reliable Change category frequencies per surgery confound category

	Testing Prior to Surgery			Less than 2 weeks			Greater than 2 weeks		
Variable	Declined	Stable	Improved	Declined	Stable	Improved	Declined	Stable	Improved
HVLT-R									
Total	2	9	3	1	3	4	0	10	3
Learning									
Trial 1	0	10	4	0	6	2	0	9	2
Learning	5	9	0	1	5	2	1	9	1
Delayed Recall[a]	4	4	5	1	0	4	1	6	1
Percent Retention[a]	3	8	2	0	3	2	2	5	0
Recognition[a]	2	8	3	0	2	3	1	5	2
Trail Making Test									
Form B	2	11	1	2	6	1	0	10	2
(B-A)	3	10	1	1	7	1	0	9	3
(B/A)	1	11	2	1	6	2	1	9	2

Figure 1

Relationship between dose to 55% LHC and total learning score

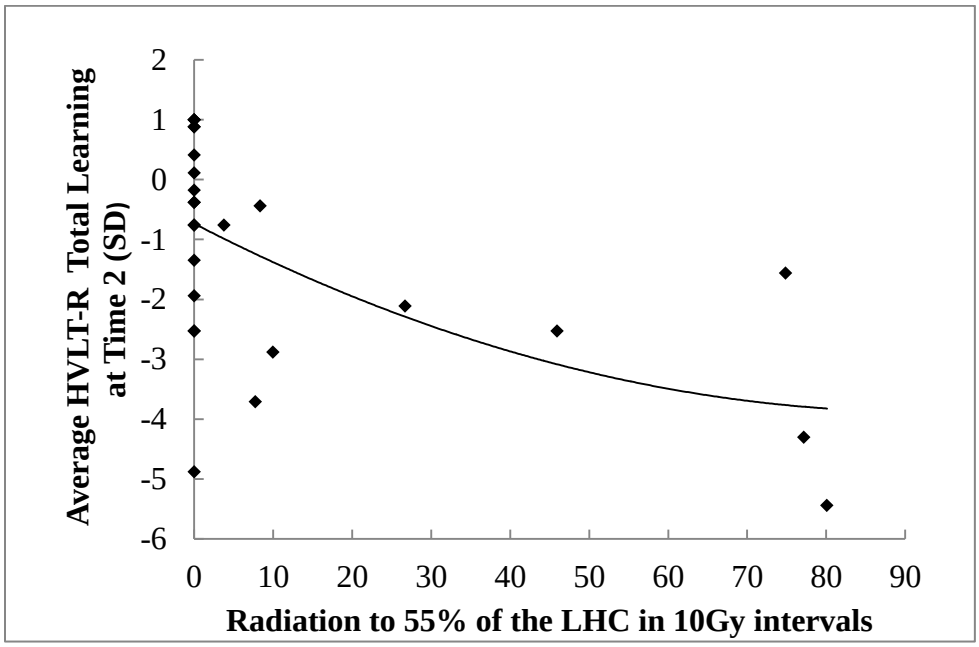

Figure 2

Relationship between dose to 55% LHC and mean total learning score per 10Gy intervals

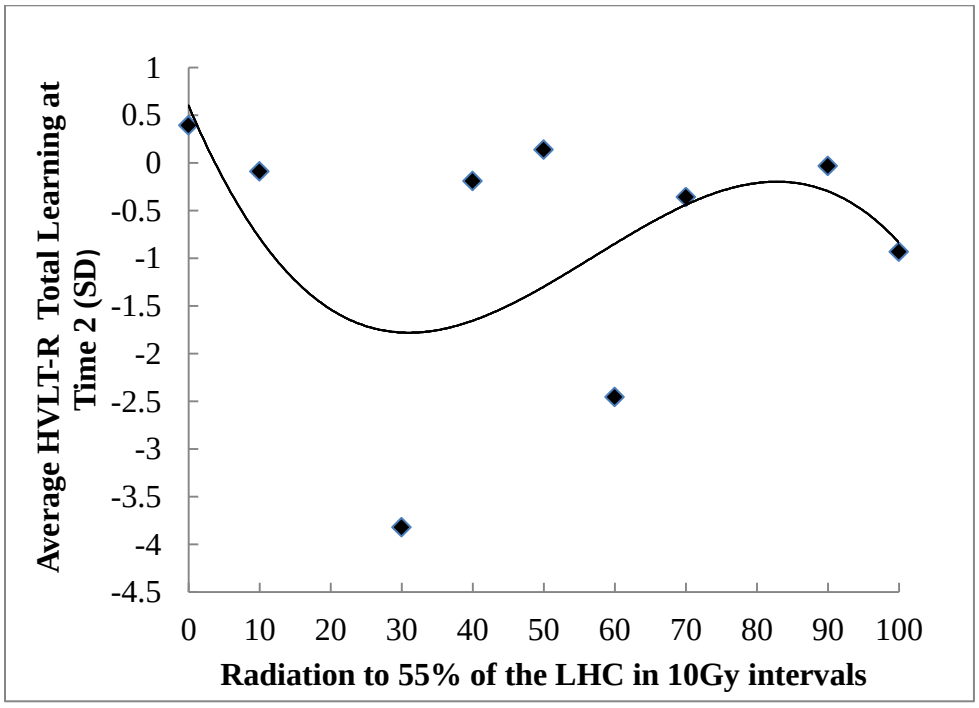

Figure 3

Relationship between dose to 50% LHC and delayed recall score

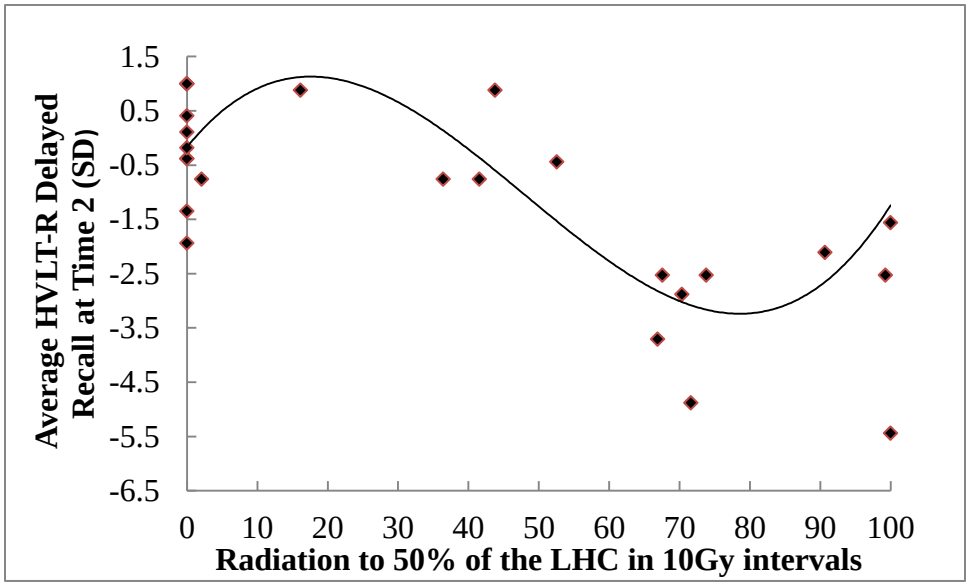

Figure 4

Relationship between dose to 50% LHC and mean delayed recall score per 10 Gy intervals

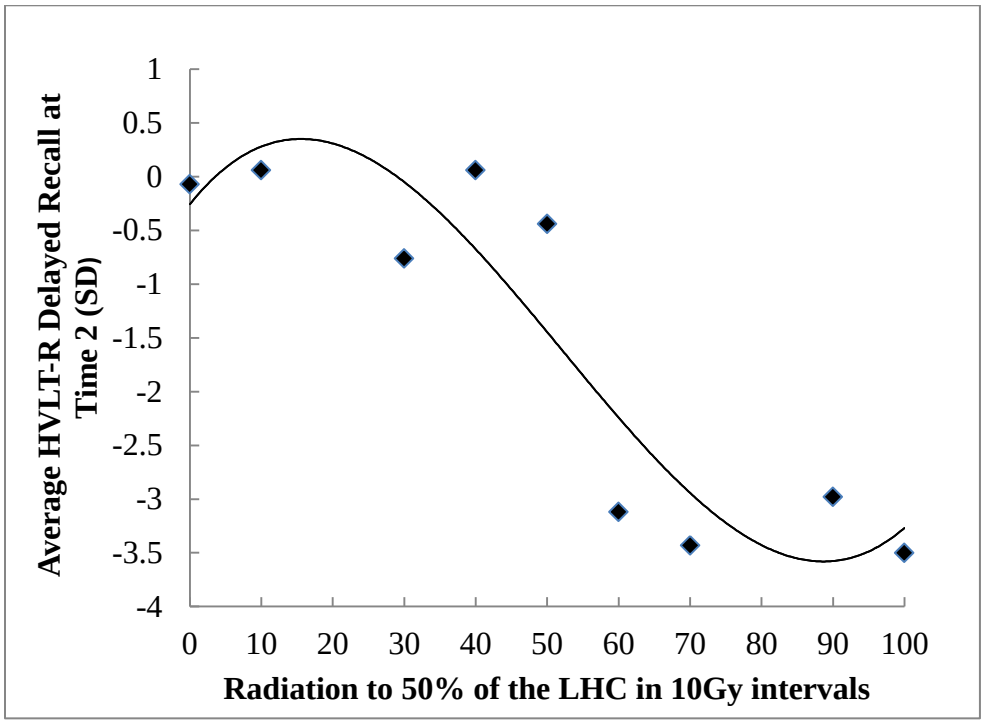

Figure 5

Relationship between dose to 50% LHC and percent retention score

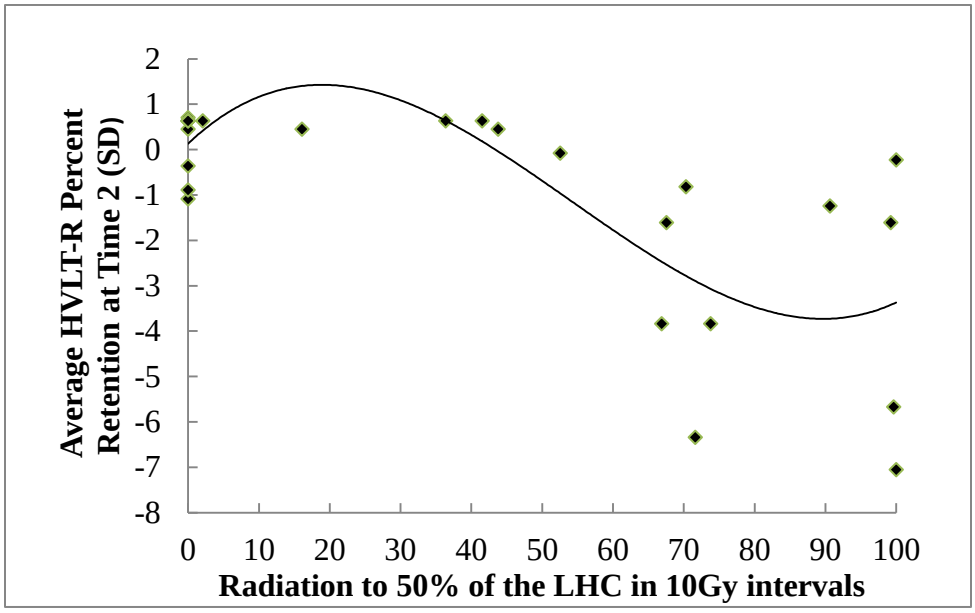

Figure 6

Relationship between dose to 50% LHC and mean percent retention score in 10 Gy intervals

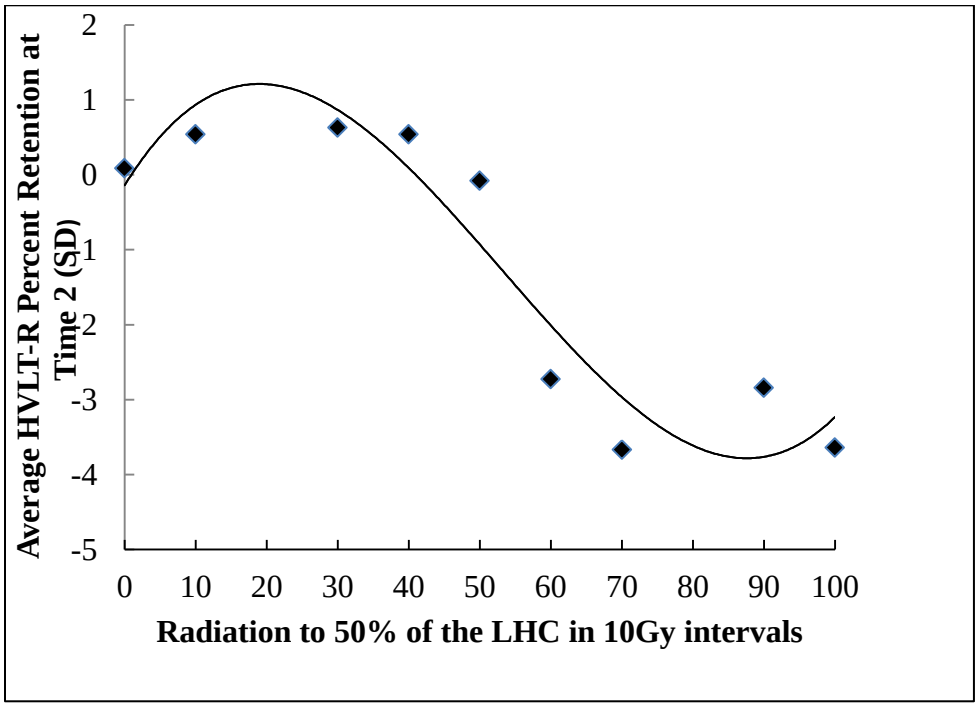

Figure 7

Relationship between dose to 50% LHC and recognition discriminability index score

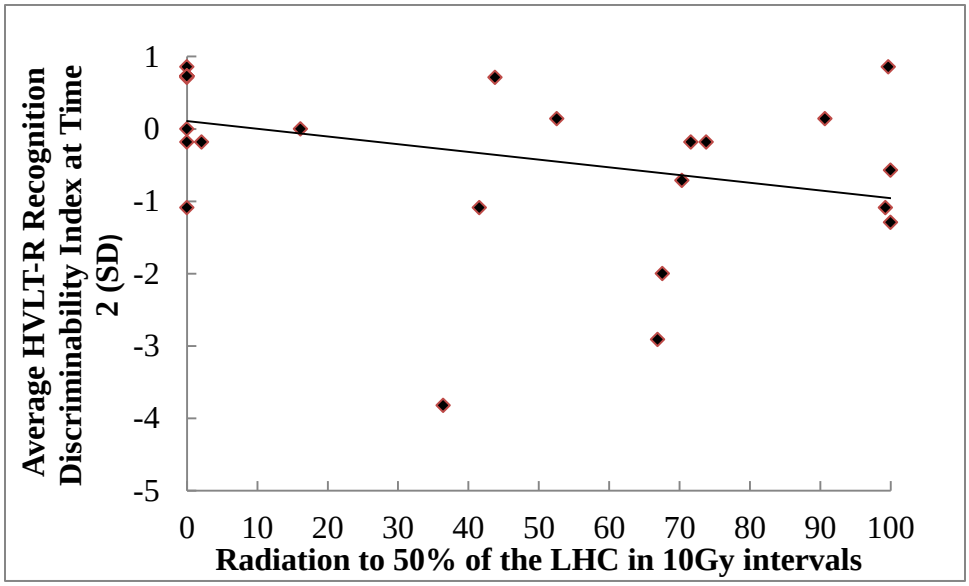

Figure 8

Relationship between dose to 50% LHC and mean recognition discriminability index score per 10 Gy intervals