Environmental Enrichment and Cortical Changes among Brain Tumor Survivors

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Abstract

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Though rare compared to other types of cancer, brain tumors can leave an individual with devastating neurological disabilities that impact cognition, function, independence, and overall quality of life. Glioma, those histologically classified as oligodendroglioma or astrocytoma with World Health Organization (WHO) 2 or 3 are brain tumors that commonly affect adults, with a mean age at diagnosis of 41 years old. The multimodal treatment approach of surgery, chemotherapy, and radiation has extended overall median survival, yet, minimal evidence exists to guide the management of chronic complications that arise from such life-saving measures. Brain radiation therapy (RT) is closely associated with accelerated brain aging, as evidenced by increased global cortical atrophy rate and progressive cognitive decline. Multiple domains of cognition, such as impairment in processing speed, attention, executive function, and memory, are commonly observed. Despite the potential cognitive preservation associated with the use of proton-beam radiation (PBRT), conventional photon RT (XRT) may be the only type of RT available and accessible to an individual. Studies indicate social support, physical activity, economic stability, and employment status, comprehensively known as environmental

enrichment (EE), have associated health benefits on the well-being and quality of life in the general cancer survivor population. However, the effects of EE on cognitive impairment, healthy brain aging, functioning, and symptom burden have not been studied among brain tumor survivors. Thus, the overall purpose of this dissertation is to examine the role of EE in promoting cognitive function, healthy brain aging, functionality, and reducing symptoms after treatment. Specifically, this dissertation has the following aims: 1) Conduct a literature review of the neuroimaging measures that can be employed by nurse scientists to assess the association between brain and cognitive changes; 2) Examine the association between EE and health outcomes (cognitive function, cortical changes, functional status, and symptoms) at five years in a cohort of BT survivors diagnosed with glioma treated with RT; and 3) Describe the health outcomes (cognitive function, cortical changes, functional status, and symptoms) in patients who received conventional photon radiation and those that received proton-beam radiation in relation to levels of EE among patients diagnosed with glioma five years from the time of diagnosis. The 39 individuals we recruited experienced varying levels of EE. We observed distinct increasing patterns in estimates and Odds Ratio of improved health outcomes in multiple measures (Montreal Cognitive Assessment [MoCA], Symbol Digit Modality Test, and Karnofsky Performance Status) with increasing levels of EE. We also noted higher MoCA scores, lower brain atrophy, and lower symptom burden) with in the High EE category. Comprehensively understanding the relationship between environmental, behavioral, and social factors with health outcomes is necessary to advance the paucity of research among BT survivors. Future research is necessary to examine the potential mechanism by which EE improves cognitive function and functional status, thereby promoting healthy brain aging, and reducing symptom burden after brain RT.

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One hundred and twenty-one pages later does not seem sufficient to summarize the last four years of my life as a PhD graduate student. One thing is certain, with all the challenges I encountered, I was not alone. I had the unyielding support of my family, friends, mentors, and colleagues. I would like to thank Dr. Hilaire J. Thompson, my supervisory committee chair, for her patience, guidance, advocacy, and mentorship in allowing me to be myself and to facilitate my evolution in this process. Dr. Fran Lewis, for believing in my potential and being one of my biggest cheerleaders when everything seemed so low. Dr. Tresa McGranahan for continuously challenging me in my scientific inquiries. Dr. Christine Mac Donald, for your patience and understanding of the questions I didn't even know I was asking. Dr. Jason Rockhill, for your wisdom and candor; I sometimes didn't want to hear it but knew I had to. And, Dr. Tracy Mroz, for seeing the potential in me.

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TABLE OF CONTENTS

Chapter 1. Introduction

Approximately 93,000 individuals in the United States are diagnosed annually with benign or malignant brain tumors.[1] Glioma with the World Health Organization grading of 2 or 3 are histologically classified as oligodendroglioma or astrocytoma. These gliomas are brain tumors that commonly affect adults, with a mean age at diagnosis of 41 years old.[2] The multimodal treatment approach for such tumors includes surgery, chemotherapy, and radiation. This approach has extended overall medial survival from 7 to 14 years.[3] With patients living longer, the concern for the long-term toxicity of therapy becomes a priority for care. Yet, minimal evidence exists to guide the management of chronic complications that arise from such life-saving measures.[4]

Brain radiation therapy (RT) is closely associated with accelerated brain aging, as evidenced by increased global cortical atrophy rate and progressive cognitive decline.[5-8] Approximately 25 to 80% of patients report mild to severe cognitive impairment as early as six months post-RT. [5,6,9-12] Multiple domains of cognition, such as impairment in processing speed, attention, executive function, and memory, are commonly observed with cortical atrophy.[5,6,9-12] Severity of these neurological complications may depend on the type of RT.[13] Photon radiation therapy (XRT) has both an entrance and exit dose, affecting the surrounding healthy tissue. In comparison, proton beam radiation (PBRT) deposits the maximum dose at the target tissue depth with no exit dose, minimizing irradiation of surrounding healthy tissue.[14]

Despite the potential cognitive preservation associated with the use of PBRT, XRT may be the only type of RT available and accessible to an individual. Barriers to receiving PBRT include high cost, lack of coverage by insurance, and lack of access to a center providing PBRT.[15] In addition to type of RT received, other factors may play a neuroprotective role in brain aging. Studies indicate social support,[16] physical activity,[17] economic stability,[18] and employment status,[19] comprehensively known as environmental enrichment (EE),[20] have associated health benefits on the well-being and quality of life in the general cancer survivor population. However,

the effects of EE on cognitive impairment, healthy aging, functioning, and symptom burden have not been studied among brain tumor [21] survivors.

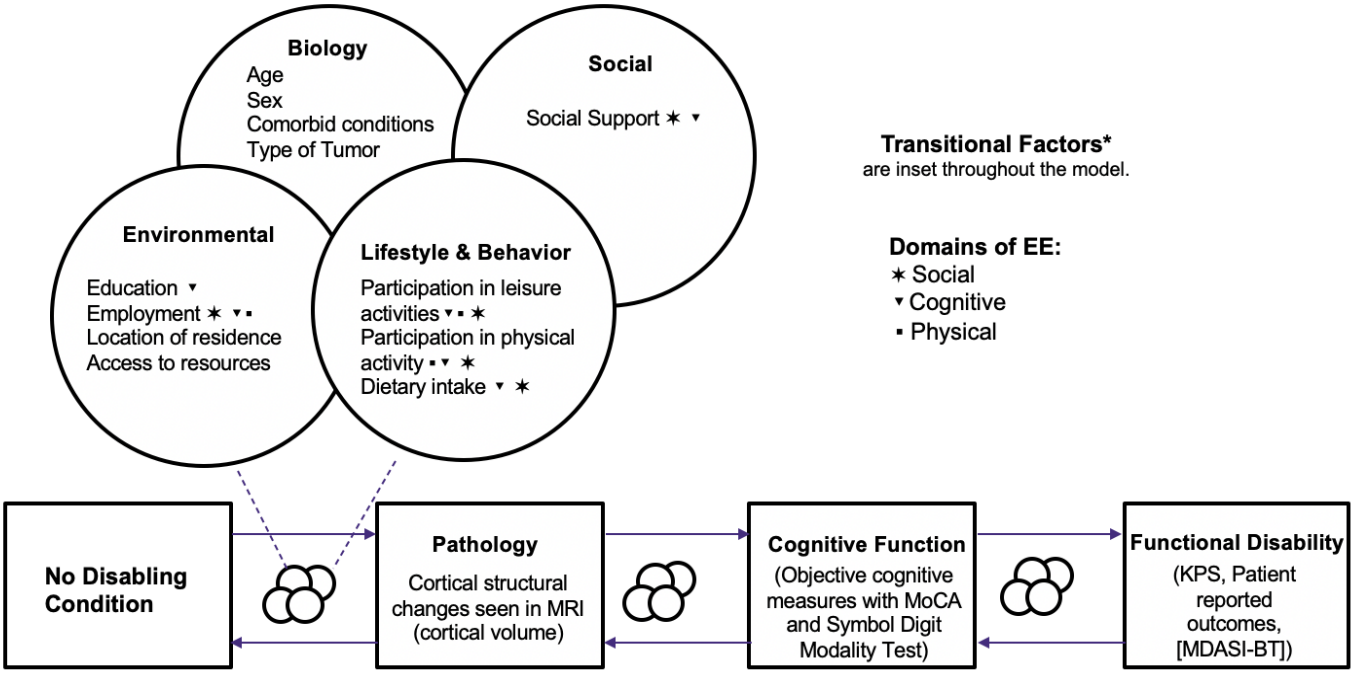
The purpose of this dissertation is to examine the role of EE in promoting cognitive function, healthy brain aging, functionality, and reducing symptoms after brain radiation in patients with glioma. Comprehensively understanding the relationship between environmental, behavioral, and social factors with health outcomes is necessary to advance the paucity of research among BT survivors. EE may be a potential intervention to improve cognitive function and functional status, promoting healthy brain aging, and reducing symptom burden after brain RT.

Conceptual Framework

The theoretical framework that informed this dissertation research is grounded from the Institute of Medicine Disabling-Enabling Process of impairment and disability.[22] The framework depicts disability as a product of the interaction between individual and their environment (See Figure 1). EE is part of the Transitional Factors that are inserted throughout the model. The Transitional Factors, specifically components of EE, can either promote or protect from the transition from one phase of the disabling process to another (e.g., no disabling condition to accelerated brain aging).[22] Notably, the arrows in the model are bidirectional (e.g., an individual can have a reduction in functional disability or improvement of impairment in cognitive function). Identifying factors that reduce or contribute to worsening disability could lead to interventions that reduce symptom burden, promote healthy brain aging, improve cognitive and functional status, and increase the quality of life. The weakness of the theoretical model is that it does not explain the critical influence of social determinants of health (i.e., access to resources, location of residence, and neighborhood conditions) in achieving EE. Impairment in cognitive function and functional disability following BT treatment may interfere with an individual's ability to engage with their environment; these impairments, however, should not affect the availability of external resources and support available to enrich their lives.

This dissertation research has a significant broader impact; not only can this work narrow the gap in health outcomes among BT survivors, but it has implications among general cancer survivors and those with chronic neurological disabilities which have no known cure. Examining EE in BT survivors and its role in reducing symptom burden, promoting healthy brain aging, and improving cognitive and functional status can provide fundamental development of personalized biobehavioral interventions.

Figure 1. *Institute of Medicine Disabling-Enabling Process (1997)*



Dissertation Elements

The overall aims of this dissertation is to examine the role of EE in promoting cognitive function, healthy brain aging, functionality, and reducing symptoms after treatment. Specific aims are as follows:

Aim 1: Examine the association between EE and health outcomes (cognitive function, cortical changes, functional status, and symptoms) at five years in a cohort of BT survivors diagnosed with glioma treated with RT.

Aim 2: Describe the relationship between EE and health outcomes (cognitive function, cortical changes, functional status, and symptoms) in patients who received conventional photon radiation and those that received proton-beam radiation in patients diagnosed with glioma five years from the time of diagnosis.

Each chapter in the dissertation is formatted in the style of its either published or prospective journal. A brief overview of each chapter is as follows:

Chapter 2. Integrating Neuroimaging Measures in Nursing Research

In Chapter 2, we conducted a literature review of the neuroimaging methodologies to assess brain changes such as cortical atrophy. We discussed both the qualitative examination and quantitative interrogation to introduce nurse scientists to neuroimaging measures that can be employed to assess the association between brain and cognitive changes. Neuroimaging measures indirectly assess cognitive function and thus allow for the inclusion, participation, and evaluation of individuals with severe cognitive impairment, as described in this dissertation research.

Chapter 3: Environmental Enrichment and Health Outcomes Among Brain Tumor Survivors

The implication of EE as an intervention among BT survivors to promote neuroplasticity after radiation is promising, yet operationalizing EE is limited in human health studies. Chapter 3 examines the association between EE and health outcomes (cognitive function, cortical

changes, functional status, and symptoms) among 39 BT survivors diagnosed with glioma approximately five years from the initial diagnosis.

Chapter 4. Environmental Enrichment after Brain Irradiation

Individuals who receive XRT are at a higher risk of developing increased cognitive impairment, cortical atrophy, and symptom burden compared to those who received PBRT, yet this may be the only treatment available to them. Chapter 4 explores the interaction between EE and the type of RT to describe the role of EE in health outcomes among individuals who received XRT.

Chapter 5. Conclusion

Chapter 5 summarizes the main findings of this research and its clinical implications to support BT survivors. This chapter also describes the study limitations and recommends needed future research.

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Chapter 2: Integrating Neuroimaging Measures in Nursing Research

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Chapter 2: Integrating Neuroimaging Measures in Nursing Research

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Abstract

Background: Medical and scientific advancement worldwide has led to a longer lifespan. With the population aging comes the risk of developing cognitive decline. The incorporation of neuroimaging measures in evaluating cognitive changes is limited in nursing research. The aim of this review is to provide an introduction to nurse scientists of neuroimaging measures employed to assess the association between brain and cognitive changes.

Methods: Relevant literature was identified by searching CINAHL, Web of Science, and PubMed databases using the following keywords: "neuroimaging measures," "aging," "cognition," "qualitative scoring," "cognitive ability," "molecular," "structural," and "functional."

Results: Neuroimaging measures can be categorized into structural, functional, and molecular imaging approaches. The structural imaging technique visualizes the anatomical regions of the brain. Visual examination and volumetric segmentation of select structural sequences extract information such as white matter hyperintensities and cerebral atrophy. Functional imaging techniques evaluate brain regions and underlying processes using blood-oxygen-dependent signals. The molecular imaging technique is the real-time visualization of biological processes at the cellular and molecular levels in a given region. Examples of biological measures associated with neurodegeneration include decreased glutamine level, elevated total choline, and elevated Myo-inositol.

Discussion: Nursing is at the forefront of addressing upstream factors impacting health outcomes across a lifespan of a population at increased risk of progressive cognitive decline. Nurse researchers can become more facile in using these measures both in qualitative and quantitative methodology by leveraging previously gathered neuroimaging clinical data for research purposes to better characterize the associations between symptom progression, disease risk, and health outcomes.

Keywords: "neuroimaging measures," "nursing research," "cognition," and "health outcomes."

Introduction

Nurse scientists are at the forefront of health prevention, promotion, and healthy aging research. And with the recent announcement of the National Institute of Nursing Research to prioritize nursing science informed by health equity lenses brings forth the critical roles of nursing scientists in bridging healthcare disparities across the lifespan. The risk of developing cognitive decline increases with a diverse aging population, and its evaluation is even more complex. Most studies often exclude patients with severe cognitive impairment due to their inability to participate in performance-based cognitive exams or subjective patient reports. This indirectly excludes those who may potentially benefit greater from interventions and limits the broader implication of scientific discoveries in understanding the progression of severe cognitive impairment.

Using performance-based cognitive exams and subjective patient reports is challenging when evaluating persons with known neurological deficits (i.e., motor weakness, aphasia) or with severe cognitive impairment, as the results skew cognitive exams and subjective reports. Therefore, there is a growing interest in incorporating objective neuroimaging measures in research to expand the generalizability of implications among the broader population experiencing cognitive changes. Neuroradiographic images, especially those obtained for clinical use, are utilized in various research inquiries across patient populations, as seen in persons with mild cognitive impairment (MCI) and dementia (Scheltens et al., 2016), multiple sclerosis (Filippi et al., 2016), Parkinson's disease (Yarnall et al., 2014), traumatic brain injury (Sharp et al., 2014), Huntington's Disease (Unschuld et al., 2012) as well as cancer survivors (Deprez et al., 2012).

Despite the advantages of integrating neuroimaging measures in the assessment of cognitive function, its use remains limited to scientists with radiological expertise. Recent reviews within the nursing literature describe different imaging modalities (e.g., Magnetic Resonance Imaging [MRI], Positron Emission Tomography [PET], etc.) and discuss challenges

when incorporating neuroimaging measures. The reviews, however, do not include methods of analysis (Atalla et al., 2020; Johnson et al., 2006; Kolanowski et al., 2019). Integrating neuroimaging measures in nursing research allows objective characterization of the physiological underpinnings between diseases, symptoms, and health outcomes. Clinical neuroimaging can be readily downloaded and then qualitatively and quantitatively analyzed by nurse researchers as a way to understand and advance the research of individuals experiencing severe cognitive changes. This paper aims to build on prior nursing literature and provide an introductory overview of neuroimaging measures that can be employed to assess brain changes associated with cognitive changes.

Methods

Relevant literature was identified by searching CINAHL, Web of Science, and PubMed databases using the following keywords: "neuroimaging measures," "aging," "cognition," "qualitative scoring," "cognitive ability," "molecular," "structural," and "functional." The following restriction criteria were used to narrow the search to the most relevant articles: publication year from 2000 to August 31, 2021, English language, adult (≥18 years old), and humans. Relevant articles were identified first by initial screening of titles and abstracts, followed by a full-text review. Seminal studies describing the development of widely used neuroimaging measures were also included in the review. Articles not pertaining to neuroimaging measures, humans, and cognition were excluded.

Results

Neuroimaging measures can be extracted through qualitative examination and quantitative analysis. Qualitative examination or direct visual scoring refers to examining and scoring the characteristics of the brain from the neuroimaging modality (i.e., MRI or CT). Quantitative analysis refers to the extraction of the measurement of the region of interest manually, automated, or semi-automated by a trained personnel.

Qualitative Visual Examination

Extracting overall global or regional structural changes from radiographic images via direct visual examination is termed qualitative examination. Common qualitative analyses for brain imaging can evaluate brain changes such as white matter hyperintensities (WMH) and cerebral atrophy. WMH refers to signal abnormality (hyperintensity) in the white matter region of the brain using the Fluid-Attenuated Inverted Recovery (FLAIR)/T2 MRI sequence (Merino, 2019). Cerebral atrophy is a general term used to describe brain tissue loss and can be characterized by the gradual widening of the cortical sulci, enlargement of the ventricles, cortical thinning, and shrinkage of subcortical structures such as the hippocampus (Harris et al., 2019). WMH and cerebral atrophy have long been associated with cognitive impairment across diverse populations (Appelman et al., 2009; Crutch et al., 2012; Debette & Markus, 2010; Mariani et al., 2007; Wang et al., 2021). The most commonly used tools for direct visual examinations of brain MRI include the Fazekas Scale (Fazekas et al., 1987), Rotterdam Scale (de Leeuw et al., 2001), Prins Scale (Prins et al., 2004), Global Cortical Atrophy (GCA) (Pasquier et al., 1996), Koedam Scale (Koedam et al., 2011) and Scheltens Scale (Scheltens et al., 1993). The Scheltens Scale has both WMH and medial temporal atrophy scoring.

Direct visualization of WMH uses the FLAIR sequence of an MRI. These WMH are often periventricular and thus can be further subcategorized into three regions: frontal and occipital caps and lateral bands (See Image 1). Depending on the research question, deep WMH is evaluated in either general or lobar terms (de Leeuw et al., 2001; Fazekas et al., 1987). The Prins and Scheltens scales subdivide global areas into respective lobar regions, with the latter also including basal ganglia and the infra-tentorial regions. See Table 1 for the grading criteria of these scales.

Cerebral atrophy can also be assessed qualitatively through direct visual analysis. The Koedam scale (Koedam et al., 2011) examines regional sulcal widening and gyral atrophy, whereas the Global Cortical Atrophy Scale (Pasquier et al., 1996) also evaluates ventricular enlargement. Alternatively, Schelten's Medial Temporal Atrophy (MTA) scoring evaluates the

width of the choroid fissure, the temporal horn of the lateral ventricles, and the height of the hippocampus (Scheltens et al., 1995). See Table 2 for the grading criteria of these scales.

Visual rating analyses using neuroimaging scales are relatively easy to perform. Numerically defining WMH changes has facilitated grading and agreement between raters, as seen in Scheltens WMH (Scheltens et al., 1993) and Rotterdam Study Scale (de Leeuw et al., 2001). However, visual rating is prone to a ceiling effect due to its categorical nature; therefore, the severity of WMH and cerebral atrophy is often not fully appreciated when using such methods (de Leeuw et al., 2001; Fazekas et al., 1987; Kapeller et al., 2003; Pasquier et al., 1996; Prins et al., 2004; Scheltens et al., 1995). In addition, qualitative assessment of WMH or cerebral atrophy can either be under or over-estimated or dependent on the examiner's expertise and experience. While there is good interrater reliability when used cross-sectionally (Prins et al., 2004), this reliability is difficult to replicate when images are evaluated longitudinally. The Prins Scale can detect WMH change over time but, unfortunately, does not take into account the extent of WMH (Prins et al., 2004).

Quantitative Interrogation

Quantitative interrogation obtains objective measurements of specific neuroimage properties. Measurements are commonly derived in three categories of imaging approaches: structural, functional, and molecular. All three can be used in conjunction with visual scoring. A summary of these neuroimaging measures is described in Table 3. For a more comprehensive overview of these three neuroimaging methods, please refer to the 2020 review by Attala and colleagues which also includes a summary of neuroimaging vocabularies for nurse scientists. In the next section, we expand upon the Attala review by introducing neuroimaging measures that can be obtained from these modalities.

Structural Imaging. Structural imaging refers to the visualization of the anatomical regions of the brain. For this purpose, MRI is more commonly used than Computerized tomography (CT) in research settings (Hasan et al., 2019; Merino, 2019; Rocca et al., 2015).

Visual qualitative examination and volumetric quantitative segmentation of select structural sequences extract information such as WMH and cerebral atrophy, both globally and regionally. Advanced MRI techniques such as diffusion tensor imaging (DTI) are employed to interrogate changes in white matter microstructure using mean diffusivity (MD) and fractional anisotropy (FA). MD is the global movement of water diffusion within a brain tissue, whereas FA refers to the directional dependence of water diffusion in one direction over another (Aung et al., 2013). Water molecules more readily diffuse along the direction of axons compared to other directions (i.e., perpendicular to the axon); thus, DTI describes the directionality and magnitude of water molecules in the brain tissue and can estimate changes in white matter fiber organization and illustrate the fiber bundles connecting different brain areas. Significant differences in FA and MD, particularly in the corpus callosum, have been described among patients with Alzheimer's disease, mild cognitive impairment, and healthy controls (Douaud et al., 2011). DTI can also be particularly useful in further elucidating microstructural alterations in the brain when a routine MRI is deemed unremarkable (Mac Donald et al., 2017).

Quantitative structural imaging approaches often use the segmentation method (demarcation and labeling of brain structure), which can be performed manually, automated, or a combination of both (semi-automated). The manual technique refers to the hand segmentation and labeling of an image. Manual segmentation is intensive, time-consuming, and prone to errors with wide intra and inter-operator variability (Collier et al., 2003). In contrast, the automated approach refers to the processing of the image using a software pipeline and brain atlas to perform the segmentation. Automated segmentation, though it can be processed in a relatively shorter amount of time, requires knowledge of the limitations of the method. For example, the accuracy of automated segmentation pipelines is highly dependent on image quality. The optimum resolution of the 3D T1 weighted image is used for segmentation with the following voxel dimensions: 1 x 1 x 1 mm (Despotovic et al., 2015). In addition, the field strength of the MRI machine and the presence of significant noise from MRI artifacts can affect intensity

distribution and lead to the misclassification of brain structures (Despotovic et al., 2015). Automated software uses atlas-based segmentation of generally healthy participants; therefore, it is also prone to mislabeling structures when the images have significant structural abnormalities (i.e., large resection cavities or edema present). Techniques to increase accuracy with post-processing software include the use of a probabilistic atlas in image registration and spatial context or neighboring system. The spatial context in image registration refers to the software labeling an area of the brain based on its surrounding region (Fischl et al., 2002). A few examples of automated segmentation software include Statistical Parametric Mapping (SPM) (Ashburner, 2012), FMRIB Software Library (FSL) (Jenkinson et al., 2012), Multi-atlas-based multi-image segmentation (MABMIS) (Jia et al., 2012), and FreeSurfer (Fischl, 2012). Software programs such as FreeSurfer use a probabilistic atlas in labeling data sets and integrate manual correction in the three orthogonal planes after automated segmentation (See Image 2). It is prudent to know the limitations and strengths of each software processing package when designing a study to account for them during image acquisition and post-processing analyses.

Functional Imaging. Imaging techniques such as functional MRI (fMRI) evaluate brain regions and underlying processes associated with performing a particular cognitive or behavioral task using blood-oxygen-dependent signals (Johnson et al., 2006; Sala-Llonch et al., 2015). Fluctuations in the BOLD signal can signify decreased or increased neuronal activity during the task, inferring brain functioning (Belliveau et al., 1991; Kwong et al., 1992) or compensatory mechanisms (Park & Reuter-Lorenz, 2009; Sala-Llonch et al., 2015). Studies have investigated resting-state functional MRI (rs-fMRI), and low fluctuations in BOLD signaling to characterize brain connectivity at rest, without a cognitive or directed task, and describe neuronal activity patterns among groups across the life span (Ferreira & Busatto, 2013). Abnormalities in the amplitude of low-frequency fluctuations of BOLD signals at rest, specifically in the posterior cingulate cortex, precuneus, right lingual gyrus, and thalamus have been

identified in patients with early and late mild cognitive impairment and Alzheimer's disease (Liang et al., 2014).

Other advanced imaging techniques include perfusion studies, commonly employing arterial spin labeling or phase-contrast imaging (Dolui et al., 2016). Perfusion studies evaluate cerebrovascular blood flow and can provide a surrogate marker for cerebrovascular function and health (Dolui et al., 2016; Frank J Wolters et al., 2017). Cerebral blood flow is the rate of delivery of arterial blood to a capillary bed in the brain tissue per minute (Liu & Brown, 2007). Cerebral hypoperfusion is associated with a higher risk of developing dementia in the general population (F. J. Wolters et al., 2017).

Molecular Imaging. Molecular imaging refers to the real-time visualization of biological processes at cellular and molecular levels in a given region. Examples of molecular imaging approaches include PET, single-photon emission computed tomography (SPECT), and Magnetic Resonance Spectroscopy. PET with radiotracers assesses the uptake distribution of a specific ligand to localize tissues with altered cellular or metabolic processes. For example, Fluorodeoxyglucose (FDG) radiotracer is used to evaluate glucose metabolism. In patients with amnesic mild cognitive impairment, PET using FDG has revealed bilateral glucose hypometabolism in several brain regions, including the limbic system, posterior cingulate cortex, parahippocampal gyri, and temporal lobes (Landau et al., 2011). Other ligands for β-Amyloid (Villemagne et al., 2013) and Tau (Schöll et al., 2016) proteins are used to evaluate and predict the conversion of mild cognitive impairment to Alzheimer's disease. The Food and Drug Administration recently approved Tauvid radiotracer to clinically diagnose Alzheimer's disease (Jie et al., 2021). This indication could transform clinical prognostication, assessment, and research for the aging brain. Thus, PET imaging should be considered a potential modality when designing studies that include neuroimaging measures.

SPECT is a type of perfusion imaging that uses an intravenously injected reagent, hexamethyl propylene amine oxime, to estimate regional blood volume flow via tracer uptake

(Duncan et al., 1996). Decreased regional cerebral blood flow has been observed in specific brain regions in a broad spectrum of patients with cognitive decline. For example, in patients with depression and cognitive impairment, decreased perfusion was noted in the right thalamus, right lentiform nucleus, and the left medial temporal cortex (Staffen et al., 2009). Lastly, MR Spectroscopy measures biological metabolites, such as lactate, glutamine, glutamate, choline, creatinine, N-acetylaspartate (Ghodasara et al., 2020) and Myo-inositol in a region of interest or globally (Griffith et al., 2009; Öz et al., 2014). Whole-brain N-acetylaspartate was found to be significantly decreased in patients with cognitive impairment, and individuals with Alzheimer's disease compared with healthy controls, and thus has been hypothesized to be an indicator for early Alzheimer's Disease (Glodzik et al., 2015). Examples of other biologic measures that can be accessed via SPECT include glutamine (Rupsingh et al., 2011; Unschuld et al., 2012), choline (Kantarci et al., 2000), and Myo-inositol, which can be used in global or specific regions depending on the research question (Miller et al., 1993; Öz et al., 2014).

Nursing Research Implication

Neuroimaging measures can expand the evaluation of cognitive impairment and include those with severe cognitive impairment and others unable to participate in routine neuropsychological evaluation and subjective reporting. Incorporating neuroimaging measures allows the inclusion and participation of these individuals, bridging the known scientific gap and addressing the challenges in cognitive tests and patient reports. Neuroimaging measures, as described above, indirectly measures cognitive function and allow for consistency of evaluation across participants.

To date, limited research and behavioral interventions are in place to prevent or stabilize brain changes associated with cognitive decline. As such, an opportunity to harness the expertise of nursing scientists in biobehavioral and social science research to develop interventions that will provide stability of cognitive changes and preservation of function among individuals at risk for progressive neurological decline. Nursing scientists have long been

leaders in evaluating the intersection between the environment (societal, structural, social, as well as behavioral factors) and the individual's health (i.e., progression of symptoms, functionality, quality of life, and overall well-being). With neuroimaging measures, nursing scientists can elucidate how, for example, certain behaviors (i.e., physical activity, diet, work, social determinants of health) influence the progression of brain changes before the onset of symptoms or progression of symptoms. Nurse scientists can also investigate if certain cognitive stimulations (i.e., music therapy, speech therapy, mindfulness, etc.) induce brain changes that facilitate stability or improve cognitive symptoms. Lastly, nurse researchers can strongly advocate for program planning, community resources, and policy change for the potential impact of their interventions at the physiological level among all individuals across lifespans.

Discussion

Clinical neuroimaging is a valuable data source for nursing scientists to understand the pathophysiology underlying cognitive impairment and brain aging. While clinical images are limited compared to ones obtained explicitly for research purposes, the use of clinically obtained studies decreases the participation burden and study costs. These neuroimages can be qualitatively examined, processed, and segmented for research purposes. Qualitative examination or visual scoring refers to an expert in the field examining and scoring the characteristics of the brain. Quantitatively interrogating images refers to segmenting and measuring the voxel signal intensity using manual, automated, or semi-automated methods.

The use of neuroimaging modalities is not without disadvantages. Accessibility and availability of imaging techniques such as MRI and PET are scarce in rural communities (Khaliq et al., 2014), requiring patients to travel long distances for diagnostic evaluation and/or research participation. Similarly, required technical expertise in image acquisition and interpretation by expert neuroradiologists are also limited in rural and underserved communities (Barreto et al.; Culler et al., 2006; Khaliq et al., 2015), exacerbating these disparities. Insurance coverage also poses an issue in performing these modalities. When using neuroimaging modality for the sole

purpose of research, the cost is an important consideration as this requires a substantial budget. MRI machines also use magnets and are thus contraindicated in patients with a magnetic implantation device. And lastly, qualitative scoring and quantitative segmentation methods to extract the data have their weaknesses, as described in this review.

Nursing is at the forefront of advancing health prevention, promotion, and healthy aging research with a particular focus on health equity, addressing upstream factors impacting health outcomes across a population's lifespan. Nurse scientists are proficient and well-versed in using performance-based examinations and subjective reports to evaluate cognitive changes. While some nurse scientists have spearheaded the use of neuroimaging in their research, they remain limited in number. Nurse researchers can become more facile in using these measures both in qualitative and quantitative methodology. Integrating and leveraging previously gathered neuroimaging clinical data for research purposes can better characterize the associations between environmental factors, symptom progression, disease risk, and health outcomes. This scientific foundation will allow for the development of biobehavioral and social interventions inclusive of all patients, regardless of the severity of their cognitive impairment. Neuroimaging can bridge the limitations of performance-based cognitive exams and subjective patient reports and allows for inclusion, evaluation, and understanding of complex neurological and severe cognitive impairment among a diverse aging population.

Table 1. Commonly used visual scoring scales for white matter

Qualitative Examination: White Matter Hyperintensity Scales				
Measure	**Periventricular**	**Deep White Matter**	**Examples of cognitive changes and correlation**	**References**
Fazekas Scale	(Periventricular white matter (PVWM) 0 = Absent 1 = "Caps" or pencil-thin lining 2 = Smooth "halo" 3 = Irregular periventricular signal extending into the deep white matter	0 = Absent 1 = Punctate foci 2 = Beginning confluence 3 = Large confluent areas		
Schelten's Scale (WMH)	Periventricular Hyperintensities (PVH 0-6) 0 = Absent 1= ≤ 5mm 2 = > 5 mm and < 10 mm Caps Occipital 0/1/2 Frontal 0/1/2 Bands Lat Ventricles 0/l/2	White matter hyperintensities (WMH 0-24) 0 = no abnormalities 1 = <3 mm, *n* ≤ 5 2 = <3 mm, *n* > 6 3 = 4-10 mm, *n* ≤ 5 4 = 4mm, *n* > 6 5 = > 11 mm, *n* > l 6 = confluent Frontal 0/1/2/3/4/5/6 Parietal 0/1/2/3/4/5/6 Occipital 0/1/2/3/4/5/6 Temporal 0/1/2/3/4/5/6 Basal ganglia hyperintensities (BG 0-30) Caudate Nucleus 0/1/2/3/4/5/6 Putamen 0/1/2/3/4/5/6 Globus Pallidus 0/1/2/3/4/5/6 Thalamus 0/1/2/3/4/5/6 Internal capsule 0/1/2/3/4/5/6	Increasing score (increasing size and volume) of WMH is associated with decreasing cognitive function (such as psychomotor speed), increasing cognitive impairment (i.e. executive function, memory, verbal fluency).	(Debette & Markus, 2010; Defrancesco et al., 2013; Dufouil et al., 2009; Mariani et al., 2007).

		Infra-tentorial foci of hyperintensity (ITF 0-24) Cerebellum 0/1/2/3/4/5/6 Mesencephalon 0/1/2/3/4/5/6 Pons 0/1/2/3/4/5/6 Medulla 0/1/2/3/4/5/6 *N* refers to the number of lesions.		
Rotterdam Scan Study	Periventricular (0-9) 0 = No white matter lesions 1 = Pencil thin periventricular lining 2 = Smooth halo or thick lining 3 = large confluent white matter lesions Frontal Capping Occipital Capping Lateral ventricles (bands)	White Matter Lesions (Categorized based on number and size) Small: < 3mm Medium: 3-10 mm Large: > 10 mm		
Prins Scale (WML Change Scale)	Rated as: -1 Decrease 0 No change +1 Increase Scored in three periventricular locations - Frontal caps - Lateral bands - Occipital caps Results in a periventricular score of -3 to +3.	Rates: Frontal Parietal Temporal Occipital Resulting in a subcortical score of -4 to +4. An increase is defined as the occurrence of a new focal lesion or the enlargement of a previously visible lesion; a decrease is defined as the reverse (i.e., disappearance or shrinkage).		

Table 2. Commonly used visual scoring scales for cerebral

Qualitative Examination: Cerebral Atrophy Scales				
Measure	**Regions**	**Grading Scale**	**Examples of cognitive changes/impairment and correlation**	**References**
Koedam Scale (Posterior Atrophy Score)	Sagittal plane - Posterior cingulate sulcus - Parieto-occipital sulcus - Precuneus gyrus Coronal plane - Posterior cingulate sulcus - Parietal gyrus Axial plane - Posterior cingulate sulcus - Parietal lobes The worse features are used to generate a grade of 0 to 3	0: Closed sulci, no gyral atrophy 1: Mild sulcal widening, mild gyral atrophy 2: Substantial sulcal widening, substantial gyral atrophy 3: Marked sulcal widening, knife-blade gyral atrophy	Increasing posterior cortical atrophy is associated with progressive decline in visuospatial, visuoperceptual, literacy, and praxic skills.	(Crutch et al., 2012; Mimenza-Alvarado et al., 2018)
Pasquier Scale (Global Cortical Atrophy scale)	Sulcal dilatation - Frontal (right and left) - Parieto-occipital (right and left) - Temporal (right and left) Ventricular dilatation - Frontal (right and left) - Prieto-occipital (right and left) - Temporal (right and left) - Third ventricle	0: Normal volume/no ventricular enlargement 1: Opening of sulci/mild ventricular enlargement 2: Volume loss of gyri/moderate ventricular enlargement 3: 'Knife blade' atrophy/severe ventricular enlargement	Progressive decline in global cortical atrophy rate is associated with progressive cognitive decline in psychomotor speed and executive function.	(Jokinen et al., 2012)

Scheltens's Scale (Medial Temporal Atrophy scale)	Width of the choroid fissure Width of the temporal horn of the lateral ventricle Height of the hippocampus	0: No CSF is visible around the hippocampus 1: Choroid fissure is slightly widened 2: Moderate widening of the choroid fissure, mild enlargement of the temporal horn and mild loss of hippocampal height 3: Marked widening of the choroid fissure, moderate enlargement of the temporal horn, and moderate loss of hippocampal height 4: Marked widening of the choroid fissure, marked enlargement of the temporal horn, and the hippocampus is markedly atrophied, and internal structure is lost	Increasing atrophy of the medial temporal is associated with increasing forgetfulness or memory deficits	(Mimenza-Alvarado et al., 2018)

Table 3. Examples of quantitative neuro-imaging measures.

Quantitative Interrogation			
Imaging Method	**Examples of neuroimaging measures to evaluate cognitive function**	**Examples of cognitive changes/impairment and correlation**	**References**
Structural			
Structural MRI	Regions of interest (i.e., cortical and subcortical structures)	Volume atrophy in neocortical, caudate, putamen, globus pallidus, thalamus and nucleus accumbens are associated with decreased information-processing speed in patients with multiple sclerosis.	(Batista et al., 2012)
Diffusion Tensor Imaging	Fractional Anisotropy (FA) and Mean Diffusivity (MD) (Can estimate changes in white matter fiber organization and illustrate the fiber bundles connecting different brain areas.)	Reduced FA of the genu of the corpus callosum is associated with the rate of global cognitive decline (memory, language, attention/executive and visuospatial function) in individuals with mild cognitive impairment.	(Raghavan et al., 2020)
Functional			
fMRI	Blood-oxygen-dependent signals during a task (Fluctuations in the BOLD signal can signify decreased or increased neuronal activity during the tasks and infer brain functioning)	Higher levels of BOLD-signal variability in the left inferior frontal area is associated with reduced errors during task switching and thus infer cognitive flexibility.	(Armbruster-Genc et al., 2016)
rs-fMRI	BOLD signals during a resting state	BOLD signal variability located in the posterior medial temporal lobes, hippocampus, visual cortex, and striatum showed that in healthy individuals (normal score on Montreal Cognitive Assessment [MOCA]), higher BOLD signal variability at rest was related to higher scores on the cognitive control/speed and intelligence factors. This relationship is reversed among those who	(Good et al., 2020)

		are at-risk (those who score below normal threshold <26 in MOCA.	
Perfusion Studies	Cerebral blood flow	Lower total global cerebral perfusion is associated with accelerated decline in global cognition, particularly in memory and executive function and at increased risk for developing dementia.	(Wolters et al., 2017)
Molecular			
PET Ligand-dependent	Fluorodeoxyglucose (FDG), β-Amyloid, Tau	Lower FDG- ROIs (right and left angular gyri, bilateral posterior cingulate, right and left inferior temporal gyri) is associated with greater decline in cognitive function (language, memory, praxis, and comprehension) and is predictive of functional decline (daily tasks such as shopping, preparing meals, handling finances, and understanding current events).	(Landau et al., 2011)
MR Spectroscopy	Biologic metabolites, such as lactate, glutamine, glutamate, choline, creatinine, N-acetylaspartate and Myo-inositol in a region of interest depending on the research query.	Lower concentration of whole-brain N-acetylaspartate is associated with mild cognitive impairment among older adults.	(Glodzik et al., 2015)
SPECT	Estimates regional blood volume flow via tracer uptake.	Hypoperfusion in the left middle temporal gyrus, right inferior frontal gyrus, right lingual gyrus, left lingual gyrus, right postcentral gyrus, right cingulate gyrus, left thalamus is associated with lower visuospatial functioning in older individuals at risk for developing Alzheimer's disease.	(Yoon et al., 2012)

Image 1. Regions in qualitatively assessing and grading white matter hyperintensities are the frontal caps (**A**), occipital caps (**B**), and lateral bands (**C**) as shown above.

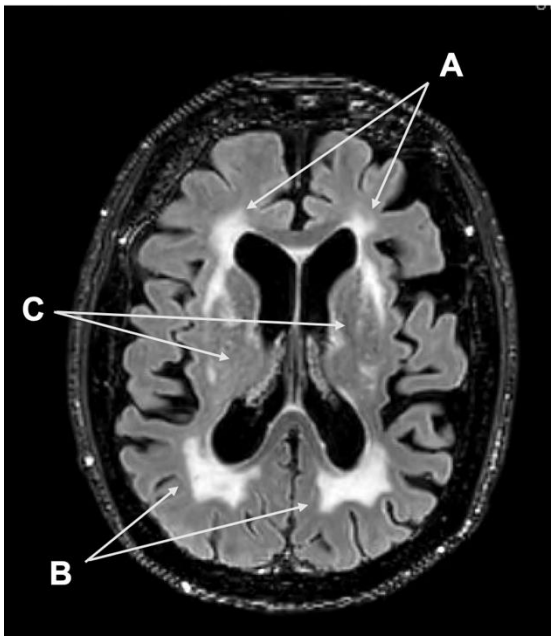
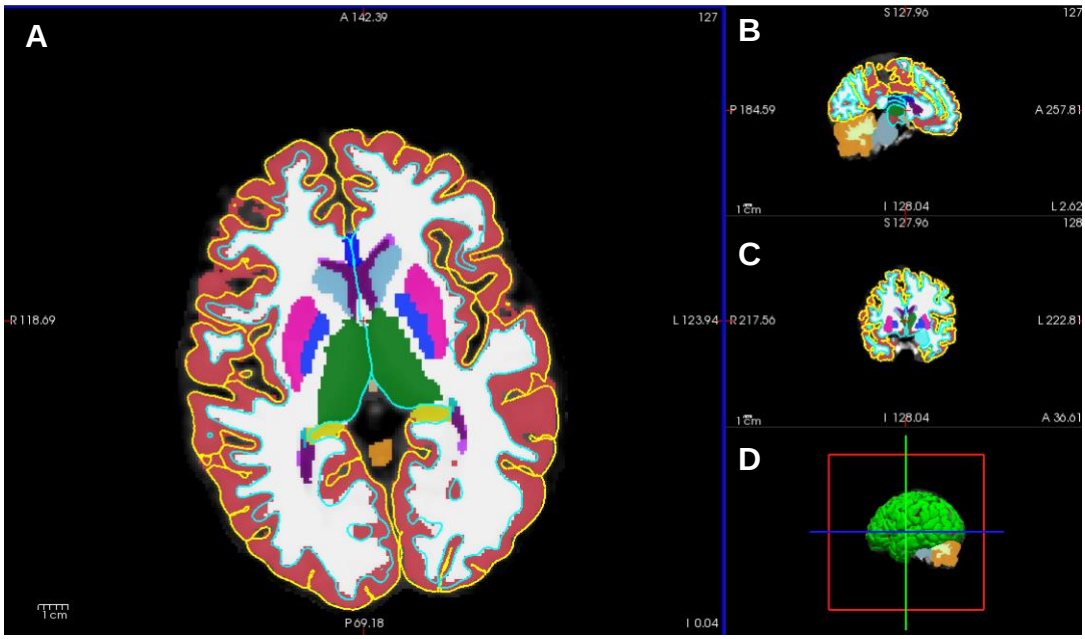


Image 2. Using FreeSurfer software to automatically segment and manually correct structures of the brain using 3D view (**D**) in three orthogonal planes: Axial (**A**), and Sagittal (**B**) and Coronal (**C**).



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Chapter 3: Environmental Enrichment and Health Outcomes among Brain Tumor Survivors
Target Journal: *Neuro-Oncology*

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Abstract

Background: Individuals who receive brain radiation are at increased risk of developing accelerated cognitive decline. Yet, limited interventions exist to mitigate these progressive neurological complications or how to promote neuroplasticity after brain irradiation. The aim of this study is to the findings of the association between environmental enrichment (EE) and health outcomes among individuals with glioma survivors who received brain radiation.

Methods: The study employed a retrospective design among persons with glioma treated with radiation approximately 5 years from the original brain tumor (BT) diagnosis. EE as a construct consisted of social network/engagement, physical activity, and employment status/financial stability measured by the Berkman-Syme Social Network Index, International Physical Activity Questionnaire, Vocational Index Scale, and Socioeconomic Questionnaires, respectively. The distribution of EE was classified into high, moderate, or low. Montreal Cognitive Assessment (MoCA) and Symbol Digit Modality Test (SDMT) measured cognitive function. Global cortical atrophy was ascertained using temporal brain MRI images from the time of diagnosis, 3 years after diagnosis, and at the time of recruitment. Brain MRI images were processed using semi-automated FreeSurfer segmentation software. Karnofsky Performance Status Scale (KPS) and the MD Anderson Symptom Inventory – Brain Tumor module measured functional status. EE, cognitive and functional status were measured at enrollment. Ordinal logistic regression was used to estimate levels of EE and health outcomes as described. Age, sex, and dose of radiation were used as covariates.

Results: Thirty-nine participants consented and completed the study protocol. The median age of the sample was 44 years old, ranging from 26 to 78 years old. Nineteen individuals were diagnosed with oligodendroglioma, and 18 were diagnosed with astrocytoma. Thirteen participants were in the Low EE category, 17 in the Moderate category, and 9 were in the High category. The 39 individuals experienced varying levels of EE. Though we observed distinct

increasing patterns in estimates and OR of improved health outcomes (MoCA, SDMT, KPS) with increasing levels of EE, this was not statistically significant.

Conclusion/Impact: This study provided an initial exploration into the role of EE in health outcomes for persons with BT. Comprehensive biobehavioral and social interventions are necessary to promote, restore, and maintain the health of individuals with BT after radiation. Early evidence in this exploratory study suggests that providing an enriched environment may reduce symptom burden, promote neuroplasticity, and improve cognitive and functional status after brain radiation.

Keywords: Brain tumor survivors; Environmental Enrichment; Neuro-oncology survivorship; Brain radiation.

Introduction

Individuals with a brain tumor (BT) treated with radiation are at a disproportionately increased risk of symptom burden,[1-3] accelerated brain aging,[4-6] and development of other chronic complications[7] when compared to the general cancer survivor population.[8] Yet, limited evidence exists to guide patient management of these chronic complications.[9] Although surgery, chemotherapy and radiation therapy (RT) have improved the overall survival of patients with a BT,[10,11] there is a need to identify interventions to mitigate the long-term sequela of these life-saving measures.

Accelerated brain aging and increased symptom burden significantly impact cognitive function, functional status, and quality of life in persons with BT. Comprehensively understanding factors that can mitigate symptom burden and functional limitations is necessary to advance the research among BT survivors. Studies indicate social support,[12] physical activity,[13] economic,[14] employment status,[15] and healthy dietary intake[16-18] collectively known as Environmental Enrichment (EE),[19] have health benefits in the general cancer survivor population. However, EE has not been examined for its health benefits in BT survivors. The aim of this study is to assess if a higher level of EE is associated with better health outcomes (cognitive function, functional status, symptom burden, and global cortical atrophy) compared to those with lower EE at 5 years post-diagnosis and treatment with RT in a cohort of BT survivors with glioma (WHO Grades 2 and 3).

Materials and Methods

Setting

The setting was the Alvord Brain Tumor Center (ABTC), a multi-disciplinary neuro-oncology clinic located at the UW Medical Center-Montlake (UWMC), Seattle, Washington. Persons were eligible if they: 1) were diagnosed with a primary glioma (WHO grade 2 and 3) five years (+/- 1 year) from the time of study recruitment 2) were aged 21 years old or above at the time of diagnosis, and 3) had completed treatment for the BT, including RT. Persons were excluded if

they: 1) had an active central nervous system (CNS) disease at the time of enrollment; 2) were receiving active anti-cancer therapy; 3) had a history of other systemic cancer; 4) had a history of other CNS tumors at the time of recruitment and 5) were non-English-speaking.

The research protocol was approved by the University of Washington Institutional Review Board. Written informed consent was obtained from participants or proxies. For individuals unable to provide informed consent due to severe impairment in cognitive function (Montreal Cognitive Assessment [MoCA] ≤ 10),[20,21] the proxy was the individual's Legally Authorized Representative (LAR) willing to give consent and complete questionnaires on behalf of the study participant.

Design

The study employed a retrospective design. See Figure 1 for the study protocol. The research assistant or the principal investigator (PI) recruited individuals when they presented to the ABTC for a regularly scheduled follow-up visit. All participants were asked to self-report their race, ethnicity, and current residential zip code. Age, gender, and sex were obtained from the electronic health record (EHR) along with BT treatment history, classification of BT type, location, dose, and type of RT. Magnetic Resonance Imaging (MRI) of the brain from the time of initial diagnosis (Timepoint 1), prior to radiation, approximately 2-3 years after diagnosis (Timepoint 2), and at the time of recruitment (Timepoint 3) were obtained for further processing and analysis. The goal was to enroll 40 participants for the study. We chose this sample size as with N=40 and power = 0.8, the smallest detectable effect size is 0.45, which corresponds to a mean decrease in cortical volume of 1.45%. Prior studies in persons with BT reported decreases of 5-6% gray matter volume loss 6-10 years post-diagnosis.[22] See Figure 1 for an overview of the study protocol.

Assessment of Environmental Enrichment

EE is defined as an individual's social, physical, and cognitive domains that encourage positive stimulations, interactions, and activities in their surroundings.[19] To assess all

components of the full construct and build upon prior research, the Berkman-Syme Social Network Index (SNI) was used to measure social support and interaction;[23] the International Physical Activity Questionnaire[24] (IPAQ) was used to measure physical activity; the Vocational-Independence Scale (VIS) was used to evaluate an individual's activity as a student, employee or volunteer.[25] Rather than using the level of gross income, two questions were used to ascertain financial stability: Was there time in the last 12 months when you needed to see a doctor but could not because of cost?" and "How many times in the last 12 months would you say you were worried or stressed about having enough money to pay your rent/mortgage?" Responses are on a 5-point ordinal scale 1=Always, 5=Never.[26] Prior studies suggest participants are more willing to answer similar items than provide specific income data.[26]

The SNI assessed the type, size, closeness, and frequency of contacts in a respondent's current social network. It is a self-report questionnaire with Cronbach's alpha of 0.84.[23,27] The SNI has been validated in patients with cancer[28] and with neurological impairment.[29] The level of social connectedness summed cutoff score (0 or 1 = least socially connected; 2, 3, or 4 corresponds to increasing levels of connectedness).[29]

The IPAQ measured job-related physical activity, transportation physical activity, housework, recreation activity, and time spent sitting.[24] This is a self-administered questionnaire[24] and has been used in patients with BT[30,31] with test-retest reliability of 0.80.[24] Low physical activity is assigned to those with 2 or fewer days of vigorous activity. Moderate activity is defined as 3 or more days of vigorous-intensity activity of at least 20 minutes per day or 5 or more days of moderate-intensity activity and/or walking at least 30 minutes per day per 5 or more days. Health-Enhancing physical activity [32] (HEPA) or high physical activity is classified as a vigorous-intensity activity for at least 3 days, achieving a minimum physical activity of at least 1500 MET-minutes/week or 7 or more days of any moderate-intensity or vigorous-intensity.[24]

The VIS measured the participant's vocational status and scored if they can work more than 15 hours per week as 5, work with reduced hours as 4, community-based work with assistance including volunteering as 3, and work in a sheltered workshop as 2, or unemployed as 1. VIS has been used among individuals with BT.[25,33]

To determine the level of EE, raw scores from each measures (the SNI, IPAQ, VIS and 2 Socioeconomic questions) were totaled. Based on this composite score, a tertile was calculated to reflect Low EE, Moderate EE, and High EE for the study sample. Higher scores denoted higher levels of EE.

Health Outcomes

Global Cortical Atrophy

The global cortical atrophy rate (GCAR) was measured using the brain MRI obtained for clinical surveillance. Follow-up MRI protocols for glioma include pre- and post-contrast 3D T1-weighted images with 3D T2-weighted FLAIR sequences. Timepoint 1 was the initial diagnosis/pre-RT imaging, Timepoint 2 was approximately 2-3 years from the time of diagnosis and Timepoint 3 was during study participation, approximately 5 years (-/+ 1 year) from diagnosis.

FreeSurfer pipeline (http://surfer.nmr.mgh.harvard.edu/) was used to process the clinical imaging. This pipeline allows adjustment using all three orthogonal planes to account for these structural anomalies in the gray matter (cortical) regions.[34-40] [6,41,42] All images were maintained in native coronal slice orientation to Digital Imaging and Communication in Medicine (DICOM) files, which were converted into Neuroimaging Informatics Technology Initiative (NIFTI) files prior to using the FreeSurfer automated segmentation software. Imaging processing includes motion correction and averaging [43] of all the scans available on the patient's volumetric 3D T1 weighted images. This is followed by the removal of non-brain tissue using a hybrid watershed/surface deformation procedure[44] automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures,[45] intensity

normalization[46] tessellation of the gray matter/white matter boundary, and automated topology correction.[44] Surface deformation is performed following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[34-40] Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across magnetic field strengths.[47,48]

Surgical scars, tumors, tumor beds, and resection cavities were censored from the analyses to mitigate against mislabeling of the cortex. All images were inspected for errors during manual segmentation[5,49] (see Figure 2). To increase the signal-to-noise ratio and perform accurate automatic segmentation of the clinical imaging, the senior research engineer used Synthase, an artificial intelligence technique that uses deep machine learning models to create synthetic MR images from low-resolution clinical imaging.[50] Notably, SynthSR was performed for images in Timepoint 1 and Timepoint 3 to generate high, isotropic resolution.

Cortical volume loss was calculated as the difference in volume from Timepoint 1 and the subsequent interval images. Freesurfer automation was performed by the first author in collaboration with a senior neuroimaging research scientist. Manual segmentation was cross-checked and verified by an expert in neuro-imaging analysis for correctness and congruity. The Freesurfer processing pipeline ran independently for each time point (Timepoint 1 = Pre-RT, Timepoint 2 = 2-3 years following diagnosis, and Timepoint 3 = time of enrollment/approximately 5 (-/+ 1 year from diagnosis). GCAR was calculated as the difference in volume from Timepoint 1, Timepoint 2, and Timepoint 3 (see Table 2).

Cognitive Function

Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), which assesses multiple cognitive domains, including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. The MoCA is sensitive detecting impairment in cognitive function among patients with BT.[51] Impaired

cognitive function is defined as a MoCA score of less than 26, with severe impairment defined as a MoCA score of ≤10.[20,21]

Processing speed was evaluated using the Symbol Digit Modalities Test (SDMT) Written version.[52] Increasing number of z-score indicates an increased processing speed. Greater than 0.6 is considered average, while less than -2.05 is considered having an impairment in processing speed. SDMT is predictive of employment status among patients with neurological disabilities.[53] The SDMT Written version has a test-retest reliability of .80 and has been widely used among patients with BT.

Functional Status and Symptoms

Function was measured using Karnofsky Performance Status (KPS) Scale Index and MD Anderson Symptom Inventory – Brain Tumor module (MDASI-BT). The ABTC clinic providers use KPS as a standard of care to evaluate function during routine clinic visits. A KPS score of 100 indicates normal full functioning without evidence of disease, a score of 90 indicates normal activity with minor signs and symptoms of disease, and so forth with declining function, increasing assistance and effort with activities of daily living.[54] KPS was extracted from the EHR. KPS allows the classification and clinical monitoring of a patient's functional disability. KPS Scale Index is widely used in patients with BT[55] and has an with interrater reliability of 0.89.[54]

BT-related symptoms were measured using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT). It is specifically designed for individuals with BT. MDASI-BT is comprised of 22 items, measuring six underlying constructs: affective factor, cognitive factor, focal neurological deficits, treatment-related symptoms, generalized disease symptoms, and gastrointestinal factor. MDASI-BT also includes six additional questions on the level of symptom interference with daily activities. The measure assesses the severity and impact of the symptom during the last 7 days using a Likert format from 0, indicating symptom "not present" to 10, "as

bad as you can imagine." Increasing scores indicate increasing symptom burden with a Cronbach's alpha of 0.67-0.90.[3]

Statistical Analysis

The primary aim of this research was to examine the association between increasing levels of EE with improving health outcomes (increased cognitive function [MoCA and SDMT]; promote healthy brain aging [reduced GCAR], improved functional status [KPS], and reduced symptom burden [MDASI-BT]. Response variables were transformed for ease of clinical interpretation and translation. We transformed GCAR and MoCA were transformed into ordinal categories. GCAR was categorized as normal (0.05% and less), mild (0.05% to 1.2%) or moderate/severe atrophy (greater than 1.3%). We chose these categories based on prior literature indicated that a normal cortical atrophy rate of 0.2% occurs beginning of age 35 and gradually accelerates to an annual volume loss of 0.5% at the age of 60, increasing to greater than 0.5% annually over age 60. [56] In addition, mild cognitive impairment is associated with a global cortical atrophy rate of approximately 1% and severe cognitive impairment greater than 1.3%.[57,58] We education-adjusted the MoCA score, adding one point to the score with education 12 years or lower.[20] We then categorized it into normal function or mild or moderate/severe cognitive impairment.[59] We adjusted the SDMT for age and education and used previously established descriptors based on the z-score.[52] Since the mean of symptoms (MDASI-BT) was positively skewed, a square-root transformation was performed.

Statistical analyses were performed using IBM SPSS Statistics software Version 29.0 (Antioch, NY, USA). Means, standard deviations, and distributional properties describe the change in cortical volume loss, cognitive impairment, and functional limitation/disability. We examined the distribution of each measure for non-normality and outliers. For normally distributed variables, Analysis of Variance (ANOVA), Analysis of Covariance (ANCOVA), and Student t tests were used to compare groups. Ordinal logistic regression was used for ordinal response categorical variables (MoCA, SDMT, GCAR, KPS). Linear regression modeling was

used for continuous response variables (MDASI-BT). For all planned analyses, $p < 0.05$ was considered statistically significant. It is noteworthy that during ordinal logistic modeling, certain categories were collapsed to promote model fit (i.e. moderate and severe to moderate/severe category). The dose of radiation, age, and sex were included in the statistical model as covariates.

Missing Data

Data were evaluated using complete-case analysis to determine the category of missingness (i.e., missing completely at random, missing at random, missing not at random). Clinical data imputation was performed. For example, if a score for MoCA and SDMT were missing because of severe cognitive impairment due to aphasia, a score of 0 was given. If KPS was missing due to an assessment not performed during the study visit, prior clinical KPS from a visit 3-6 months ago was used. For missing radiation doses, the median dose in Gy for the entire sample was used.

Results

Demographics and Clinical Characteristics

From March 2022 to February 2023, 792 participants were screened from the ABTC schedule for study eligibility. See Table 3 for a summary of demographics and clinical characteristics. Forty-one individuals meeting eligibility criteria were approached and 39 participants consented and completed the study protocol. Eighteen individuals received photon radiation (XRT) and 21 received proton-beam radiation (PBRT). The median age of the sample was 44 years old, range 26 to 78 years old. Mean time from diagnosis to study participation was 55 months (SD $\pm$ 11 months), range 39 to 75 months. Nineteen individuals were diagnosed with oligodendroglioma and 18 were diagnosed with astrocytoma. Two participants were diagnosed with brainstem glioma.

The median composite score for EE was 17 (range of 11-21). Thirteen participants were in the Low EE category, 17 in the Moderate category and 9 were in the High category. There were no statistically significant differences on age, sex, treatment history, tumor history, grading, treatment, dose, and type of radiation among the three groups of EE categories using ANOVA. See Table 3 for clinical characteristics based on EE Category.

Health Outcomes: Global Function

After adjusting for education, the global cognitive function as measured by MoCA was 25.03, with a range of 10 to 30. See Table 4 for descriptive statistics on measured health outcomes. Twenty-five individuals scored 26 and above and thus were categorized as normal with no impairment. Eight had mild cognitive impairment (score of 25-18), and six had moderate to severe cognitive impairment (17 or less). Individuals in the high category of EE were approximately 75% less likely to have moderate/severe cognitive impairment compared to those with low EE. However, this was not statistically significant (OR: 0.27, 95% CI 0.03, 2.09). Though a trend in OR was observed with decreasing levels of EE (OR: 0.60, 95% CI 0.114, 3.11), this was not statistically significant ($p = 0.54$).

After adjusting for education and age, z-scores for processing speed as measured by SDMT were calculated. Nineteen individuals scored above average and higher and 14 individuals were noted to have impairment in processing speed. Please refer to Table 4. Similar to MoCA, individuals in the high category of EE were 70% less likely to have impaired processing speed compared to those with low EE (OR: 0.3, 95% CI 0.06, 1.8). Similar to MoCA with decreasing level of EE, individuals with moderate EE were also less likely to have impaired processing speed (OR: 0.64, 95% CI 0.15, 2.69). Refer to Table 5 for the summary of results.

Health Outcomes: Cortical Atrophy

Approximately 87% of MRI images were obtained with 3.0T scanners. One hundred seventeen images were processed. Thirty-eight individuals had Timepoint 1 as pre-radiation RT, with 17 of the participants having the MRI scans at the time of diagnosis (with tumor included) or

approximately 2 weeks after surgery. After adjusting for age, sex, and dose of radiation, the mean GCAR was -0.06 (range -0.48-0.30). Twenty-five individuals were categorized as having normal cortical atrophy and 14 had mild to severe cortical atrophy approximately five years from the time of diagnosis. Those with high levels of EE were approximately 70% less likely to have moderate or severe cortical atrophy when compared to those with low levels of EE. However, the result was not statistically significant (OR: 0.30, 95% CI 0.05, 1.90, $p = 0.20$).

Health Outcomes: Functional Status and Symptoms

Of the 39 participants, the median score of KPS was 90, the range 60 to 100. Persons with a higher level of EE were approximately three times more likely to fall in the category of normal full functioning when compared to those with low level of EE. This result was not statistically significant (OR: 1.87, CI 95% 0.33, 10.5, $p = 0.48$).

The participants' mean score on MDASI-BT was 1.41 (range 0.091-7.09). Using linear regression modeling, there was no statistically significant relationship between levels of EE and symptom burden (95% CI -0.1, 0.05, $p = 0.52$) after adjusting for age, sex, and dose of radiation. Please refer to Table 5 for a summary of statistical analyses.

Exploratory Post-Hoc Analyses

Given the composite score of EE was obtained from five measures (IPAQ, SNI, VIS and 2 Socioeconomic questions), post-hoc analysis was performed using the same covariates in the primary analysis to explore the association of each of these components. Similar trends in increasing levels of social connectedness (SNI), physical activity (IPAQ) were more likely associated to have normal scores on the MoCA. However these findings were not statistically significant. Individuals who scored high in physical activity (defined by vigorous-intensity activity for at least 3 days)[24] were 6 times more likely to have normal functioning than those who were inactive (1.9, CI 95% 0.2, 3.5, $p < 0.05$). Ordinal regression could not accurately model health outcomes with socioeconomic questionnaires due to empty cells; therefore, linear regression was used. Those individuals who expressed increasing financial difficulties in being able to pay

rent had a positive association with increasing symptom burden (0.2, CI 95% 0.3 – 0.36, $p < 0.05$, $r = 0.38$). This finding was echoed by those who expressed financial challenges in being able to see a healthcare provider (0.26, CI 95% 0.01 – 0.5, $p < 0.045$, $r = 0.34$). A summary of these findings is presented in Table 6.

Discussion

Our research study is highly innovative as it seeks to shift current research by utilizing and refining the novel concept of EE in the neuro-oncology field. EE, as a concept in the human population health, remains in its infancy even though the term can be traced back to seminal studies describing neuroplasticity with varying experiences in animal models.[60] EE in animal models pertains to the motor, sensory, cognitive, and social stimulations that promote positive biological functioning and disrupt aberrant behavioral patterns.[61] [62] A few human health research studies[63] [64,65] have used the term EE, but the metrics employed did not assess the construct's comprehensive attributes (physical activity, social engagement, employment, financial stability).[19] Our present study addressed this measurement gap. To capture the full construct of EE, SNI was used to measure social support and interaction,[23] the IPAQ to measure physical activity,[24] and the VIS to evaluate an individual's activity as a student, employee or volunteer.[25] Socioeconomic questionnaires were also used to also highlight financial stability as a critical component of survivorship issues.

The 39 individuals we recruited experienced varying levels of EE. Though 39 is a relatively small sample size for the statistical approach selected, this is comparable and relatively larger than other studies in the BT population.[5,22,66] Though we observed distinct increasing patterns in estimates and OR between improved health outcomes and increasing levels of EE, results were not statistically significant. It is unclear if these observations would have reached statistical significance with more participants. Recall that this pattern of association was observed on multiple different health outcomes (MoCA, SDMT, and KPS). Such results, although not statistically significant may have clinical significance. Our post-hoc analysis

revealed increasing levels of social support and physical activity of MoCA and KPS, however, not statistically significant. Prior literature has described a direct cause-and-effect relationship between physical activity and cognitive functioning.[67,68] Social isolation is a risk-factor for worsening cognitive function[69] and the recent COVID-19 pandemic has highlighted the detrimental effects of social isolation in older adults.[70,71]

There are several limitations to the study in addition to the limited sample size and heterogeneity of the sample. As the current state of the literature does not identify which of EE factors is most effective, we integrated all measures (SNI, IPAQ, VIS, and 2 socioeconomic questionnaires) into a single score treating each factor equally in the analysis. Furthermore, EE was only evaluated cross-sectionally at the time of enrollment, approximately five years from diagnosis. Thus, the level of EE was not ascertained prior to the diagnosis or post-treatment. It is possible the patterns in OR of improved health outcomes with increasing levels of EE were related to the level of EE prior to the diagnosis which could not be assessed with this cross-sectional collection of EE and health outcomes.

Another limitation is the processing of MRI images. When evaluating the different time points of individual participants' neuroimaging data, certain participants had increased cortical volume from Timepoint 1 to Timepoint 3. And as noted earlier, 17 individuals had Timepoint 1 imaging at the time of diagnosis or approximately 2 weeks after surgery. The tumor causes significant swelling and surgery has associated post-operative changes. As these changes were censored during the manual segmentation, it is possible that these structural anomalies were overly censored. It is also possible that Timepoint 1, before RT and around the time of initial diagnosis or 2 weeks after surgery, may not have been the most appropriate baseline for longitudinal assessment of the cortical volume analysis. It is also reasonable to conclude that perhaps a more focused region of interest (i.e. hippocampal volume, medial temporal lobe etc.) may provide better modeling and should be explored in future studies.

Lastly, limited evidence exists at present to guide the categorization of the cortical atrophy and cognitive impairment that occurs after radiation. Thus, placing GCAR and MoCA into clinical categories in this study posed a limitation as these were adapted from multiple studies that do not include individuals with brain tumors.[20,56,58,59] The categorization performed for ease of translation and interpretation may not be appropriate among persons with a brain tumor.

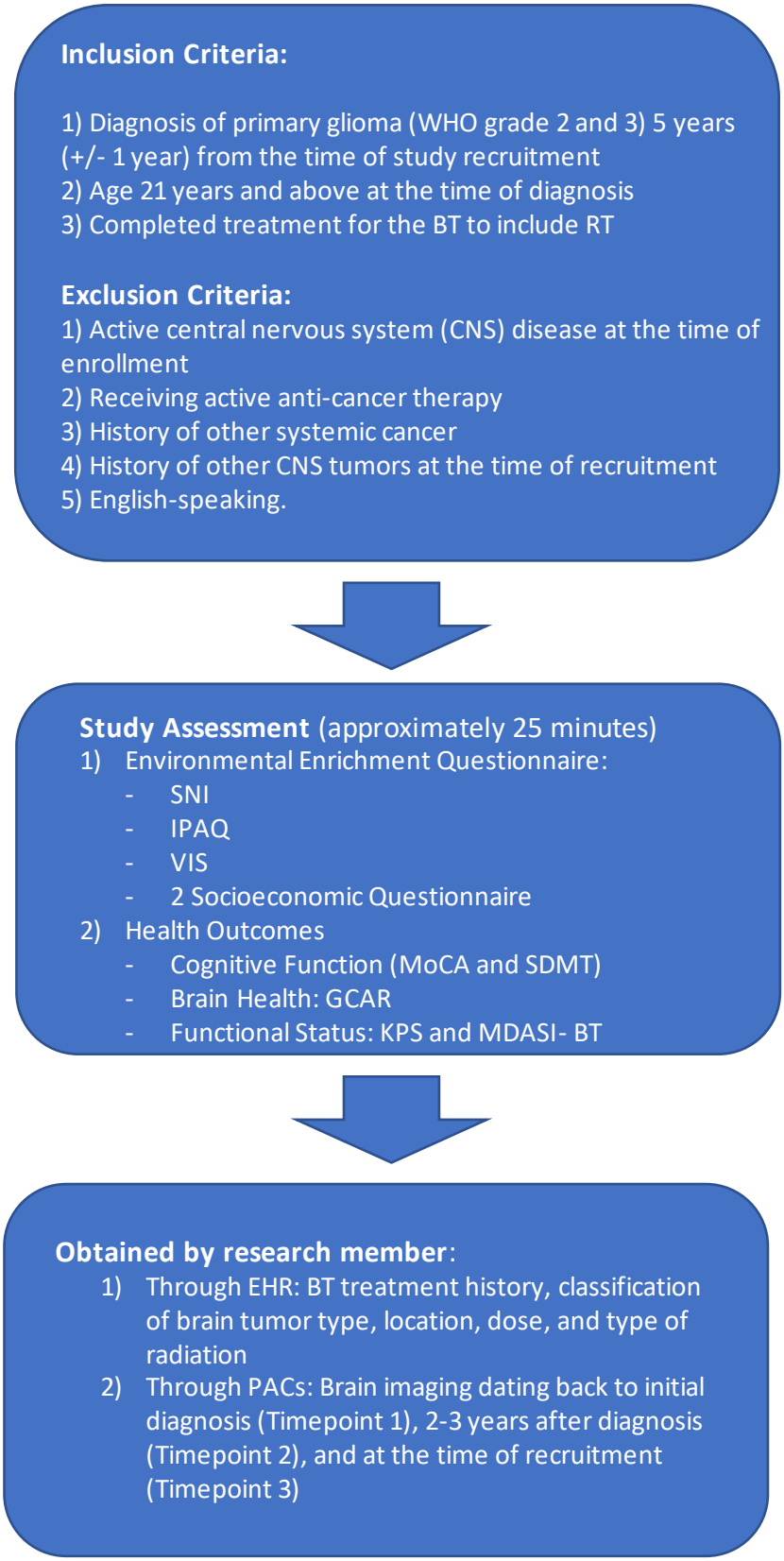
Due to the limitations described, future research is recommended. Factor analysis and structural equation modeling should be performed in future studies to analyze the structural relationship within the measures and variables of EE to better operationalize this in human health studies. Future studies should include an assessment of EE prior to treatment or at the time of diagnosis and longitudinally followed to accurately assess the association between EE and health outcomes. Lastly, it is also critical to consider the effect of time on an aging brain as rates of atrophy change with time and age.[56] When screening participants for eligibility, some participants complained of symptoms several months prior to their first initial MRI, thus the time difference is variable in others (i.e. 39 months). Future statistical modeling should include the effect of time.

Understanding the relationship between EE and health outcomes may provide insight into the mechanisms leading to impaired cognitive function, symptoms, functional status, and accelerated aging. The application of EE can also be used among other populations with cancer or those with chronic diseases without a cure. By closely examining the conditions in which BT survivors live, future interventions can incorporate individualized interventions that are most attainable to the individual with regard to socioeconomic barriers. For example, if an individual resides in a rural area and is isolated, what other interventions or counseling can be initiated? Increasing physical activity, connections to social or supportive programs, ability to return to work, and vocational support may be considered based on EE. Understanding the relationship

between environmental, behavioral, and social factors with health outcomes is necessary to advance the paucity of health promotion and restoration research among BT survivors.

This study provided an initial exploration into the role of EE in health outcomes, and survivorship programs for persons with BT. Individuals with BT may benefit from assessment and interventions in these areas. Comprehensive neuro-oncology survivorship programs are necessary to promote, restore, and maintain the health of individuals with brain tumors after radiation. Providing an enriched environment may serve to reduce symptom burden, promote healthy brain aging, and improve cognitive and functional status after brain radiation.

Figure 1


Inclusion Criteria:
1) Diagnosis of primary glioma (WHO grade 2 and 3) 5 years (+/- 1 year) from the time of study recruitment
2) Age 21 years and above at the time of diagnosis
3) Completed treatment for the BT to include RT
Exclusion Criteria:
1) Active central nervous system (CNS) disease at the time of enrollment
2) Receiving active anti-cancer therapy
3) History of other systemic cancer
4) History of other CNS tumors at the time of recruitment
5) English-speaking.
Study Assessment (approximately 25 minutes)
1) Environmental Enrichment Questionnaire:
- SNI
- IPAQ
- VIS
- 2 Socioeconomic Questionnaire
2) Health Outcomes
- Cognitive Function (MoCA and SDMT)
- Brain Health: GCAR
- Functional Status: KPS and MDASI- BT
Obtained by research member:
1) Through EHR: BT treatment history, classification of brain tumor type, location, dose, and type of radiation
2) Through PACs: Brain imaging dating back to initial diagnosis (Timepoint 1), 2-3 years after diagnosis (Timepoint 2), and at the time of recruitment (Timepoint 3)

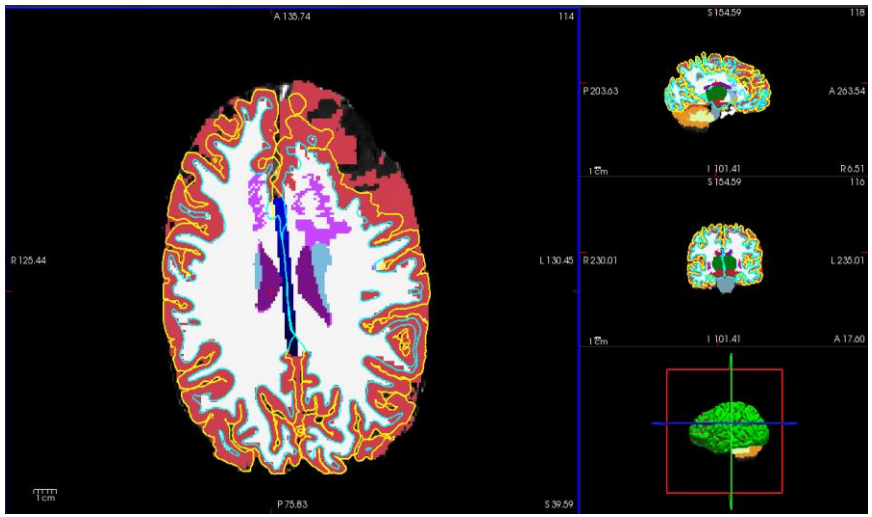


***Figure 2a**. Automatic segmentation prior to manual segmentation of current study.*

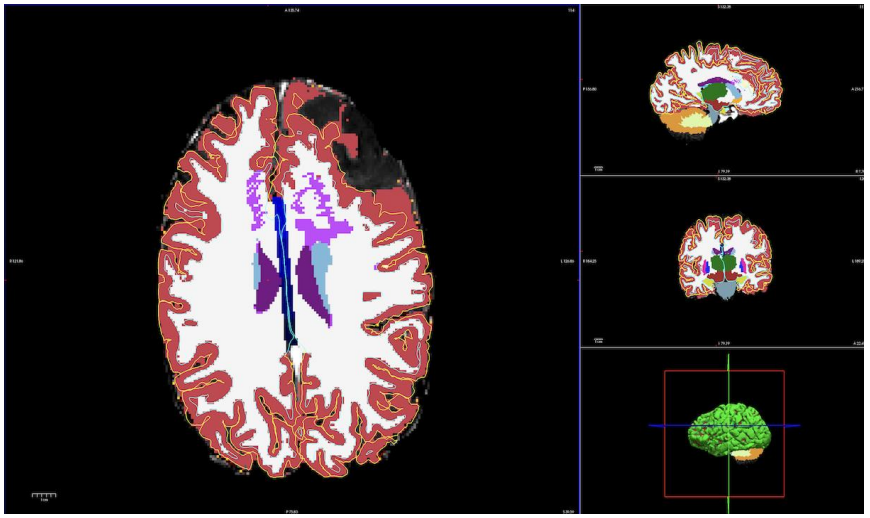


***Figure 2b.** After manual editing of mislabeled cortex along resection cavity of current study .*

Tables:

Table 1.

Environmental Enrichment Measure	
SNI (Range 0-4)	0: Least Socially Connected/ Most Isolated 4: Most Socially Connected/Not Isolated
IPAQ	1: Low activity 2: Moderate activity 3: High activity
VIS	1: Unemployed 2: Sheltered workshop 3: Community-volunteer 4: Part-time employment 5: Full employment/student
Socioeconomic Questionnaire: Was there time in the last 12 months when you needed to see a doctor but could not because of cost?"	1: Always 2: Often 3: Sometimes 4: Rarely 5: Never
Socioeconomic Questionnaire: How many times in the last 12 months would you say you were worried or stressed about having enough money to pay your rent/mortgage?"	1: Always 2: Often 3: Sometimes 4: Rarely 5: Never
Total Score	Range 4-22

Table 2.

Formulas for Calculation of Global Cortical Atrophy Rate (GCAR)			
Timepoint (TP)	Brain Volume (BV)	Rate	Rate of Brain Atrophy (% per year)
1 (Pre-RT)	BV1		
2 (2-3 years from dx)	BV3	$Rate_1$	$(BV_1 - BV3)/ BV_1$
3 (~ 5Years from dx - time of enrollment)	BV5	$Rate_2$	$(BV3 - BV5)/ BV_2$
Mean GCAR	(Rate1 + Rate2)/2		

Table 3.

Demographic and Clinical Characteristics by Level of Environmental Enrichment					
EE Category	Low	Moderate	High	Total	P-Value
n	13	17	9	39	
Median (Range)	13(11–14)	17(15–18)	20 (19–21)	17(11–21)	
Age, years at enrollment, median (range)	46 (28–78)	34 (26–78)	39 (31–62)	44 (26–78)	0.31
Time difference from diagnosis to enrollment, months, mean (range)	54.7 (41.72 – 72.37)	54.72 (39.16 – 75.52)	59 (45.4 – 70.82)	55.57 (39.16 – 75.52)	
Sex (%)					0.9
Male	8 (61.5)	9 (52.9)	5 (55.6)	22 (56.4)	
Female	5 (38.5)	8 (47.1)	4 (44.4)	17 (43.6)	
WHO Grading (%)					0.64
2	9 (69.3)	6 (35.2)	5 (55.5)	20 (51.3)	
3	3 (23.1)	10 (62.6)	4 (44.4)	17 (43.6)	
Tumor Histology (%)					.14
Oligodendroglioma	9 (69.3)	6 (35.2)	4 (44.4)	19 (48.7)	
Astrocytoma	3 (23.1)	10 (62.6)	5 (55.5)	18 (46.2	
Hemisphere Location (%)					
Left	10 (83.3)	10 (62.5)	6 (66.7)	26 (70.3)	0.8
Right	2 (16.7)	6 (37.5)	3 (33.3)	11 (29.7)	
Lesion Location (%)					
Frontal	9 (69.3)	12 (70.6)	8 (88.9)	29 (74.4)	0.54
Parietal	2 (15.4)	2 (11.8)	0	4 (10.3)	0.51
Temporal	2 (15.4)	6 (35.3)	1 (11.1)	9 (23)	0.29
Occipital	0	0	0	0	
Brainstem	1 (7.7)	1 (5.9)	0	2 (5.1)	0.58
Surgery (%)					

None	2 (15.4)	0	2 (22.2)	4 (10.3)	
Subtotal	2 (15.4)	6 (35.3)	3 (33.3)	11 (28.2)	
Near-Total	5 (38.5)	3 (17.6)	0	8 (20.5)	
Gross-Total	4 (30.8)	7 (41.2)	4 (44.4)	15 (38.5)	
Chemotherapy (%)					
No Chemotherapy	1 (7.7)	1 (5.9)	1 (11.1)	3 (7.7)	0.9
TMZ	9 (69.2)	14 (82.4)	5 (55.6)	28 (71.8)	
PCV	2 (15.4)	2 (11.8)	3 (33.3)	7 (18)	
TMZ + PCV	1 (7.7)	0	0	1 (3)	
Concurrent Chemoradiation	7 (53.8)	10 (58.8)	5 (55.6)	22 (56.4)	0.965
Radiation					
Dose of Radiation, Gy, Median (range Gy)	54 (46 – 60)	56.7 (46.8 – 60)	54 (54 – 60)	54 (46 – 60)	0.188
Type of Radiation **(%)**					0.387
Photons	5 (38.)	10 (58.8)	3 (33.3)	18	
Protons	8 (61.5)	7 (41.2)	6 (66.7)	21	

Table 4

Health Outcomes	N	Mean	Std. Deviation	Median	Min	Max
MOCA		25	4.9	27	10	30
Normal (26 and above)	25					
Mild (25 – 18)	8					
Moderate/Severe (≤ 17)	6					
SDMT		-0.86	1.5	-0.7	-5.2	1.5
Above Average (≥ 0.63)	8					
Average (0.6 – -0.73)	11					
Below Average (-0.75 – -1.37)	6					
Borderline Impaired (-1.43 – -1.95)	5					
Impaired (≤ 2.05)	9					
Global cortical atrophy						
Global cortical atrophy rate		-0.06	0.2	-0.05	-0.48	0.30
Normal	25					
Mild	8					
Moderate/Severe	6					
Function						
KPS		88.7	11.3	90	60	100
Normal without evidence of disease (100)	11					
Normal effort with minimal signs and symptoms (90)	18					
Normal activity with some effort (80)	3					
Cares for self but unable to work (70)	4					
Requires assistance (60 and below)	3					
Symptoms						
MDASI-BT	39	1.896	1.642	1.41	0.091	7.09

Table 5.

Odds Ratio of Experiencing Health Outcomes at 5 years post-diagnosis by Categories of Environmental Enrichment Adjusted for sex, age and dose of radiation							
MoCA (Reference Group, impairment)							
		95% Confidence Interval (CI)			**95% CI**		
	Estimates	**Lower**	**Upper**	**Odds Ratio (OR)**	**Lower**	**Upper**	**P-value**
High EE	-1.31	-3.36	.74	0.27	.035	2.09	0.21
Moderate EE	-0.52	-2.17	1.13	0.60	.114	3.11	0.54
Low EE	Reference			1			
SDMT (Reference Group, impairment)							
		95% CI			**95% CI**		
	Estimates	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
High EE	-1.13	-2.85	.59	0.32	.06	1.8	0.2
Moderate EE	-0.44	-1.87	.99	0.64	.15	2.69	0.55
Low EE	Reference			1			
GCAR (Reference Group, moderate/severe atrophy)							
		95% CI			**95% CI**		
	Estimates	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
High EE	-1.19	-3.03	.64	0.30	.05	1.90	0.20
Moderate EE	-1.73	-3.50	.05	0.18	.03	1.05	0.06
Low EE	Reference			1			
KPS (Reference Group, full function)							
		95% CI			**95% CI**		
	Estimates	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
High EE	.63	-1.11	2.36	1.87	.33	10.5	0.48
Moderate EE	.01	-1.54	1.55	1.01	.21	4.7	0.1
Low EE	Reference			1			
Symptoms							
		95% CI					
	Estimates	**Lower**	**Upper**	**OR (N/A)**			**P-Value**
EE-total	-0.023	-0.1	.05				0.519

Table 6

Post-Hoc Analysis								
MoCA (normal as reference)								
			95% Confidence Interval (CI)			**95% CI**		
SNI	**N**	**Estimates**	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
Socially integrated	12	1.01	-0.67	2.84	2.64	.51	17.2	0.23
Isolated/Integrated	16	0.82	-.82	2.45	2.005	.44	11.6	0.33
Most Isolated	11	Reference			1			
IPAQ								
Health-Enhancing Physical Activity	17	1.16	-.452	2.778	3.199	.636	16.093	0.16
Minimally Active	10	.86	-1.024	2.740	2.358	.359	15.489	0.37
Inactive	12	Reference						
VIS								
Full-Time	19	1.25	-.37	2.87	3.5	.693	17.7	0.13
Part-time/Volunteer	5	3.20	.1	6.31	24.6	1.1	548.5	0.04**
Unemployed	15	Reference						
Rent								
Financial Issues	10	.21	-1.73	2.14	1.2	.177	8.5	.84
Rarely issues	11	.23	-1.4	1.9	1.3	.247	6.4	.78
Never having issues	18	Reference						
			95% CI		Partial	OR Not Application (N/A)		
Cost	N	Estimates	Lower	Upper	Correlation			P-value
Linear Regression*	39	-1.62	-4.02	.79	-.23			0.18
SDMT (Above average as reference)								
			95% CI			**95% CI**		
SNI	**N**	**Estimates**	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
Socially integrated	12	.33	-1.13	1.8	1.4	.32	6.01	.66
Isolated/Integrated	16	-.86	-2.24	.53	.43	.11	1.7	.23
Most Isolated	11	Reference						
IPAQ								
Health-Enhancing Physical Activity	17	.19	-1.14	1.52	1.21	.32	4.58	.78
Minimally Active	10	-.14	-1.8	1.53	.87	.17	4.61	.87

Inactive	12	Reference						
VIS								
Full-Time Employed	19	.76	-.52	2.03	2.14	.60	7.64	.24
Part-time/Volunteer	5	.65	-1.11	2.4	1.91	.33	11.05	.47
Unemployed	15	Reference						
Rent								
Financial Issues	10	-.87	-2.4	.65	.42	.09	1.9	.26
Rarely issues	11	-.33	-1.7	1.1	.72	.18	2.95	.69
Never having issues	18	Reference						
			95% Confidence Interval		Partial	OR (N/A)		
Cost	N	Estimates	Lower	Upper	Correlation			P-value
Linear Regression*	39	0.38	-.42	1.19	0.16			0.34
GCAR (Reference Group, normal)								
			95 % CI			**95 % CI**		
SNI	**N**	**Estimates**	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
Socially integrated	12	1.40	-.26	3.07	4.06	.77	21.44	0.09
Isolated/Integrated	16	2.19	0.44	3.94	8.93	1.55	51.38	0.01**
Most Isolated	11	Reference						
IPAQ								
Health-Enhancing Physical Activity	17	-1.30	-2.95	0.34	0.27	.05	1.4	.12
Minimally Active	10	.48	-1.62	2.58	1.61	.2	13.1	0.66
Inactive	12	Reference						
VIS								
Full-Time Employed	19	.64	-.83	2.1	1.9	.44	8.19	.40
Part-time/Volunteer	5	-.42	-2.62	1.8	.66	.07	5.91	.71
Unemployed	15	Reference						
Rent								

Financial Issues	10	-.38	-2.22	1.45	.68	.11	4.28	.68
Rarely issues	11	-.22	-1.82	1.38	.80	.16	3.97	.79
Never having issues	18	Reference						
			95% CI		Partial	OR (N/A)		
Cost	N	Estimates	**Lower**	**Upper**	Correlation			P-value
Linear Regression*	39	0.11	-.26	.48	0.1			0.55
KPS (Reference Group, normal function)								
			95% CI			95% CI		
SNI	**N**	**Estimates**	**Lower**	**Upper**	**OR**	**Lower**	**Upper**	**P-value**
Socially integrated	12	.11	-1.5	1.7	1.1	.23	5.5	.89
Isolated/Integrated	16	.4	-1.1	1.9	1.5	.33	6.8	.6
Most Isolated	11	Reference						
IPAQ								
Health-Enhancing Physical Activity	17	1.72	.18	3.3	5.58	1.2	25.97	.03**
Minimally Active	10	.91	-.82	2.6	2.5	.44	13.9	.157
Inactive	12	Reference						
VIS								
Full-Time Employed	19	.99	-.44	2.41	3.646	.64	11.18	.18
Part-time/Volunteer	5	-.19	-2.22	1.83	.774	.11	6.25	.85
Unemployed	15	Reference						
Rent								
Financial Issues	10	-.42	-2.08	1.23	.66	.13	3.4	.62
Rarely issues	11	.63	-.85	2.11	1.88	.43	8.2	.4
Never having issues	18	Reference						
			95% CI		Partial	OR (N/A)		
Cost	N	Estimates	Lower	Upper	Correlation			P-value
Linear Regression*	39	-5.1	-10.5	.33	-.31			0.07

Symptoms						
			95% CI			
SNI	**N**	**Estimates**	**Lower**	**Upper**	**P-value**	**Partial Correlation**
	39	-0.03	-0.24	0.17	0.76	-0.053
IPAQ						
	39	-0.09	-0.32	0.13	0.41	-0.14
VIS						
	39	0.112	-0.03	0.25	0.11	0.27
Rent						
	39	-.204	-.38	-0.03	0.02**	-0.38
Cost						
	39	-.27	-.536	0.004	0.05**	-0.32

** Statistically significant at alpha level less than 0.05.

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Chapter 4: Environmental Enrichment after Brain Irradiation

Target Journal: *Psycho-Oncology*

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Abstract:

Background:

Individuals from underserved communities who received photon radiation are at a disproportionately increased risk of accelerated aging and symptom burden that significantly impact independence and overall functioning. There is limited knowledge of environmental factors that mitigate these long-term sequelae. The aim of the study is to explore and describe the health outcomes experienced by brain tumor (BT) survivors who received Photon radiation and Proton-Beam Radiation in relation to levels of environmental enrichment (EE).

Methods:

The study employed a cross-sectional cohort design among persons with glioma treated with radiation approximately 5 years from the original diagnosis (N=39). EE consists of social network/engagement, physical activity, and employment status/financial stability measured by the Berkman-Syme Social Network Index, International Physical Activity Questionnaire, Vocational Index Scale, and two Socioeconomic Questions, respectively. EE level at enrollment is classified into low, moderate, or high tertile. Montreal Cognitive Assessment (MoCA) and Symbol Digit Modality Test (SDMT) measured cognitive function. Cortical atrophy is measured using temporal brain MRI images from the time of diagnosis, 3 years after diagnosis, and at the time of recruitment. Images are processed using semi-automated FreeSurfer segmentation software. Karnofsky Performance Status (KPS) Scale and the MD Anderson Symptom Inventory – BT module were used to measure functional status. Descriptive statistics characterize the health outcomes of individuals who received photons radiation (XRT) and proton-beam radiation (PBRT) in relation to Low, Moderate and High levels of EE.

Results:

Thirty-nine participants completed the study protocol. The median age is 44, 22 are male, and 27 are female. There are 18 Individuals diagnosed with astrocytoma and 19 with oligodendroglioma. Eighteen individuals received photon radiation (XRT) and 21 received

proton-beam radiation (PBRT). Among persons who received XRT, 5 were categorized into Low EE, 10 to Moderate EE and 3 had High levels of EE. Of those who received PBRT, 8 were categorized into Low EE, 7 had Moderate EE and 6 had High EE. Those individuals who received XRT and had High levels of EE had higher scores in MoCA, SDMT, and lower GCAR than individuals who received PBRT.

Conclusion:

BT survivors are at an increased risk of accelerated aging and progressive neurological decline. Comprehensively understanding the relationship of environmental, behavioral, and social factors with health outcomes is necessary to advance the paucity of health promotion and restoration research among BT survivors. Strategies that support higher EE may serve as interventions to improve neuroplasticity and ameliorate the extent of accelerated brain aging after brain radiation. Providing an enriched environment may serve to reduce symptom burden, promote healthy brain aging, and improve cognitive and functional status in BT survivors receiving radiation.

Keywords:

Brain tumor survivors; Environmental Enrichment; Neuro-oncology survivorship; Photon radiation; Proton-Beam radiation.

Introduction

Normal brain aging is associated with cortical structural changes, including cortical atrophy.[1] Pathological brain aging is characterized by accelerated atrophy of cortical and subcortical structures along with cognitive decline.[2,3] Cranial irradiation, a standard treatment for patients with glioma (World Health Organization [WHO] 2 or 3) brain tumors, is closely associated with progressive cortical atrophy and cognitive impairment.[4-6] Thus, individuals with glioma treated with radiation (RT) are at a disproportionately increased risk of accelerated brain aging[7-9] and associated symptom burden,[10-12]as well as development of other chronic complications[13] compared to the general cancer survivor population.[14] The cortical structural brain changes may be highly dependent on the type of radiation a patient receives for treatment. Photon radiation therapy (XRT), affects surrounding healthy tissue as it has both an entrance and exit dose. Whereas proton beam radiation (PBRT) deposits the maximum dose at the target depth with no exit dose, minimizing irradiation of the surrounding healthy tissue.[15] Critically examining the environmental, behavioral, and social factors may provide insight into interventions that are neuroprotective after brain RT.

Along with progressive neurological impairment, glioma brain tumor (BT) survivors experience high rates of unemployment,[16-18] reduction in income, and loss of social relationships.[19] Studies indicate that environmental enrichment (EE)[20] is associated with overall well-being and quality of life in the general cancer survivor population. EE is multidimensional and is comprised of social support,[21] physical activity,[22] economic stability,[23] and employment status.[24] Studies in animal models have shown that higher levels of EE are associated with greater neuroplasticity following brain injury, therefore, EE may also offer a neuroprotective benefit among BT survivors. However, the association between EE and health outcomes (improving cognitive and functional status, promoting healthy brain aging, and reducing symptom burden) has not been examined in BT survivors. Examining the role of EE in persons who receive RT may provide possible behavioral and social health interventions that could be

broadly used to promote neuroplasticity and decrease cognitive impairment among BT survivors. The aim of this paper is to describe the health outcomes (cognitive function, functional status, symptom burden, and global cortical atrophy) among glioma BT survivors treated with XRT and those who received PBRT five years following diagnosis.

Materials and Methods

Setting

The setting is the Alvord Brain Tumor Center (ABTC), a multi-disciplinary neuro-oncology clinic located at the UW Medical Center-Montlake (UWMC), Seattle, Washington. Inclusion criteria included persons with: 1) a diagnosis of primary glioma (WHO grade 2 and 3) five years (+/- 1 year) from the time of study recruitment 2) aged 21 years and above at the time of diagnosis, 3) completed treatment for the BT to include PBRT or XRT. Exclusion criteria included: 1) having an active central nervous system (CNS) disease at the time of enrollment; 2) receiving active anti-cancer therapy; 3) a history of other systemic cancer; 4) a history of other CNS tumors at the time of recruitment and 5) English-speaking.

The research protocol was approved by the University of Washington Institutional Review Board. Written informed consent was obtained from participants or proxies. For individuals unable to provide informed consent due to severe impairment in cognitive function (Montreal Cognitive Assessment [MoCA] ≤ 10),[25,26] the proxy was the individual's Legally Authorized Representative (LAR) willing to give consent and complete questionnaires on behalf of the study participant.

Design

The study employed a retrospective cohort approach to meet the study aim. The study protocol was completed in one visit. The research assistant or the principal investigator (PI) recruited individuals when they presented to the ABTC for a regularly scheduled follow-up visit. All participants were asked to self-report their race, ethnicity, and current residential zip code. Age, gender, and sex were obtained from the electronic health record (EHR) along with BT

treatment history, classification of BT type, location, dose, and type of RT. Magnetic Resonance Imaging (MRI) of the brain from the time of initial diagnosis (Timepoint 1), prior to RT, approximately 2-3 years after diagnosis (Timepoint 2), and at the time of recruitment (Timepoint 3) were obtained for further processing and analysis. The goal was to enroll 40 participants for the study (equivalent numbers of participants who received XRT and PBRT, n=20). We chose this sample size as with N=40 and power = 0.8, the smallest detectable effect size is 0.45, which corresponds to a mean decrease in cortical volume of 1.45%. Prior studies in persons with BT reported decreases of 5-6% 6-10 years post-diagnosis.[27]

Assessment of Environmental Enrichment (EE)

EE is defined as an individual's social, physical, and cognitive domains that encourage positive stimulations, interactions, and activities in their surroundings.[20] To capture the full construct and build upon prior research, we used the Berkman-Syme Social Network Index (SNI) to measure social support and interaction.[28] The International Physical Activity Questionnaire[29] (IPAQ) measured physical activity.[29] Vocational-Independence Scale (VIS) evaluated an individual's activity as a student, employee, or volunteer.[30] Rather than using the level of gross income, two questions were used to ascertain financial stability: Was there time in the last 12 months when you needed to see a doctor but could not because of cost?" and "How many times in the last 12 months would you say you were worried or stressed about having enough money to pay your rent/mortgage?" Responses are on a 5-point Likert-type scale 1=Always, 5=Never.[31]

The SNI assessed the type, size, closeness, and frequency of contacts in a respondent's current social network. It is a self-report questionnaire with Cronbach's alpha of 0.84.[28,32] The SNI has been validated in patients with cancer[33] and with neurological impairment.[34] The level of social connectedness summed cutoff score (0 or 1 = least socially connected; 2, 3, or 4 corresponds to increasing levels of connectedness).[34]

The IPAQ measured job-related physical activity, transportation physical activity, housework, recreation activity, and time spent sitting.[29] This is a self-administered questionnaire and has been used in patients with BT[35,36] with test-retest reliability of 0.80.[29] Low physical activity is assigned to those with 2 or fewer days of vigorous activity. Moderate activity is defined as 3 or more days of vigorous-intensity activity of at least 20 minutes per day or 5 or more days of moderate-intensity activity and/or walking at least 30 minutes per day per 5 or more days. Health-enhancing physical activity [37] (HEPA) or high levels of physical activity is classified as a vigorous-intensity activity for at least 3 days, achieving a minimum physical activity of at least 1500 MET-minutes/week or 7 or more days of any moderate-intensity or vigorous-intensity.[29]

The VIS measured the participant's vocational status and scored if they can work more than 15 hours per week as 5, work with reduced hours as 4, community-based work with assistance including volunteering as 3, and work in a sheltered workshop as 2, or unemployed as 1. VIS has been used among individuals with BT.[30,38] To determine the level of EE, categorical scores from the SNI, IPAQ, VIS, and Socioeconomic questions were totaled, with increasing scores indicating increasing levels of EE. Based on this composite score, individuals were placed into tertiles, categorized as Low, Moderate, or High EE.

Health Outcomes

Global Cortical Atrophy

The global cortical atrophy rate (GCAR) was measured using the brain MRI obtained for clinical surveillance. Follow-up MRI protocols for glioma include pre- and post-contrast 3D T1-weighted images with 3D T2-weighted FLAIR sequences. Timepoint 1 was the initial diagnosis/pre-RT imaging, Timepoint 2 was approximately 2-3 years from the time of diagnosis and Timepoint 3 was during study participation, approximately 5 years (-/+ 1 year) following diagnosis.

The FreeSurfer pipeline (http://surfer.nmr.mgh.harvard.edu/) was used to process the clinical imaging. This pipeline allows adjustment using all three orthogonal planes to account for

these structural anomalies in the gray matter (cortical) regions.[39-45] [9,46,47] All images were maintained in native coronal slice orientation which were converted into Neuroimaging Informatics Technology Initiative (NIFTI) files prior to using the FreeSurfer automated segmentation software. Imaging processing includes motion correction and averaging [48] of all the scans available on the patient's volumetric 3D T1 weighted images. This is followed by the removal of non-brain tissue using a hybrid watershed/surface deformation procedure[49] automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures,[50] intensity normalization[51] tessellation of the gray matter/white matter boundary, and automated topology correction.[49] Surface deformation is performed following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[39-45] Freesurfer morphometric procedures have demonstrated to show good test-retest reliability across scanner manufacturers and across magnetic field strengths.[52,53]

Surgical scars, tumors, tumor beds, and resection cavities were censored from the analyses to mitigate mislabeling of the cortex. All images were inspected for errors during manual segmentation[8,54] To increase the signal-to-noise ratio and perform accurate automatic segmentation of the clinical imaging, the senior research engineer used SynthSR, an artificial intelligence technique that uses deep machine learning models to create synthetic MR images from low-resolution clinical imaging.[55] Notably, SynthSR was performed for images in Timepoint 1 and Timepoint 3 to generate high, isotropic resolution.

Cortical volume loss was calculated as the difference in volume from Timepoint 1 and the subsequent interval images. Freesurfer automation was performed by the first author in collaboration with a senior neuroimaging research scientist. Manual segmentation was cross-checked and verified by an expert in neuro-imaging analysis for correctness and congruity. The Freesurfer processing pipeline ran independently for each time point (Timepoint 1 = Pre-RT, Timepoint 2 = 2-3 years following diagnosis, and Timepoint 3 = time of enrollment/approximately

5 (-/+ 1 year from diagnosis). GCAR was calculated as the difference in volume from Timepoint 1, Timepoint 2, and Timepoint 3.

Formulas for Calculation of Global Cortical Atrophy Rate (GCAR)

Timepoint	*Brain Volume (BV)*	*Rate*	*Rate of Brain Atrophy (% per year)*
1 (Pre-RT)	*BV1*		
2 (2-3 years from dx)	*BV3*	$Rate_1$	$(BV1 – BV2)/ BV_1$
3 (~5 years from dx/time of enrollment)	*BV5*	$Rate_2$	$(BV2 – BV3)/ BV_2$

$$Mean\ Brain\ Atrophy\ (Rate_1 + Rate_2)/2$$

Cognitive Function

Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) while processing speed was evaluated using the Symbol Digit Modalities Test (SDMT) Written version.[56] MoCA assessed multiple cognitive domains, including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. The MoCA is sensitive detecting impairment in cognitive function among patients with BT.[57] Impaired cognitive function is defined as a MoCA score of less than 26, with severe impairment defined as a MoCA score of ≤10.[25,26] SDMT is predictive of employment status among patients with neurological disabilities.[58] Z-score greater than 0.6 is considered average, while less than -2.05 is considered to have an impairment in processing speed. The SDMT Written version has a test-retest reliability of .80 and has been used among patients with BT.

Functional Status and Symptoms

The function was measured using Karnofsky Performance Status (KPS) Scale Index and MD Anderson Symptom Inventory – Brain Tumor module (MDASI-BT). A KPS score of 100 indicates normal full functioning without evidence of disease, 90 indicates normal activity with minor signs and symptoms of disease, and so forth with declining function, increasing

assistance and effort with activities of daily living.[59] KPS has an interrater reliability of 0.89. KPS score was extracted from the EHR.

BT-related symptoms were measured using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT), a 22-item questionnaire measuring six underlying constructs: affective factor, cognitive factor, focal neurological deficits, treatment-related symptoms, generalized disease symptoms, and gastrointestinal factor.[12] MDASI-BT has a Cronbach's alpha of 0.67-0.90. Increasing mean scores indicate increasing symptom burden.

Statistical Analysis

The primary aim of this paper is to describe the health outcomes among glioma BT survivors treated with XRT and those who received PBRT. Categorical levels of EE (low, moderate, and high tertiles) were used as a predictor. The type of radiation (XRT or PBRT) was also used as another predictor. The interaction between the type of RT and level of EE was used to describe the health outcomes of those who received XRT and PBRT.

Statistical analyses were performed using IBM SPSS Statistics software Version 29.0 (Antioch, NY, USA). Means, standard deviations, and distributional properties describe the change in cortical volume loss, cognitive impairment, and functional limitation/disability and symptoms. Data were evaluated using complete-case analysis to determine the category of missingness. Clinical data imputation was performed. For example, if a score for MoCA and SDMT were missing because of severe cognitive impairment due to aphasia, a score of 0 was given. If KPS was missing due to an assessment not performed by during the study visit, prior clinical KPS from a visit 3-6 months ago was used. In regards to missing RT doses, the median dose in Gy for the entire sample was used.

Descriptive statistics were used to distinguish the clinical and demographic characteristics by levels of EE and type of RT. The response variables were treated as continuous variables. As per scoring guidance, we adjusted the MoCA score for education and the SDMT z-score (adjusted for age and education) was calculated.[56] Sensitivity analyses were

conducted excluding extreme values to determine if those data were influencing the magnitude and direction of the observed relationships. None of the analyses indicated that there was an impact from the suspected outliers, therefore the entire data set was used in the primary analysis. No adjustments were made for multiple analyses since the purpose was to look for clinically important patterns in the data that would inform future research. For all planned analyses, an alpha of <0.05 was considered statistically significant. The dose of RT, age, and sex were included in the statistical model as covariates.

Results

Demographics and Clinical Characteristics

From March 2022 to February 2023, participants were screened from the ABTC schedule for study eligibility. Forty-one individuals meeting eligibility criteria were approached and 39 participants consented and completed the study protocol. Eighteen individuals received XRT and 21 received PBRT. See Figure 1 for a summary of study recruitment and enrollment.

The median age of individuals who received XRT was 42, ranging from 26 to 78. Nine were diagnosed with astrocytoma, 7 had oligodendroglioma and 2 had brainstem glioma. The median RT dose was 54 Gray (Gy), ranging from 46 – 60 Gy. Six were female and 12 were male. Five individuals were categorized to Low EE, 10 to Moderate EE and three had High levels of EE.

PBRT had a median range age of 46 (range from 27 to 70). Nine individuals were diagnosed with astrocytoma and 12 were diagnosed with oligodendroglioma. The median RT dose was 54 Gy (54-60 Gy). Eleven were female and 10 were male. Eight individuals were categorized into Low EE, seven had Moderate EE and six had High EE. Please refer to Table 1 for a summary of descriptive characteristics between XRT and PBRT and Table 2 for a comparison between the type of RT and levels of EE.

Health Outcomes: Cognitive Function

After adjusting for education, sex, age, and dose of RT, the mean global cognitive function as measured by MoCA for XRT was 22.9 whereas PBRT mean score was 24.3. Please refer to Table 3 for a summary of results and Figure 3 for a graphical representation of descriptive statistics. Similarly, after adjusting for education, sex, age, and RT dose, the mean processing speed as measured by SDMT z-score for XRT was -0.9749 and -1.0584 for PBRT. Means and 95% CIs for the PBRT and XRT groups are depicted in Figure 3b.

Health Outcomes: Cortical Atrophy

One hundred seventeen images were processed. Approximately 87% of MRI images were obtained with 3.0T scanners. The mean GCAR for XRT was -0.075 and PBRT was -0.049. Similar to MoCA, the individuals in XRT and High EE group (n=3), had better outcomes with GCAR as depicted in Figure 3c.

Health Outcomes: Functional Status and Symptoms

The XRT mean scores for functional status (KPS score) for both Low EE (90.094, n = 5) and High EE (98.832, n = 3) were higher than the PBRT group. The mean number of symptoms in the High EE group were lower among individuals who received XRT (0.584, n =3) than individuals who received PBRT (2.196, n = 6). Refer to Figures 3d and 3e for means and 95% CIs levels of EE among individuals who received different types of RT.

Exploratory Post-Hoc Analyses

Given the composite score of EE was obtained from five measures (IPAQ, SNI, VIS, and 2 Socioeconomic questions), post-hoc analysis was performed using the same covariates in the primary analysis to explore the association of each of these components. Those BT survivors approximately 5 years from diagnosis who received PBRT who are most socially integrated (n = 5) and engaged in HEPA (n = 9), scored higher in MoCA and SDMT compared to individuals who received XRT. Individuals who received XRT and engage in HEPA (n = 8) have a lower mean GCAR (-.070) when compared to the PBRT group (n = 9). Linear regression was used to examine the relationship between socioeconomic factors and outcomes. We observed an

interaction between financial difficulties seeing a provider and the type of RT used with the KPS score ($p = 0.04$). Please refer to Table 4 for the post-hoc analysis.

Discussion

This study seeks to explore potential non-pharmacologic interventions such as EE that may be neuroprotective against the negative effects of XRT in brain tumor survivors. Identifying interventions is a critical health equity issue as XRT may be the only type of RT available and accessible to many individuals living in rural and medically underserved communities. PBRT remains inaccessible to many due to high cost, lack of coverage by insurance, and lack of access to a center providing PBRT.[60] Similar to prior studies,[60,61] we found that individuals who received PBRT had a higher mean score in cognitive functioning (MoCA) than those who received XRT, five years from the time of diagnosis.

The 39 individuals (XRT n = 18, PBRT n = 21) in the study presented varying levels of EE at the time of enrollment. Individuals who received XRT and were in the High EE Category (n =3) scored higher in MoCA and had lower GCAR and lower MDASI-BT scores than individuals who received PBRT in the same EE category. Though clinically promising, further research is necessary to examine and compare the relationship between EE and type of radiation. The type of tumor, size of resection cavity, and target volume of radiation as well as the type of brain tumor should also be considered as covariates in the future.

It is also critical to mention, that only 3 (17%) out of 18 individuals and 6 (28%) out of 21 individuals, a total of 9 (23%) out of 39 patients after brain tumor RT have high levels of EE (most socially integrated, engaged in HEPA, able to return to work and are financially stable) approximately 5 years after initial diagnosis. It is clear that comprehensive social and behavioral interventions are necessary to address issues that arise at the initial diagnosis of a brain tumor and during survivorship. Similar to Chapter 3, we observed an relationship between one of the socioeconomic questionnaires (cost of seeing a provider) with a health outcome (KPS). It is critical to examine and address how financial challenges play a role in a patient's decision in

choosing treatment and how these financial challenges perpetuate well into survivorship, significantly impacting health outcomes.[62]

Aside from the small sample size and heterogeneous characteristics of the participants, another limitation of the study was the cross-sectional evaluation of EE approximately five years after diagnosis, which may not reflect baseline or intervening levels of EE. Future studies should include an assessment of EE at the time of diagnosis and longitudinally follow this measure to determine both the change in EE over time to enable the assessment of the association between changes in EE and health outcomes. It is unclear which factor within EE generated better health outcomes (MoCA, GCAR, and MDASI-BT) among individuals who received XRT and have high levels of EE. These improved health outcomes (MoCA, GCAR, and MDASI-BT) were not consistently observed in the post-hoc analysis between XRT and PBRT. Or perhaps, as suggested by the findings in Chapter 3, it is rather the cumulative effects of physical activity, social network, community engagement, and financial activity that resulted in improved outcomes after RT.

Comprehensively understanding the relationship of environmental, behavioral, and social factors with health outcomes is necessary to advance the paucity of health promotion and restoration research among BT survivors. Providing an enriched environment may serve to reduce symptom burden, promote healthy brain aging, and improve cognitive and functional status for BT survivors following RT.

Figure 1. Flow Diagram of Study Recruitment.

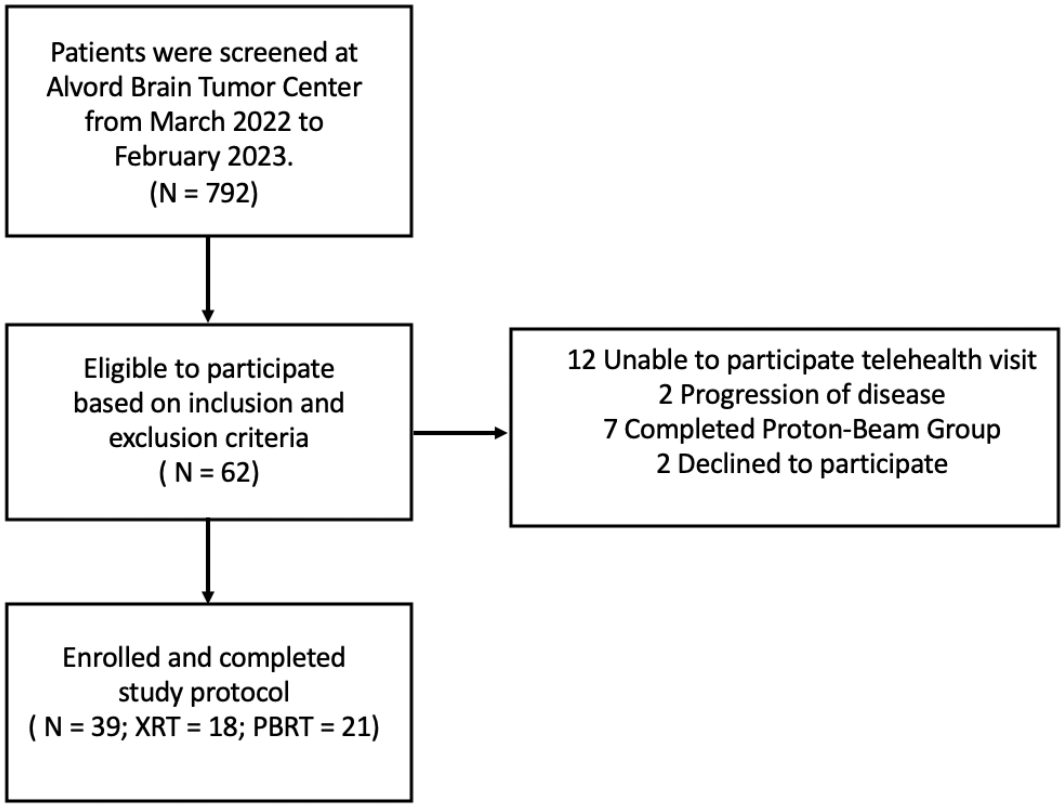

Table 1. Comparison of demographic and clinical characteristics of patients with glioma receiving XRT or PBRT.

Clinical Demographics	Photons (XRT)	Proton-Beam (PBRT)	P-Value
Age (median range)	40 (26 – 78)	44 (27 – 70)	.025**
Dose of Radiation, Gy, Median (range)	54 (46 – 60)	54 (54 – 60)	.008**
Sex			.243
Male	9	10	
Female	6	11	
WHO Grading			.428
2	9	8	
3	7	13	
Tumor Histology			.433
Oligodendroglioma	7	11	
Astrocytoma	9	10	
Hemisphere			.026**
Left	9	17	
Right	7	4	
Lesion Location			
Frontal	14	15	.661
Parietal	1	3	.384
Temporal	3	6	.392
Occipital	0	0	
Brainstem	2	0	.053
Chemotherapy			.018**
No Chemotherapy	3	0	
TMZ	14	11	
PCV	3	7	
TMZ + PCV	1	3	
Surgery			.812
No surgery	2	2	
Subtotal	4	7	
Near Total	4	4	
Gross total	8	8	
Concurrent Chemoradiation	12	9	.068
History of Seizure	12	17	.194

** Statistically significant at alpha level less than 0.05.

Table 2. Demographic and clinical characteristics of patients with glioma by tertile of Environmental Enrichment at 5-years post diagnosis.

	Low EE		Moderate EE		High EE	
	XRT, *n* = 5	PBRT, *n* = 8	XRT, *n* = 10	PBRT, *n* = 7	XRT, *n* =3	PBRT, *n* = 6
Age (median range)	44 (40 – 66)	46 (28 – 70)	33.5 (26 –78)	36 (27 – 53)	38 (31 – 62)	43(32 – 55)
Dose of Radiation, Gy, Median (range)	50.4 (46 – 54)	54 (54 – 60)	57.6 (46.80 –60.00)	54 (54 – 60)	56 (54 – 59.40)	54(54 – 60)
Sex			78			
Male	3	5	6	3	3	2
Female	2	3	4	4	0	4
WHO Grading						
2	4	3	4	2	1	3
3	0	5	5	5	2	3
Tumor Histology						
Oligodendroglioma	4	5	2	3	1	3
Astrocytoma	0	3	7	4	2	3
Hemisphere						
Left	2	8	6	4	1	5
Right	2	0	3	3	2	1
Lesion Location						
Frontal	4	5	7	5	3	5
Parietal	0		1	2	0	1
Temporal	0	2	0	3	0	1
Occipital	0	0	0	0	0	0
Brainstem	1	0	1	0	0	0
Chemotherapy						
No Chemotherapy	1	0	1	0	1	0
TMZ	4	5	8	4	1	3
PCV	0	2	0	2	1	2
TMZ + PCV	0	1	1	1	0	1
Surgery						
No surgery	1	1	0	0	1	1

Subtotal	0	2	3	3	1	2
Near-Total	1	4	3	0	0	0
Gross Total	3	1	3	4	2	3
Concurrent Chemoradiation	2	4	8	2	2	3

Table 3. The overall mean of health outcomes among participants with glioma receiving XRT and PBRT.

Health Outcomes	Type of Radiation	N	Mean	Std. Deviation	Min	Max
MoCA	Photons	18	22.9	8.8	1	30
	Proton-Beam	21	25	5.4	11	30
SDMT z-score	Photons	18	-0.98	1.7	- 4.0	1.46
	Proton-Beam	21	-1.06	1.65	-5.2	1.25
GCAR	Photons	18	-0.08	0.18	-.47	.264
	Proton-Beam	21	-0.05	0.21	- .48	.244
KPS	Photons	18	90	11.4	60	100
	Proton-Beam	21	85.7	12.5	60	100
Symptoms	Photons	18	1.99	1.93	.09	7.1
	Proton-Beam	21	1.9	1.39	.14	5.5

Figure 3. Health Outcomes Means and Confidence Intervals (CI)

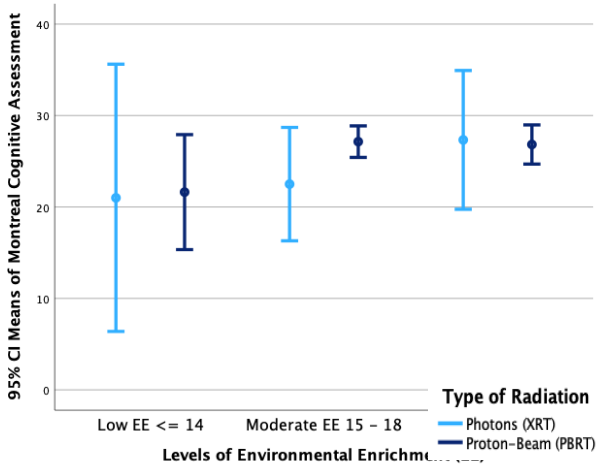

Figure 3a. Higher score in Montreal Cognitive Assessment (MoCA), indicates higher cognitive.

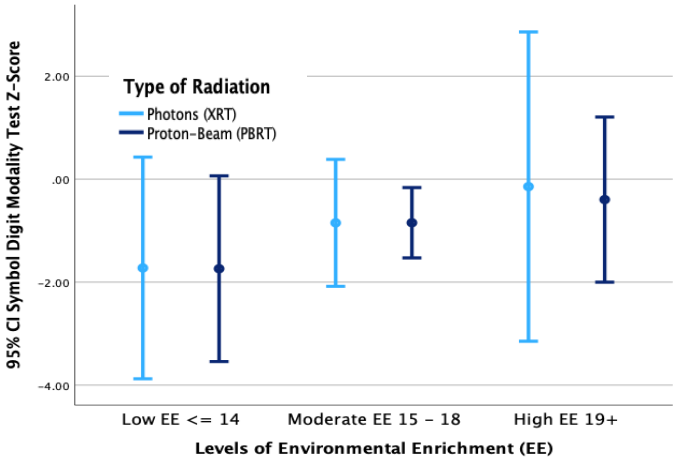

Figure 3b. Higher score in z-score Symbol Digit Modality Test indicates higher processing speed.

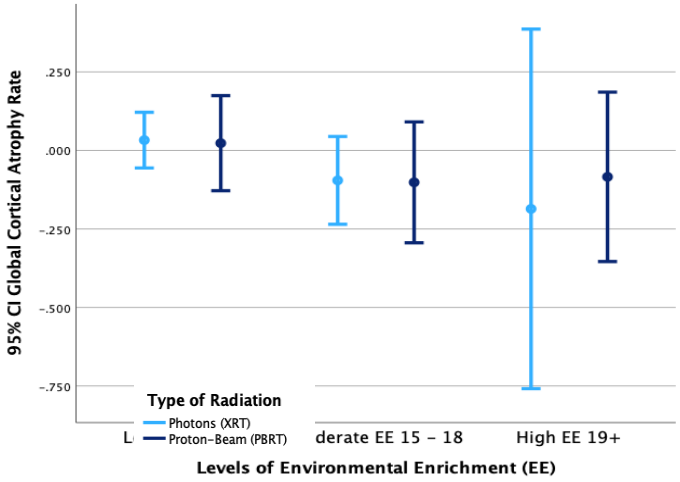

Figure 3c. Lower score in Global Cortical Atrophy Rate indicates lower cortical atrophy

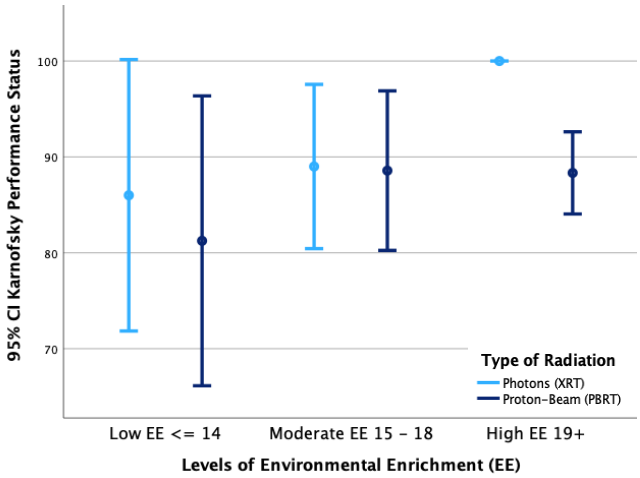

Figure 3d. Higher score in Karnofsky Performance Status (KPS) indicates higher

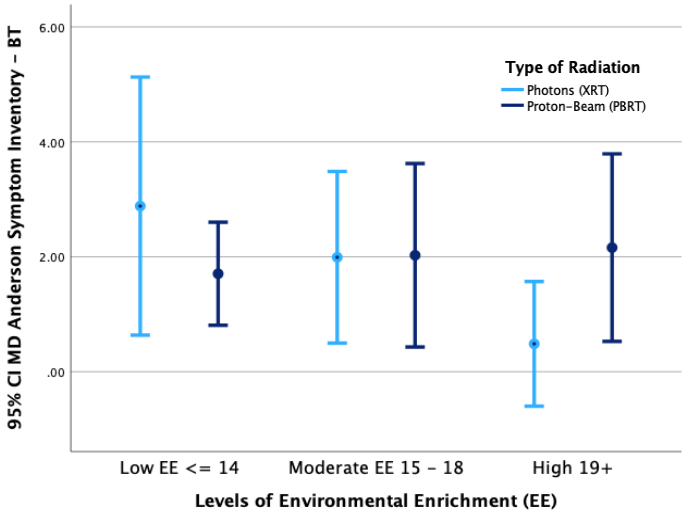

Figure 3e. Lower score in MDASI-BT indicates lower symptom burden

Table 4: Post-Hoc Analysis of with Components of EE interaction with RT adjusted for age, sex, and radiation dose.

Montreal Cognitive Assessment (MoCA)								
EE Component: SNI								
Most Socially Isolated	**N**	**Mean**	**Mean Difference**	**Std. Error**	**P-Value**	**Lower**	**Upper**	**Partial Eta Squared**
Photons	6	22.62	-1.84	4.06	0.65	-10.12	6.44	0.007
Proton-Beam	5	24.46						
Isolated/Integrated								
Photons	7	23.07	-0.91	3.42	0.79	-7.88	6.06	0.002
Proton-Beam	9	23.97						
Socially Integrated								
Photons	5	24.33	-1.26	4.06	0.76	-9.54	7.029	0.003
Proton-Beam	7	25.6						
EE Component: IPAQ								
Health-Enhancing Physical Activity [37]	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	8	24.14	-2.4	3.25	0.47	-9.03	4.24	0.018
Proton-Beam	9	26.54						
Minimally Active								
Photons	4	21.51	-3.5	4.56	0.44	-12.9	5.8	0.02
Proton-Beam	6	25.05						
Inactive								
Photons	6	22.76	1.5	3.95	0.72	-6.62	9.5	0.004
Proton-Beam	6	21.31						
EE Component: VIS								
Employed	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	11	25.17	-1.36	3.0	0.65	-7.5	4.8	0.007
Proton-Beam	8	26.54						
Part-time/Volunteer								

Photons	1	30.97	4.82	7.56	0.53	-10.63	20.27	0.013
Proton-Beam	4	26.15						
Unemployed								
Photons	6	18.44	-4.07	3.31	0.23	-10.83	2.7	0.05
Proton-Beam	9	22.5						
EE: Component Financial Stability: Socioeconomic Questionnaire: Seeing a provider								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	-2.18	0.38	-20.4	7.95	-0.16			
EE Component Financial Stability: Socioeconomic Questionnaire: Rent								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	0.72	0.29	-2.0	6.6	0.19			
Symbol Digit Modality Test								
EE Component: SNI								
Most Socially Isolated	**N**	**Mean**	**Mean Difference**	**Std. Error**	**P-Value**	**Lower**	**Upper**	**Partial Eta Squared**
Photons	6	-0.72	0.21	0.97	0.98	-1.96	2.003	0
Proton-Beam	5	-0.74						
Isolated/Integrated								
Photons	7	-1.27	0.58	0.82	0.48	-1.09	2.25	0.016
Proton-Beam	9	-1.85						
Socially Integrated								
Photons	5	-0.55	-0.06	0.97	0.95	-2.04	1.9	0
Proton-Beam	7	-0.49						
EE Component: IPAQ								
HEPA	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	8	-1.42	-1.13	0.57	0.15	-2.6	-0.26	0.07
Proton-Beam	9	-.29						
Minimally Active								
EE Component: VIS								

Employed	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	11	-.69	0.3	0.83	0.72	-1.382	1.99	0.004
Proton-Beam	8	-.99						
Part-time/Volunteer								
Photons	1	-.08	0.44	2.1	0.8	-3.8	4.7	0.002
Proton-Beam	4	-.52						
Unemployed								
Photons	6	-1.4	0.11	0.91	0.9	-1.75	1.97	0
Proton-Beam	9	-1.51						
EE: Component Financial Stability: Socioeconomic Questionnaire: Seeing a provider								
	Standardized coefficient	P-value	Lower	Upper	Partial Correlation			
Linear Regression	-2.0	0.5	-11.5	23.8	0.13			
EE: Component Financial Stability: Socioeconomic Questionnaire: Rent								
	Standardized coefficient	P-value	Lower	Upper	Partial Correlation			
Linear Regression	-0.72	0.33	-1.6	0.56	-0.17			
Global Cortical Atrophy Rate								
EE Component: SNI								
Most Socially Isolated	**N**	**Mean**	**Mean Difference**	**Std. Error**	**P-Value**	**Lower**	**Upper**	**Partial Eta Squared**
Photons	6	0.02	-0.08	0.12	0.5	-0.33	0.16	0.015
Proton-Beam	5	0.1						
Isolated/Integrated								
Photons	7	-0.16	-0.09	0.101	0.4	-0.29	0.12	0.024
Proton-Beam	9	-0.07						
Socially Integrated								
Photons	5	-0.05	0.08	0.12	0.53	-0.17	0.32	0.013
Proton-Beam	7	-0.13						

EE Component: IPAQ								
HEPA	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	8	-.07	-0.11	0.1	0.27	-0.31	0.09	0.04
Proton-Beam	9	.04						
Minimally Active								
Photons	4	-.03	0.188	0.14	0.18	-0.09	0.47	0.06
Proton-Beam	6	-.22						
Inactive								
Photons	6	-.05	-0.03	0.12	0.82	-0.27	0.22	0.002
Proton-Beam	6	-.02						
EE Component: VIS								
Employed	**N**	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	11	-.09	0.03	0.1	0.75	-0.18	0.24	0.003
Proton-Beam	8	-.12						
Part-time/Volunteer								
Photons	1	-.19	-0.19	0.26	0.47	-0.72	0.341	0.017
Proton-Beam	4	-.001						
Unemployed								
Photons	6	.012	0.03	0.11	0.78	-0.2	0.26	0.003
Proton-Beam	9	-.020						
EE: Component Financial Stability: Socioeconomic Questionnaire: Seeing a provider								
	Standardized coefficient	P-value	Lower	Upper	Partial Correlation			
Linear Regression	-0.93	0.75	-0.53	0.38	-0.06			
EE: Component Financial Stability: Socioeconomic Questionnaire: Rent								
	Standardized coefficient	P-value	Lower	Upper	Partial Correlation			

Linear Regression	0.39	0.63	-0.1	0.17	0.09			
Karnofsky Performance Status								
EE Component: SNI								
Most Socially Isolated	**N**	Mean	Mean Difference (Photons - Proton-Beam)	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	6	86.2	-0.29	6.9	0.97	-14.28	13.7	0
Proton-Beam	5	86.5						
Isolated/Integrated								
Photons	7	95.9	13.7	5.8	0.02	1.887	25.5	0.153
Proton-Beam	9	82.3						
Socially Integrated								
Photons	5	88.9	1.31	6.9	0.85	-12.684	15.3	0.001
Proton-Beam	7	87.6						
EE Component: IPAQ								
HEPA	N	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	8	93.187	-0.282	0.54	0.605	-1.384	0.82	0.009
Proton-Beam	9	90.367						
Minimally active								
Photons	4	87.089	-0.086	0.758	0.91	-1.635	1.462	0
Proton-Beam	6	86.226						
Inactive								
Photons	6	88.090	-1.196	0.656	0.078	-2.536	0.144	0.1
Proton-Beam	6	76.131						
EE Component: VIS								
Employed		Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	11	92.94	4.3	5.6	0.45	-7.15	15.7	0.019

Proton-Beam	8	88.67						
Part-time/Volunteer								
Photons	1	100.6	16.7	14.1	0.25	-12.1	45.4	0.044
Proton-Beam	4	83.9						
Unemployed								
Photons	6	84.22	1.4	6.2	0.8	-11.2	14.0	0.002
Proton-Beam	9	82.82						
EE: Component Financial Stability: Socioeconomic Questionnaire: Seeing a provider								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	-5.1	0.04**	-48.3	-0.65	-0.35			
EE: Component Financial Stability: Socioeconomic Questionnaire: Rent								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	0.6	0.4	-4.4	10.9	0.15			
MDASI-BT (symptoms)								
EE Component: SNI								
Most Socially Isolated	**N**	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	6	1.65	0.59	0.98	0.55	-1.41	2.58	0.011
Proton-Beam	5	1.06						
Isolated/Integrated								
Photons	7	2.67	0.1	0.82	0.9	-1.58	1.78	0
Proton-Beam	9	2.568						
Socially Integrated								
Photons	5	1.14	0.98	0.98	0.4	-2.84	1.15	0.02
Proton-Beam	7	1.98						
EE Component: IPAQ								
HEPA		Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared

Photons	8	2.19	0.48	0.84	0.58	-1.25	2.2	0.01
Proton-Beam	9	1.71						
Minimally Active								
Photons	4	1.37	-0.69	1.18	0.56	-3.11	1.73	0.011
Proton-Beam	6	2.06						
Inactive								
Photons	6	2.19	-0.19	1.03	0.85	-2.28	1.9	0.001
Proton-Beam	6	2.38						
EE Component: VIS								
Employed	**N**	Mean	Mean Difference	Std. Error	P-Value	Lower	Upper	Partial Eta Squared
Photons	11	2.58	0.61	0.78	0.44	-0.96	2.17	0.02
Proton-Beam	8	1.98						
Part-time/Volunteer								
Photons	1	-.6	-3.94	1.93	0.05**	-7.9	0.004	0.12
Proton-Beam	4	3.34						
Unemployed								
Photons	6	1.38	-0.12	0.85	0.89	-1.85	1.61	0.001
Proton-Beam	9	1.5						
EE: Component Financial Stability: Socioeconomic Questionnaire: Seeing a provider								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	1.12	0.66	-0.94	1.48	0.08			
EE: Component Financial Stability: Socioeconomic Questionnaire: Rent								
	Standardized coefficient	**P-value**	**Lower**	**Upper**	**Partial Correlation**			
Linear Regression	0.8	0.24	-0.15	0.58	0.21			

** Statistically significant at alpha level less than 0.05.

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Chapter 5: Conclusion

Though rare compared to other types of cancer, brain tumors can leave an individual with devastating neurological disabilities that impact cognition, function, independence, and overall quality of life. As such, brain tumor (BT) survivors experience high unemployment rates,[1-3] reduction in income, and loss of social relationships.[4] Understanding environmental, behavioral, and social factors that can mitigate cognitive symptoms and functional limitations is necessary to advance neuro-oncology survivorship care. The present study aimed to examine the role of social connectedness, physical activity, community engagement, and financial stability or collectively known as Environmental Enrichment (EE), on symptoms, cognition, and function among BT survivors treated with radiation. We incorporated patient-reported outcomes via questionnaires and volumetric analysis of previously obtained MRI images of the brain to address the specific aims of the dissertation.

Using the Institute of Medicine enabling and disabling process framework, we hypothesized that EE can either promote or protect an individual from progressive, worsening neurological impairment after brain irradiation. We included participants with severe cognitive impairment to have broader implications of this research for persons with BT. Therefore, we included persons whose impairment required consent from their legally authorized representative (LAR). Chapter 2 described the use of neuroimaging measures as an indirect assessment of brain tumor survivors' cognitive health and function. Chapter 2 was written to introduce neuroimaging measures to other nurse scientists to support healthy aging research and to advance social and biobehavioral research for individuals with neurological conditions without a cure.

Chapter 3 aimed to comprehensively operationalize EE in neuro-oncology research and examine its association with health outcomes (cognitive function, cortical changes, functional status, and symptoms) after radiation (RT). A higher likelihood of improved outcomes was

observed with increasing levels of EE in global cognition (MoCA), processing speed (SDMT), and function (KPS). While not statistically significant, the pattern that emerged is clinically promising.

Lastly, Chapter 4 sought to describe the health outcomes of individuals who received conventional photon radiation (XRT) in relation to levels of EE. This is a critical issue as XRT may be the only type of RT a person who lives in rural or underserved communities may have access to. Persons living in rural or underserved communities experience a higher symptom burden, poorer health status, greater psychological distress, higher reported non-cancer comorbidities, and higher unemployment rates when compared to their urban counterparts.[5,6] It is noteworthy that some eligible participants were not approached due to the telehealth nature of their clinic visits. These individuals live approximately 2-4 hours from the ABTC or reside in another state within the clinic service region. In Chapter 4, it is clinically promising that those who received XRT and high levels of EE at five years following diagnosis scored higher in MoCA score, had reduced global cortical atrophy rate (GCAR), and had lower symptom burden (MD Anderson Symptom Inventory-BT module).

The results of our research are scientifically and clinically motivating. Unanswered questions include: What was the survivor's baseline EE, how did this change over time, and how does this influence cognitive and functional outcomes? How is it that only 23% of individuals (only 3/18 who received XRT and 6/21 who received PBRT) achieved high levels of EE five years post-diagnosis? What are the factors that promote EE and barriers to achieving high levels of EE? And as a healthcare system, what are we doing the support BT survivors after their cancer treatment?

Nurse scientists can develop the necessary interventions for comprehensive neuro-oncology survivorship programs. Integrating environmental, biobehavioral, and social interventions may reduce symptom burden, promote neuroplasticity, and improve cognitive and

functional status after brain radiation. Nurse scientists can lead the future research necessary to advance comprehensive neuro-oncology survivorship programs in four ways:

First, future studies need to include individuals living in rural and underserved communities at higher risk of developing progressive neurological impairment and symptom burden. This will allow broader implications of research findings for developing interventions, especially among those who may benefit the most from such interventions. This critical inclusion will provide the foundational work to bridge rural-urban health outcome disparities.

Second, diet and nutrition should be added to the measurement of EE. A pattern of healthy dietary intake (i.e., increased intake of lean meat, grains, and fish) is associated with favorable health outcomes such as decreased incidences of depressive symptoms[7] and cognitive decline in older adults.[8-10]

Third, there is a need to examine the self-efficacy (the belief in one's capacity to execute behaviors to produce specific performance attainments) and psychological flexibilities of the individual, as these skills may facilitate and promote active participation in achieving high levels of EE post-treatment. Activities such as mindfulness practices and cognitive-behavioral therapy promote neuroplasticity[11-13] and self-efficacy.[14,15]

Fourth, and by far most critically, is to concurrently address the antecedents of EE, which include social determinants of health, such as the accessibility of health care, especially among individuals from underserved communities. By providing access to research opportunities among cancer survivors residing in underserved communities such as rural areas, we can best design comprehensive survivorship care programs in the future. Comprehensive neuro-oncology survivorship programs and closed-loop communication and collaboration across the hospital and community settings can facilitate the transition of patients with BT after treatment. Such communication and collaboration could promote restoration and maintenance of health, improve neuroplasticity, and reduce radiation-associated brain aging in BT survivors.

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