UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Health-Related Quality of Life and Executive Functioning among Primary Brain Tumor Patients: Associations and Causal Pathways

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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2019

The Dissertation of Tonya Marie Pan-Weisz is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2019

DEDICATION

This dissertation is dedicated to the people who have loved and supported me the most, my family. Diane Pan, Sandra Milburn, Bradley Pan-Weisz, Tom Pan, and Jian Pan, my gratitude for your ceaseless love and support is immeasurable. Indeed, without your encouragement and love I would have been incapable of completing this dissertation. Bear, I truly can't thank you enough for all of the ways in which you have supported me through completing this project.

EPIGRAPH

"There is no profit in curing the body if, in the process, we destroy the soul." – Samuel H. Golter

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ACKNOWLEDGEMENTS

In addition to the important people recognized in this dissertation's dedication, I would like to acknowledge several people who influenced this capstone project, either directly or indirectly. First, my advisor and dissertation Chair, Vanessa L. Malcarne, Ph.D. Her impact on my life, both personally and professionally, is unquantifiable. Additionally, I, undoubtedly, would not be here today without the early guidance and support of my mentor, Georgia Robins Sadler, B.S.N., M.B.A., Ph.D.

I would also like to acknowledge the other members of my committee Carrie R. McDonald, Ph.D., ABPP, Jona Hattangadi-Gluth, M.D., Scott C. Roesch, Ph.D., and Kristen Wells, Ph.D., M.P.H. I feel fortunate to have had the opportunity to learn from such a truly interdisciplinary and brilliant team. I would like to specifically thank Carrie R. McDonald, Ph.D., ABPP and Jona Hattangadi-Gluth, M.D. for their dedication to improving the lives of patients with brain tumors and for allowing me to be a part of this study. This project would not have occurred without the support obtained by Jona Hattangadi-Gluth, M.D. and Carrie R. McDonald, Ph.D., ABPP from National Institutes of Health CTRI Grant TL1TR001443l (JHG), NIH CTRI Grant KL2TR00099 (JHG), CTRI Pilot Award (JHG, CM), and American Cancer Society Pilot Award (JHG); the content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or ACS. I would also like to thank the many trainees who contributed to this project over the years, with special thanks to Michelle "Shelley" Tibbs, who was critically helpful.

I would like to acknowledge the JDP faculty and students. It has been a privilege to learn from and work alongside such remarkable people. Brian Buzzella, Ph.D., Veronica Cardenas, Ph.D., Sarah Mills, Ph.D., M.P.H., Rina Fox, Ph.D., M.P.H., Sharon Baik, Ph.D., Sandy Bohan,

M.P.H., Kate Conover, M.S., and Amy Ustjanauskas, M.S. deserve special recognition for their mentorship, support, encouragement, and friendship.

I would also like to thank Heather Royer, Ph.D. of University of California, Santa Barbara, who shared her early failures with me and told me to always remember, "perseverance is key." To my parents-in-law, Mike Weisz, Kelli Chandler, and Barbara Sheldon, my brother- and sister-in law, Brian Weisz and Kristin Hodis, and grandmothers-in-law Patricia Weisz and Hope Priest, thank you for welcoming me into your family with open arms. My gratitude is also extended to my oncologists, Janet Franklin, M.D. and David Tishler, M.D., and the many incredible staff members at Children's Hospital Los Angeles who saved my life many years ago.

Finally, I would like to acknowledge the people who took part in this study as research participants. Future people's lives will be improved because of their willingness to contribute to research. Thank you.

Chapters 1 through 5 of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Carrie McDonald, Ph.D., Jona Hattangadi-Gluth,M.D., and Vanessa L. Malcarne, Ph.D. The dissertation author was the primary investigator and author of this material.

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ABSTRACT OF THE DISSERTATION

Health-Related Quality of Life and Executive Functioning among Primary Brain Tumor Patients: Associations and Causal Pathways

by

Tonya Marie Pan-Weisz

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2019
San Diego State University, 2019

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ABSTRACT

Rationale. Patient, brain-tumor, and brain-tumor-treatment factors may negatively impact brain tumor patients' health-related quality of life (HRQOL) and executive functioning (EF). Yet, in order to inform clinical decisions, more information is needed about what factors

influence HRQOL and EF, the trajectories of HRQOL and EF overtime, and potential causal relationships between HRQOL and EF.

Methods. Adults with primary brain tumors (N = 53) were enrolled in a prospective, longitudinal study evaluating the effects of radiation therapy (RT) over the first year following RT. All patients completed a self-report measure of HRQOL and objective EF assessments at baseline (pre-RT), and three months, six months, and 12 months following RT. Descriptive statistics and general linear model regression with contrast coding were used to characterize HRQOL and EF at baseline based on patient factors, tumor factors, and treatment factors. Linear mixed effects models were used to examine the trajectories of HRQOL and EF over time, controlling for significant characteristics previously identified. Cross-lagged panel model path analysis was used to examine the interrelationships between HRQOL and EF over time.

Results. Patients in this study were primarily middle-aged, married, well-educated White men and women. Seizures, steroid use, and future RT type were related to HRQOL at baseline. Marital status, seizures, tumor laterality, steroid use, antiepileptic drug use, and future chemotherapy use were related to EF at baseline. HRQOL did not exhibit a trend over time. EF exhibited a cubic trend over time. There was one statistically causal pathway between HRQOL and EF; EF performance at six-month follow-up was predictive of HRQOL at 12-month follow-up.

Conclusions. Findings suggest that patients who receive steroids and experience seizures prior to RT and who have left-sided tumors may benefit from HRQOL and EF monitoring and possibly intervention. Additionally, there was complex pattern of change in EF over time, with early deleterious effects being followed by improvement. Patients' EF six months after RT may impact their HRQOL one-year post-RT completion. Although the mechanisms underlying this

relationship remain unclear, it is possible that interventions to improve or preserve EF prior to six-months post RT may facilitate later improvements in HRQOL.

CHAPTER 1: INTRODUCTION

The goals of this study were to better understand the relationships among health-related quality of life and executive functioning (EF) among adults with primary brain tumors; how health-related quality of life and EF differ based on patient, tumor, and treatment factors prior to radiation therapy (RT); how health-related quality of life and EF change over time (i.e., from prior to the start of RT to three-months, six-months, and 12-months following the completion of RT); and, finally, if there are any statistically causal pathways between health-related quality of life and EF over time. The data for this study were collected as part of a larger, ongoing study considering the effects of RT on patients with primary brain tumors over time.

Patients in this study were 53 adults with primary brain tumors. This study used a variety of statistical techniques, including general linear modeling (GLM), linear mixed-effects (LME) modeling, and cross-lagged panel model path analysis. Results provide useful information about the trajectories of and relationships between health-related quality of life and EF among patients with brain tumors that could inform the design of well-timed interventions and influence treatment decisions.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Carrie McDonald, Jona Hattangadi-Gluth, and Vanessa L. Malcarne. The dissertation author was the primary investigator and author of this material.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

2.1 Brain Tumors

A primary brain tumor is a mass of atypical cells that originates in the central nervous system (American Cancer Society, 2013). Brain tumors are classified based on cell origin and how the cells behave, ranging from least aggressive to most aggressive (National Cancer Institute, 2017a). Although brain tumors can spread to other brain tissue, they rarely spread to other parts of the body (i.e., brain tropism; American Cancer Society, 2013). Brain tumors cause significant morbidity and mortality (American Cancer Society, 2013). Treatments are avaiable that can prolong the lives of patients with brain tumors; however, these treatments can also have adverse effects (Bartolo, 2019).

The Epidemiology of Brain Tumors in the United States. Brain tumors can be either benign or malignant, with significant variability in length of survival. Nonetheless, any brain tumor can be devastating by causing significant deleterious neurological and psychological changes. The American Brain Tumor Association (ABTA) and the Central Brain Tumor Registry of the United States (CBTRUS) estimate that 80,000 Americans will be diagnosed with a brain tumor during 2017 (American Brain Tumor Association, 2017). Brain tumors are more likely to occur in men versus women (American Cancer Society, 2019) and in white people versus African American people (National Cancer Institute, 2017). Approximately 17,000 Americans will die of a malignant brain tumor during 2017 (American Brain Tumor Association, 2017; Ostrom et al., 2015). There are nearly 700,000 people in the United States (U.S.) living with a brain tumor (American Brain Tumor Association, 2017; Ostrom et al., 2015). The five-year relative survival rate for brain tumors (i.e., the measure of the survival of brain tumor patients in comparison to the general population in order to estimate the effect of brain tumors) from 1995 -

2012 was 34.4% (Ostrom et al., 2015). The five-year survival rate, however, varies widely depending on age at diagnosis and tumor location and histology (Day et al., 2016; National Cancer Institute, 2017a). Fortunately, brain tumors are rare, and malignant brain tumors are especially rare. As of 2010, the most prevalent cancer in American adults was breast cancer (1949/100,000); the most prevalent malignant brain tumor in adults was glioblastoma (12.76/100,000; Zhang et al., 2017). In other words, there will be an estimated 252,710 new cases of breast cancer in the U.S. in 2017, compared to only 23,800 new cases of malignant brain tumors (National Cancer Institute, 2017b).

Select Types of Brain Tumors. There are over 100 different (i.e., histologically distinct) types of brain tumors (Ostrom et al., 2015). Brain tumors, unlike other cancerous tumors, are not staged. Instead, brain tumors are classified by grades I through IV according to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (Ostrom et al., 2015). Grade I tumors are the least aggressive, are usually associated with long-term survival, and are considered benign; grades II and III tumors can invade adjacent normal tissue and can recur as higher-grade tumors; grade IV tumors are the most aggressive, form new blood vessels to maintain rapid growth, and have areas of dead cells (i.e., necrosis) in the center of the tumor (American Brain Tumor Association, 2015). Grades II – IV tumors are considered malignant or cancerous tumors. The WHO Classification of Tumors of the Central Nervous System changed in 2016 in order to include molecular parameters, the first major change since 2007 (Louis et al., 2016). Surveillance has yet to fully reflect the updated WHO Classification System. Thus, the statistics and information reported in this document are based on earlier versions of the WHO Classification System.

Meningiomas. Meningiomas are the most common primary brain tumor making up

approximately 32 to 37% of all brain tumors (American Brain Tumor Association, 2017; Merrell, 2012). Meningiomas are graded WHO I – III, with 90% being classified as grade I; grade III (anaplastic) are the most aggressive and are likely to recur (Merrell, 2012).

Gliomas. Gliomas consist of astrocytomas, oligodendrogliomas, and ependymomas in decreasing order of prevalence. Gliomas are the most common primary intracranial tumor, representing 81% of malignant brain tumors (Ostrom et al., 2014). Glioblastoma, a type of astrocytoma, is the most common malignant glioma and makes up 45 to 50% of all gliomas (American Brain Tumor Association, 2017; Merrell, 2012; Ostrom et al., 2014). Gliomas are classified according to the WHO classification system by the glial cells from which they originate and their histologic features. Grade III and IV tumors are high-grade gliomas, whereas grade II tumors are low-grade gliomas. Grade I glioma is rarely seen in adults (Merrell, 2012).

High-grade gliomas. High-grade gliomas are made up predominantly of glioblastoma and anaplastic astrocytoma (WHO grade III). Anaplastic oligodendroglioma and anaplastic ependymoma are less common types of high-grade gliomas. High-grade gliomas are aggressive, incurable tumors. The median survival for glioblastoma is 14 to 18 months and for anaplastic astrocytoma is 24 to 30 months (Merrell, 2012).

Low-grade gliomas. Despite being lower-grade tumors, low-grade gliomas are not benign. Most commonly, low-grade gliomas ultimately progress to high-grade gliomas. Low-grade gliomas make up about 15% of all primary brain tumors. Low-grade gliomas are more likely to present with seizures than high-grade gliomas. Prognosis varies considerably by tumor histology; patients with astrocytoma typically live 5 to 10 years after diagnosis, whereas patients with oligodendroglioma typically live 10 to 15 years after diagnosis (Merrell, 2012).

Pituitary tumors. Pituitary tumors account for approximately 12 to 19% of all primary

brain tumors and are classified as adenomas or carcinomas, with adenomas being more prevalent (American Brain Tumor Association, 2017). Pituitary tumors are typically benign and are classified based on the hormone they produce (Osamura, 2017).

Treatment. Brain tumors are especially difficult to treat because the brain is a complex, essential, and heterogeneous organ. The brain is compartmentalized with many regions of eloquent cortex that subserve specific sensory, motor, and cognitive functions; thus, it is rare for healthy parts of the brain to be able to quickly assume functions for damaged parts of the brain. The complexity and structural and functional organization of the brain make brain tumors very dangerous and difficult to treat. Indeed, there is often a difficult tradeoff between quantity and quality of life when treating patients with brain tumors (Dirven, Reijneveld, & Taphoorn, 2014b). Many of the treatments, outlined below, while potentially mitigating the tumor, often cause deleterious side effects.

Surgery. Surgery is often the first step toward treating a brain tumor, unless the tumor is inoperable due to the location of the tumor or the health status of the patient. The goal of surgery is to remove as much of the tumor as is safe without severely disrupting normal brain functioning (Bello, Fava, Carrabba, Papagno, & Gaini, 2010). For meningiomas, complete resection is curative in most cases, but some meningiomas can recur (Merrell, 2012). For all grade gliomas, a maximal surgical resection that leaves the patient with minimal neurologic deficits is the preferred initial treatment (Merrell, 2012). Adjuvant therapy, such as radiation or chemotherapy, however, is often still necessary to attempt to fully remove the tumor and reduce recurrence.

Radiation therapy. RT can be used as the main treatment or after surgery to try to remove any remaining tumor cells. Many different forms of RT exist. A typical schedule for radiation therapy consists of one treatment per day, five days a week, for two to seven weeks

(American Brain Tumor Association, 2014). Certain RTs are more effective for certain tumor types. Two common types of RT are Intensity modulated RT (IMRT) and proton beam RT. IMRT is typically used for patients with large malignant tumors or multiple tumors, whereas proton beam RT is typically used for patients with small, deep-seated tumors (American Brain Tumor Association, 2014). The potential impact of RT on health-related quality of life and EF are discussed below.

Chemotherapy. Chemotherapy is often used as a concomitant and adjuvant treatment to RT. Many chemotherapeutic agents administered intravenously or orally may not be able to reach the tumor due to the protection provided by the blood brain barrier (American Brain Tumor Association, 2014), and the blood brain barrier continues to be a challenge when attempting to develop chemotherapeutic agents that could be administered intravenously or orally to treat brain tumors (American Brain Tumor Association, 2014). However, researchers have discovered that some brain tumors themselves disrupt the blood brain barrier (Vick, Khandekar, & Binger, 1977), that the blood brain barrier can be disrupted using certain drugs, such as mannitol (Neuwelt & Rapoport, 1984), or focused ultrasound (Liu et al., 2010), and that some chemotherapeutic agents can cross the blood brain barrier (American Brain Tumor Association, 2014). Furthermore, chemotherapy can also be delivered directly to the brain tumor during surgery (e.g., Gliadel [BCNU] wafers; McGirt et al., 2009). Chemotherapy in addition to or after RT (i.e., concomitant or adjuvant) is now the standard of care for many brain tumors (Dirven et al., 2014c). For example, Temozolomide (TMZ; a DNA methylating agent that triggers tumor death) is included in the standard of care of glioblastoma patients, and the combination of procarbazine, lomustine, and vincristine (PVC) is recommended for patients with anaplastic oligodendrogliomas and oligoastrocytomas (Dirven et al., 2014c).

Tumor and treatment sequelae. During the time of diagnosis, patients often present with cognitive complaints and may have already experienced a seizure (American Brain Tumor Association, 2015). Indeed, the risk of seizure for patients with low-grade gliomas is 60 – 100% and 40 – 60% for patients with high-grade gliomas (Vecht, Kerkhof, & Duran-Pena, 2014). Seizures followed by cognitive deficits are the two most prevalent symptoms in patients with gliomas throughout the total disease trajectory (IJzerman-Korevaar, Snijders, de Graeff, Teunissen, & de Vos, 2018). However, some brain tumors are asymptomatic and might be discovered during an imaging scan for some other purpose (American Brain Tumor Association, 2015). Surgery will often help to alleviate some of the symptoms that were being caused by the brain tumor. However, surgery and perioperative injuries can also cause an increase in cognitive difficulties and edema in healthy tissue (Taphoorn & Klein, 2004). Additionally, patients are often quickly prescribed anti-epileptic drugs (AED) to reduce or prevent seizures. AED can produce challenging side effects. Side effects of AED include weight gain or loss, ataxia, dizziness, drug rash, Stevens-Johnson syndrome, agitation, aggression, psychosis, sedation, cognitive impairment, tremor, hair loss, pancreatitis, and Parkinsonism (Schiff et al., 2014). Furthermore, brain tumor patients also often receive corticosteroids (hereto forth, "steroids") to help reduce inflammation and swelling around the tumor (i.e., edema). Complications from steroid use can include weakness in the legs, Cushing's syndrome, hyperglycemia, anxiety, insomnia, euphoria, irritability, emotional lability, psychosis, delirium, memory loss, and osteoporosis, leading to hip and spine fractures (Schiff et al., 2014).

Patients with brain tumors may then begin RT alone or RT with chemotherapy. Fatigue, headache, nausea, vomiting, alopecia, sexual dysfunction, pain, sleep disturbance/insomnia, and skin changes are common side effects of chemotherapy and RT among cancer patients. In

addition to these side effects, patients with brain tumors face additional challenges specific to brain tumors (Goffaux, Daigle, & Fortin, 2012). Specifically, brain tumor patients often experience unique physical symptoms such as blood clots (venous thromboembolism), motor impairment (Taphoorn & Klein, 2004), hemiplegia, and dysphasia (Baker, Bambrough, Fox, & Kyle, 2015).

Furthermore, brain tumor patients may also experience subjective cognitive dysfunction and objective cognitive impairment, changes in personality, and difficulty regulating affect and behavior (Baker et al., 2015). Indeed, brain tumor patients often experience their disease as a threat to the "self" (Ownsworth, 2016). Additionally, brain tumor patients may suffer from psychological distress, which may be due to the direct effect of the tumor in the patient's brain, side effects of treatment, and/or the very experience of having a brain tumor (Baker et al., 2015). Approximately 30 to 70% of brain tumor patients experience psychological distress, including symptoms of anxiety and depression, and approximately 33% of patients experience clinically significant levels of depression and anxiety (Baker et al., 2015). Thus, there are a constellation of tumor and treatment sequelae that can negatively impact patients' health-related quality of life.

2.2 Health-Related Quality of Life

Quality of life is a subjective, multidimensional evaluation of one's current life circumstances based on one's values (Haas, 1999). Quality of life in the health context is known as health-related quality of life (Ferrans, Zerwic, Wilbur, & Larson, 2005). Health-related quality of life, however, has not been well defined (Haas, 1999; Karimi & Brazier, 2016), and is often used interchangeably with quality of life, health, and subjective health status (Karimi & Brazier, 2016). The Centers for Disease Control and Prevention (CDC) define health-related quality of life as an "individual's or a group's perceived physical and mental health over time" (CDC,

2016), and have noted that, "On the individual level, health-related quality of life includes physical and mental health perceptions (e.g., energy level, mood) and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status" (CDC, 2016). The U.S. Department of Health and Human Services and the Office of Disease Prevention and Health Promotion define health-related quality of life as "a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning" (healthypeople.gov). The 2016 National Comprehensive Cancer Network (NCCN) guidelines for central nervous system cancers state, "As the patient's treatment unfolds, their quality of life is the highest priority and should guide clinical decisions" (p. 57; National Comprehensive Cancer Network, 2016). This raises the question: What information is available about health-related quality of life during brain tumor treatment to help guide patients' and clinicians' clinical decisions?

Assessing health-related quality of life among patients with brain tumors. Health-related quality of life has been assessed in patients with brain tumors in a wide variety of ways, including physician-assigned performance scores and the patient-reported outcome approach (Deshpande, Rajan, Sudeepthi, & Abdul Nazir, 2011). The patient-reported outcome approach (compared with physician-assigned performance scores) has been noted as the most appropriate assessment of health-related quality of life because it is a self-reported assessment, and health-related quality of life is inherently subjective (Taphoorn, Sizoo, & Bottomley, 2010). Several patient-reported outcome measures of health-related quality of life exist. The two most popular patient-reported outcome measures for evaluating health-related quality of life among brain tumor patients are the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire with brain tumor-specific module (QLQ-C30/BN20; Aaronson et al.,

1993; Taphoorn et al., 2010) and the Functional Assessment of Cancer Therapy-Brain (FACT-Br; Cella et al., 1993; Weitzner et al., 1995). Both of which have been shown to be equally valid and reliable tools for measuring health-related quality of life among patients with brain tumors (Chow et al., 2014). Yet, health-related quality of life patient-reported outcome measures vary greatly in their construct emphasis, with some focusing more on the psychosocial aspects of health-related quality of life (e.g., FACT-Br) and others giving more attention to physical symptoms (e.g., EORTC QLQ-C30/BN-20; Mauer, Bottomley, & Taphoorn, 2008).

The EORTC QLQ-30 is comprised of 15 subscales: global QoL, five subscales measuring functioning (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), and six single-item scales (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties). The BN20 includes 11 subscales: future uncertainty, visual disorder, motor dysfunction, communication deficit, headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs, and bladder control. Both the QLQ-30/BN20 have a scoring manual developed by EORTC, including suggestions for administration and how to handle missing data. The items on each measure are scaled, scored, and transformed to a linear scale (0 to 100). Differences from one time point to another greater than or equal to 10 points on any given subscale are classified as clinically meaningful changes (Maringwa et al., 2011). Of note, the EORTC QLQ-C30/BN-20 includes a subscale called "global QoL." This subscale is comprised two of the questions on the QLQ-C30: "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" Studies in which health-related quality of life is a secondary outcome often only report the findings from this "global QoL" subscale (e.g., Brada et al., 2010). It is unlikely that the complexity of health-related quality of life is being captured by this subscale, despite what its

name (i.e., “global QoL”) implies.

The current study used the FACT-Br. The FACT-Br is a 50-item self-report/patient reported outcome measure of cancer and brain-tumor-specific health-related quality of life. The FACT-Br is a combination of the 27-item FACT-General scale plus 23 additional-concern items specific to brain tumor patients. The FACT-Br consists of five subscale scores: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and additional brain tumor-specific concern items (Brain Cancer Subscale; BrCS). All five subscales can be summed to yield a FACT-Br total score, or the first four subscales can be summed to yield a FACT-General total score. This study will use the FACT-Br total score and all five individual subscale scores. Higher FACT-Br scores indicate better health-related quality of life. Sample items include, for PWB: “I have lack of energy,” SWB: “I feel close to my friends,” EWB: “I am losing hope in the fight against my illness,” FWB: “I am sleeping well,” and BrCS: “I am bothered by the change in my personality.” Some of the items on the BrCS subscale capture subjective cognitive functioning (e.g., “I have difficulty expressing my thoughts,” “I am able to concentrate,” “I am able to put my thoughts into action”), which is different from objective EF. The instructions ask participants to indicate how true each statement has been for them during the past seven days on a scale ranging from 0 (*Not at all)* to 4 (*Very much*).

The FACT-General scale was developed first using data from a heterogeneous sample of cancer patients (Cella et al., 1993). Additional concerns specific to brain tumor patients were identified; the brain tumor subscale was developed and added to the FACT-General to create the FACT-Br (Weitzner et al., 1995). In the development study of the brain tumor subscale and validation of the FACT-General among brain tumor patients (Weitzner et al., 1995), Cronbach’s

alpha for all of the subscales except SWB ranged from 0.75 to 0.84, with values all in the acceptable range. The SWB subscale had a weaker internal consistency than the other subscales with a Cronbach's alpha of 0.69. During the development study, the FACT-Br was administered at two time points seven days apart in order to assess test-retest reliability, which was good (r = 0.78, $p < 0.001$). Convergent validity was examined by considering the associations between the FACT-Br total score and subscale scores, and the Beck Depression Inventory, State-Trait Anxiety Inventory, and Ferrans and Powers Quality of Life Index (PF-QLI), and all correlations were in the expected directions and expected magnitude, except for the PF-QLI, which was only minimally to moderately positively correlated (high correlations were expected). Similarly, divergent validity was examined by considering associations between the FACT-Br total score and subscale scores, and a measure of social desirability; the correlations were small (r = .11 to .29), as expected, although the correlations between the social desirability measure and the FACT-Br total, FACT-General total, EWB subscale, and PWB subscale were technically statistically significant ($p < .05$). Concurrent discriminative criterion validity was demonstrated by the measure's ability to distinguish among groups with varying levels of disease severity and other known differences; for example, patients who were still working reported having better health-related quality of life than those who were not working because of their illness. Interestingly, in the development study, patients with brain tumors reported better health-related quality of life (as measured by the FACT-G) than patients with other types of cancers and sample of general U.S. adults; the authors hypothesized that this may have been because the sample of patients with brain tumors were potentially higher functioning, with Karnofsky Performance Status (KPS) scores ranging from 60 to 100 (M = 90.3), than the samples of patients with other types of cancers and of general U.S. adults (Weitzner et al., 1995). Two psychometric studies

have been completed with patients with brain metastases (Chen et al., 2014; Thavarajah et al., 2013). However, no additional psychometric studies following the development study have been conducted with patients with primary brain tumors (Chow et al., 2014).

Chen et al. (2014) completed cognitive interviews with patients with brain metastases and health care professionals (HCPs) individually. When patients completed the FACT-Br, they were interviewed for item-specific feedback. Comments from the patients regarding the relevance of each item (yes/no) and the wording of each item (i.e., was the item difficult, confusing, annoying, or upsetting to answer?) were ascertained. A large percentage of patients (90 %) thought that the FACT-Br assessed all relevant health-related quality of life issues experienced by patients. No questions were consistently identified as upsetting, confusing, or annoying, and 49 out of the 50 patients in the study indicated that they would not change any of the current FACT-Br questions. HCPs were also asked to indicate the extent to which they found each item relevant for patients on a scale of 0 = "not at all" to 4 = "very much." If HCPs rated any item as "not at all" or "a little" relevant, they were invited to indicate why it was not relevant. Additionally, HCPs were asked to comment on the wording of the FACT-Br items along with adding any comments about relevant topics not included in the FACT-Br. The majority of HCPs rated most of the FACT-Br items as either quite or very relevant. After reviewing the combined FACT-Br, six HCPs recommended additional important QOL issues that were not covered in the questionnaire, including coping with functional loss, other side effects from treatment, ability to walk, understanding treatment options, and social acceptance/appearance. However, of these additional issues, no single issue was mentioned by more than two HCPs. Ultimately, these additional QOL issues were not added to the FACT-Br.

Thavarahah et al. (2014) administered the FACT-Br to 40 patients with brain metastases who had good performance status at baseline and one month later. All FACT-Br scores demonstrated excellent test-retest reliability, except for the SWB scale which revealed good reliability. Furthermore, at both baseline and one-month follow-up, Cronbach's alpha was in the acceptable to good range (0.75 – 0.91) for the FACT-Br and FACT-G total score and for all of the subscale scale scores, except EWB (0.58) and BrCS (0.26 – 0.54). There was no discussion about why the alpha for these subscales was so low or if removing any of the items would have improved alpha. Notably, that study aimed to validate the FACT-Br in patients with brain metastases, not primary brain tumor patients, for whom the BrCS scale was developed. Primary brain tumor patients are the population of interest for this study.

Of note, there was an additional subscale (relationship with doctor) included in the original measure that was later removed (FACIT Administration and Scoring Guidelines). The FACT-Br was not re-validated after the relationship with doctor subscale was removed. Thus, the psychometric properties of the current version are unknown. This study used the currently accepted version (version 4), which was retrieved from: http://www.facit.org/FACITOrg/Questionnaires. However, extensive psychometric work has been conducted on four of the subscales of the FACT-Br (i.e., the FACT-G), including published normative data for two reference groups: 1) a sample of the general U.S. population, and 2) a large, heterogeneous sample of adult patients with cancer (Brucker et al., 2005).

Methodological challenges in assessing health-related quality of life among patients with brain tumors. Many methodological problems in the assessment of health-related quality of life among patients with brain tumors have been discussed (Baker et al., 2015; Cheng, Zhang, & Liu, 2009; Dirven et al, 2013). First, it is difficult to obtain data on patients with brain tumors.

Brain tumors are relatively rare, and the symptom burden that brain tumor patients face can make completing assessments difficult (Baker et al., 2015; Bergo et al., 2015). Dirven et al. (2013) highlighted the numerous methodological issues that might hamper the interpretation of health-related quality of life data, including the timing of the assessments, selection bias, and missing data. Furthermore, there is a lack of consensus about the definition of health-related quality of life, which lacks a theoretical basis. This lack of consensus further translates to a lack of agreement about what measures of health-related quality of life should capture and which existing measures of health-related quality of life to use (Baker et al., 2015). The length of health-related quality of life measures for use with patients with brain tumors is also an issue (Baker et al., 2015; Bergo et al., 2015; Cheng et al., 2009). Longer measures can be time consuming and difficult to complete for patients, especially people struggling with cognitive deficits or fatigue. Yet, measures with fewer items are less likely to capture the multidimensional complexity of health-related quality of life (Cheng et al., 2009). This lack of consensus around measures of health-related quality of life makes cross-study comparisons challenging and, in addition to the methodological challenges noted above, has hindered our understanding of health-related quality of life among brain tumor patients.

Health-related quality of life in patients with brain tumors. Despite these challenges, health-related quality of life among patients with brain tumors has received considerable attention in the last two decades (see recent reviews: Baker et al., 2015; Bergo et al., 2015; Cheng et al., 2009; Chiu et al., 2012; D'Angelo, Mirijello, Addolorato, & D'Angelo, 2011; Dirven, Aaronson, Heimans, & Taphoorn, 2014a; Dirven, Armstrong, & Taphoorn, 2015; Dirven, Koekkoek, Reijneveld, & Taphoorn, 2016; Dirven et al., 2013; Dirven et al., 2014b; Dirven et al., 2014c; Goffaux et al., 2012; Liu, Page, Solheim, Fox, & Chang, 2009; Osoba,

2011; Ownsworth, Hawkes, Steginga, Walker, & Shum, 2009; Taphoorn et al., 2010). Many contradictory findings related to health-related quality of life among patients with brain tumors have been reported in the literature (Cheng et al., 2009). For example, patients with mixed types of brain tumors (high-grade gliomas, low-grade gliomas, and other types of tumors) reported better health-related quality of life than a general sample of the U.S. population and patients with a range of other cancers (Weitzner et al., 1995). When considering updated normative data from the general U.S. population and a large sample of patients with a variety of cancers (Brucker, Yost, Cashy, Webster, & Cella, 2005), patients with brain tumors (Weitzner et al., 1995) had largely comparable health-related quality of life, with patients with brain tumors exhibiting lower emotional wellbeing than both the general sample (T-score = 41.9) and the cancer sample (T-score = 44). However, separate samples of patients with high-grade gliomas and low-grade gliomas reported significantly lower health-related quality of life in all domains of functioning compared to age-matched and sex-matched healthy controls (D'Angelo et al., 2011; Liu et al., 2009), and high-grade gliomas patients reported lower social functioning and more problems with vision, motor functions, communication, headaches, and seizures than matched, non-small-cell lung cancer patients (Liu et al., 2009). Patients with primary brain tumors report worse subjective cognitive functioning than patients with brain metastases, but otherwise have similar health-related quality of life profiles to patients with brain metastases (Chiu et al., 2012). Thus, currently, we lack a clear understanding of health-related quality of life among patients with brain tumors, including the range of health-related quality of life and how brain tumor patients' health-related quality of life compares to the general population and patients with other types of cancers. Yet, decreased health-related quality of life (assessed by Sintonen's 15D scale) has been associated with shorter survival among low-grade glioma patients (Tuunanen, et al., 2006).

Further efforts to better understand health-related quality of life among patients with brain tumors are necessary.

Both the primary brain tumor itself as well as treatment side effects may negatively impact patients' health-related quality of life (Dirven, et al., 2014a; Schiff et al., 2014). Liu et al. (2009) proposed a simple model to examine the differential effects of patient, tumor, and treatment factors on brain tumor patients' overall health-related quality of life. Patient factors include demographic characteristics and comorbidities; tumor factors include tumor side, size, and location; and treatment factors include surgery, RT, chemotherapies, and concomitant medications (Liu et al., 2009). Studies of patient factors that have been examined in relation to health-related quality of life have mostly resulted in inclusive or unsubstantiated results (Baker et al., 2015). For example, gender differences have been noted in four studies of health-related quality of life among brain tumor patients, with women reporting lower health-related quality of life than men (Bergo et al., 2015). However, five studies found no relationship between gender and health-related quality of life (Baker et al., 2015). In a study of symptom clusters among high-grade glioma patients, Fox, Lyon, and Farace (2007) found that depression, fatigue, sleep disturbance, cognitive impairment, and health-related quality of life tend to co-occur. Significant negative relationships with health-related quality of life have been identified for functional and motor impairment, fatigue, and mood (Baker et al., 2015). Given that emotional and functional well-being are components of health-related quality of life, these findings are unsurprising. Education and marital status have also been considered and appear to be unrelated to health-related quality of life (Baker et al., 2015).

Regarding tumor factors, interestingly, studies on the impact of tumor location and tumor grade on health-related quality of life have resulted in little evidence to suggest that they are

related to health-related quality of life (Baker et al., 2015; Bergo et al., 2015). The effects of medical treatments on health-related quality of life have been studied extensively with mixed results (Bergo et al., 2015). Health-related quality of life has become an important secondary outcome in randomized controlled (clinical) trials (RCTs) for brain tumor patients (Dirven et al., 2016). The methodological quality of these RCTs regarding the patient-reported outcomes, however, has usually been weak (Dirven et al., 2014c). In patients with high-grade gliomas, the extent of resection has been associated with health-related quality of life. Patients who received a biopsy only (i.e., a procedure to remove a piece of tissue or a sample of cells), rather than an attempt at resection, report lower health-related quality of life than patients who had a total gross resection. This finding, however, is hinder by selection bias – brain tumors that are suitable for a biopsy alone versus a total gross resection likely differ on many characteristics, such as size, multifocality, and location, and hence, expected survival, confounding this finding (Liu et al., 2009). RT can sometimes improve health-related quality of life among brain tumor patients by elevating the negative effects of the tumor, stabilizing the disease, and delaying tumor progression. RT, however, also comes with side effects that can negatively affect patients' health-related quality of life (Dirven et al., 2014a). Some of the side effects can be transient (e.g., nausea), while others (e.g., cognitive impairment) can be longer lasting (Douw et al., 2009). Treatment with chemotherapy in addition to RT has been shown to result in a dip in health-related quality of life that subsequently resolves and returns to the same level as that of patients who received RT only, implying that that this combination of treatments creates a greater symptom burden temporarily (Dirven et al., 2014c). Of the factors that have been examined in relation to health-related quality of life among brain tumor patients, fatigue, sleep quality, depression, anxiety, subjective cognitive functioning, objective cognitive functioning, KPS, and

functional impairment seem to be the most consistently related to health-related quality of life (Baker et al., 2015). Notably, sleep quality, depression, anxiety, subjective cognitive functioning, and functional impairment are components of health-related quality of life (i.e., direct indicators of health-related quality of life); thus, they would be expected to be related to health-related quality of life. Objective cognitive impairment will be discussed in more detail below.

Health-related quality of life trajectories. There is a notable paucity of prospective, longitudinal observational studies of health-related quality of life among brain tumor patients (Goffaux et al., 2012; Ownsworth et al., 2009). Within the last 10 years, six longitudinal health-related quality of life studies have been conducted (Bitterlich & Vordermark, 2017; Daigle et al., 2013; Hickmann et al., 2016; Kangas, Tate, Williams, & Smee, 2012; Kim, Joo, Kim, Han, & Kim, 2016; Yavas et al., 2012). A recent review of medical treatment RCTs that included health-related quality of life at baseline and as a secondary outcome of the trial, thus providing at least two assessments of health-related quality of life at different time points, identified 14 studies (Dirven et al., 2014c). However, only two of these medical treatment RCTs (reported across four manuscripts: Stupp et al., 2005; Taphoorn et al., 2005; van den Bent et al., 2006; Taphoorn et al., 2007) provided high quality health-related quality of life evidence (Dirven et al., 2014c). The vast majority of studies considering health-related quality of life among brain tumor patients have been at a single time point (i.e., cross sectional) or have been collected over time as part of an RCT comparing at least two different treatments. Limited information is available to help brain tumor patients predict how their quality of life might be affected by their disease and treatments over time.

Of the observational studies, two were conducted in Europe, one was conducted in Canada, one was conducted in Korea, one was conducted in Turkey, and one was conducted in

Australia. The two medical RCTs that provided high-quality health-related quality of life evidence were conducted in Europe. Seven of the eight studies will be reviewed here. The study conducted by Kangas et al. (2012) is distinct in that it examined both health-related quality of life and EF over time and will be discussed in the health-related quality of life and EF section below.

In a study conducted in Europe, health-related quality of life, as measured by the EORTC QLQ-C30/BN-20, was assessed in a small cohort of patients (N = 30) with either a benign or malignant brain tumor before RT (baseline) and at the end of RT (T2), and three (T3), six (T4) and 12 (T5) months after the end of RT (Bitterlich & Vordermark, 2017). Data at each time point were compared to a time point prior to RT (baseline), using non-parametric Mann-Whitney U tests. Global QoL subscale scores improved slightly from before RT compared to 12 months after the completion of RT. The improvement, although slight, was considered clinically significant. Global QoL subscale scores were consistently higher in the benign/meningioma group compared to the malignant/glioblastoma group, which may have driven the overall effect (trajectories were not considered separately, likely due to sample size limitations). At the end of RT (T2), patients experienced significantly higher mean levels of fatigue, appetite loss, and alopecia compared with before RT (baseline). At three months after RT (T3), there was a significant increase in reports of itchy skin. Patients in the meningioma and benign groups exhibited fewer financial difficulties, as assessed by the EORTC QLQ-C30/BN-20, over time, compared with patients in the glioblastoma and malignant groups. In addition, financial difficulties decreased at 12 months following RT in the groups receiving curative therapy, and markedly increased in groups with palliative therapy.

In an additional study conducted in Europe, 57 brain tumor patients with a range of tumor

types completed the EORTC QLQ-C30/BN20 within five days post-surgery and were reevaluated after three, six, and nine months (limited information was provided about further medical treatments during this time). Global QOL subscale scores improved over time (Hickmann et al., 2016). However, the authors noted a high dropout rate for patients whose health declined. Thus, the results are likely biased due to over-representation of healthier participants.

In a study conducted in Korea, a heterogeneous group of brain tumor patients (N = 258) completed the EORTC QLQ-C30/BN20 before surgery and at their first follow-up appointment after surgery (three to six months after surgery; RT was not mentioned; Kim et al., 2016). Global QOL improved significantly after surgery. Conversely, physical functioning significantly declined after surgery. Among the symptoms, headache, pain, and nausea and vomiting decreased, while dyspnea, communication deficit, and weakness of the legs increased (Kim et al., 2016).

In a study conducted in Turkey (Yavas et al., 2012), 118 patients with high-grade gliomas scheduled to receive RT and Temozolomide were enrolled in a longitudinal study of health-related quality of life, and were asked to complete the EORTC QLQ-C30/BN20 before RT (baseline), at the end of RT, and then three, six, 12, 18, 24, and 30 months after the end of RT. Only baseline, immediately post RT, and 18 month scores were analyzed. Only 22 patients completed the assessment at 18 months. Global health-related quality of life scores at baseline were examined based on patient-related characteristics. Male patients had higher global scores than female patients; however, the difference was only statistically significant for grade III patients. Baseline global scores did not differ between different age groups. Patients with inoperable disease and whose KPS scores were between 70 and 80 had lower scores for all

grades. Health-related quality of life scores were not different between the groups when patients were classified according to their marital status, baseline KPS scores, educational status, and localization of the tumor (either in the right or left hemisphere). Baseline global health-related quality of life scores of the "not other classified" high-grade glioma patients and patients whose tumor was subtotally resected were significantly higher than baseline scores of patients who had inoperable tumors (Yavas et al., 2012). During the follow-up, mean global and functional domains scores of EORTC QLQ-C30 decreased, implying worse health-related quality of life, while symptom (QLQ-C30 and BN20) domain scores increased, implying more symptoms. BN-20 seizure and leg weakness scores significantly increased from the baseline to 18 month follow-up. Hair loss complaints improved from the baseline to 18 months. The authors concluded that overall health-related quality of life worsens in patients as their high-grade glioma progresses (Yavas et al., 2012).

In a study conducted in Canada (Daigle et al., 2013), 35 patients with glioblastoma completed the Sherbrooke Neuro-Oncology Assessment Scale (SNAS), a measure of health-related quality of life, before surgery (biospy or craniotomy; T1) and only 19 patients completed the same measure 14 to 16 weeks later (after completing four weeks of RT and chemotherapy; T2). In the interium between T1 and T2, 12 patients died, two patients presented with confusion, and two patients refused to further participate in the study. This highlighs the challenges of obtaining health-related quality of life data from brain tumor patients. Also of note, patients with significant cognitive impairment at recruitment (as assesed by the Mini-Mental State Examination [MMSE] and with a score of less than or equal to 24), were specfically excluded from the study. Patients were not randomized to surgery type and received craniotomies whenever the treatment team felt that at least a 90% resection could be accomplished. One of the

main objectives of the study was to examine the relationship between pre-operative tumor volume and baseline health-related quality of life. Results demonstrated that, even after controlling for age and tumor location, tumor volume continued to explain individual differences in baseline health-related quality of life. This was true for baseline pain and baseline social support/acceptance of disease. With respect to pain, headache pain was the most prevalent type of pain experienced by patients in the study (62.9% of cases). Comparison of T1 and T2 health-related quality of life scores revealed that health-related quality of life generally decreased for the biopsy group, but remained stable over time for the craniotomy group (Daigle et al., 2013). This study included a very small sample size, with only five patients in the biopsy group at T2.

In sum, in studies with patients with heterogeneous brain tumor types, results have shown that global QoL has the potential to improve over time. Symptoms (such as seizure, leg weakness, levels of fatigue, appetite loss, and alopecia), however, tend to increase over time. Patients with high-grade gliomas tend to have a decline in health-related quality of life over time. These studies have been limited by small sample sizes and high rates of dropout. Furthermore, all of these studies used rudimentary statistical methods for examining change over time (e.g., Friedman's ANOVA, repeated measures ANOVA, Wilcoxon signed-rank test, Mann-Whitney U test). Of note, no longitudinal studies of health-related quality of life among brain tumor patients have been conducted in the United States.

As noted above, two brain tumor treatment RCTs (Stupp et al., 2005; van den Bent et al., 2006) have provided high-quality health-related quality of life evidence. Stupp et al. (2005) conducted an RCT of RT alone or RT plus concomitant and adjuvant temozolomide with 573 newly diagnosed glioblastoma patients. Health-related quality of life was measured by the EORTC QLQ-C30/BN20 and analyzed using linear mixed modeling (health-related quality of

life results were reported in Taphoorn et al., 2005). Treatment arms did not significantly differ at baseline. Global QoL did not deteriorate by a clinically meaningful amount in either treatment group over time after treatment. However, some differences in health-related quality of life between groups during treatment and over time were noted: a significant and clinically relevant difference during first follow-up for social functioning, in favor of RT alone; and a significant increase in nausea and vomiting, appetite loss, and constipation in those allocated RT plus temozolomide group. Furthermore, fatigue during RT was more frequent in patients assigned RT plus temozolomide. Future uncertainty decreased over time in both groups. Survival was the primary outcome of the RCT and was significantly higher with combination treatment than with RT alone. Thus, the authors concluded that because Global QoL did not decline, RT plus temozolomide was the superior treatment. RT plus temozolomide is now the standard treatment for glioblastoma.

van den Bent et al. (2006) conducted an RCT that tested RT plus adjuvant procarbazine, lomustine, and vincristine (PCV) chemotherapy versus RT alone in newly diagnosed patients with anaplastic oligodendrogliomas or anaplastic oligoastrocytomas. Health-related quality of life was measured by the EORTC-QLQ-C30/BN20, was analyzed using linear mixed effects, and was reported in Taphoorn et al., (2007). Baseline scores demonstrated considerable impairments in health-related quality of life for both treatment groups. The longitudinal analysis showed a significant increase in nausea/vomiting in the RT plus PCV chemotherapy arm during and shortly after chemotherapy. Appetite loss and drowsiness demonstrated significant differences between treatment arms during chemotherapy in favor of the RT arm. The long-term results showed no difference between arms. Over time, patients reported improvements in global QoL and in social functioning. However, these results are biased because only patients without tumor

recurrence were included in the analysis (Taphoorn et al., 2007).

Results from a recent cross-sectional study conducted in Europe also provide insights into health-related quality of life trajectories. Patients with brain tumors who were at different stages of their treatment (N = 291) and healthy control subjects (N = 110) completed a cognitive assessment and self-report measures of anxiety and depression (Giovagnoli et al., 2014). Patients with brain tumors also completed a brain tumor-specific self-report measure of health-related quality of life (the Functional Living Index for brain tumor patients; Giovagnoli, Silvani, Colombo, & Boiardi, 2005; Schipper, Clinch, McMurray, & Levitt, 1984) and received performance (KPS) and physical functioning (activities of daily living; ADL) ratings from a physician. Data from patients were sorted into five disease/treatment groups based on where patients were in their disease/treatment at the time of the assessment: 1) preoperative (n = 20), 2) postoperative (n = 30), 3) RT/chemotherapy (n = 76), 4) stable disease (n = 61), and recurrence (n = 104). Brain tumor patients with recurrence reported significantly lower health-related quality of life than patients in the postoperative or stable phases of disease. Notably, patients in the postoperative group reported the highest health-related quality of life of the treatment groups. With regard to anxiety and depression, patients in the postoperative phase did not report pathological anxiety or depression. Compared with this subgroup, patients in the preoperative, RT/chemotherapy, and recurrence phases of disease reported greater state anxiety, patients with stable disease or tumor recurrence reported greater trait anxiety, and patients with stable disease or tumor recurrence reported greater depression. Compared with controls, patients with stable disease or tumor recurrence had significantly higher state/trait anxiety and depression scores, patients in the RT/chemotherapy group had significantly higher state anxiety and depression scores, and patients assessed before surgery had higher state anxiety scores. With regard to

cognitive outcomes, compared to controls, all patients were considered impaired on tests of selective attention, visuo-motor coordination, working memory, set-shifting abilities, divided attention, and episodic memory. There were no significant group differences among the disease/treatment groups on the cognitive outcomes. Depression was negatively related to working memory and set-shifting abilities (components of EF; Giovagnoli et al., 2014). Averaging across patient groups, health-related quality of life was positively related to cognitive outcomes; post-hoc tests of specific cognitive abilities and their relationships to health-related quality of life were not reported. Results from this study provide insights into how health-related quality of life and emotional distress vary based on disease/treatment stage and how emotional distress compares to healthy controls. Furthermore, this study further supports the finding that brain tumor patients face cognitive impairments throughout their treatment and adds to the evidence for a negative relationship between depression and cognitive functioning and a positive relationship between cognitive functioning and health-related quality of life. Limitations of this study include the cross-sectional design, small and unbalanced subgroups, and potentially biased controls (hospital staff and patients' relatives).

2.3 Cognitive Deficits among Patients with Brain Tumors

Cognitive deficits in brain tumor patients have predicted lower rates of survival and tumor progression before progression was visible on medical imaging (Correa, 2010). Cognitive deficits in patients with newly diagnosed glioblastoma were found to be independently associated, over and above age, with survival (Johnson, Sawyer, Meyers, O'neill, & Wefel, 2012). Notably, relationships between survival and KPS scores, the interval from resection to evaluation, tumor laterality, AED use, or steroid use were not significant among glioblastoma patients (Johnson et al., 2012), indicating the important predictive ability of cognitive

impairment.

Over 60% of patients with gliomas have cognitive impairments prior to receiving treatment (van Kessel, Baumfalk, van Zandvoort, Robe, & Snijders, 2017) and over 80% of brain tumor patients who undergo RT report cognitive concerns (Day et al., 2016). Indeed, cognitive impairment is considered the most frequent complication among brain tumor patients (Correa, 2010). Cognitive deficits can be caused by brain tumor, brain tumor treatment (Correa, 2010; Scoccianti, Detti, Cipressi, Iannalfi, Franzese, & Biti, 2012; Taphoorn & Klein, 2004), and/or individual patient risk factors (Janelsins, Kesler, Ahles, & Morrow, 2014). Yet, cognitive deficits are not restricted to the area of the brain where the tumor is located and can affect multiple subdomains of cognition (Bergo et al., 2015). However, patients with gliomas that are localized to the language-dominant hemisphere tend to have worse cognitive deficits than those with tumors in the language non-dominant hemisphere (Bergo et al., 2015; Giovagnoli et al., 2014). Whole-brain RT (WBRT) alone or in combination with chemotherapy tends to produce greater cognitive impairment than either partial RT or chemotherapy alone (Correa, 2010). Cognitive side effects of RT can be acute (within days of RT), early delayed (weeks to six months after RT), or late delayed (a few months to many years after RT; Douw et al., 2009; Scoccianti et al., 2012). Among patients with low-grade gliomas, RT has been associated with cognitive deficits (Douw et al., 2009). Long-term survivors of low-grade gliomas who did not have RT were found to have stable cognitive performance over 12 years, whereas low-grade glioma patients who had RT showed significant declines in cognitive performance over time. Patients were not randomized to the two groups but did not significantly differ on clinical variables (Douw et al., 2009).

Furthermore, seizures, AED, and steroids can exacerbate cognitive impairments. A strong

association between epilepsy among brain tumor patients and cognitive impairment has been reported (Bergo et al., 2015). AED are used to assist with managing seizures yet can further add to patients' cognitive difficulties. Steroids may improve cognitive deficits by alleviating edema, but they can also induce substantial side effects including steroid dementia or psychosis (Bergo et al., 2015). Additional factors associated with cognitive impairment among brain tumor patients include fatigue, depression, drowsiness, and insomnia (Day et al., 2016). In sum, cognitive deficits in patients with brain tumors may be caused by the tumor, tumor-related seizures, treatment (surgery, RT, AED, chemotherapy, or steroids), psychological distress/mood disorders, as well as patient factors (age, genetic predisposition, pre-existing neurological diseases, systemic diseases). Lastly, cognitive impairments can have a large impact on self-care, including activities of daily living, one's ability to work, and social functioning, components of health-related quality of life (Klein, Duffau, & Hamer, 2012). Executive functioning (EF) has been identified as one of the cognitive domains most affected by brain tumors and brain tumor treatments (Bergo et al., 2015). Furthermore, impairment in EF has been identified as one of the domains most predictive of reduced survival (Johnson et al., 2012).

Executive functioning

EF encompasses skills necessary for goal-directed behavior (Strauss, Sherman, & Spreen, 2006). Thus, executive dysfunction may become evident through collection of problems in everyday life, including inappropriate social behavior; problems with decision making and showing good judgment; difficulties with devising, following, and shifting plans; problems with organization; distractibility; and difficulties in situations involving various aspects of memory (e.g., prospective memory, remembering to carry out intended actions at a future time). Executive dysfunction may be reflected in test performances by poor initiation, poor planning

and organization, poor inhibition, difficulty shifting behaviors, poor working memory, inflexibility, perseveration, difficulties generating and implementing strategies, difficulty correcting errors or using feedback, and carelessness (Strauss et al., 2006). Thus, EF is not a unitary construct (Gibbons et al., 2012; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000).

Assessment of executive functioning

EF has been identified as an essential cognitive domain to evaluate in brain tumor patients (Klein et al., 2012). The Trail Making Test (TMT) parts A and B (Heaton, Grant, & Matthews, 1991; Reitan, 1958; Tombaugh, 2004), and the Controlled Oral Word Association (COWA) F-A-S Verbal Fluency (Ruff, Light, Parker, & Levin, 1996) are the most commonly used tests in patients with brain tumor to assess EF (Klein et al., 2012). The Trails Making Test (Delis, Kaplan, & Kramer, 2001; Reitan, 1958) has been recommended as a valid and reliable measure of EF for both non-CNS cancer patients (Wefel, Vardy, Ahles, & Schagen, 2011) and brain tumor patients (Day et al., 2016). The TMT, part B captures visuo-motor set-shifting abilities. Verbal fluency is a cognitive function that places high demands on strategic lexical search and retrieval, internal response generation, and self-monitoring (Patterson, 2011). The Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) is a well-validated battery of EF tests that aims to isolate specific EFs (Strauss et al., 2006) from more basic processes (e.g., attention, motor skills) that may influence test scores. The D-KEFS contains modified versions of the TMT and COWA.

The D-KEFS, composed of nine individual tests, which can be used separately or as a set, provides a standardized assessment of executive functions in children and adults between the ages of 8 and 89 years. The D-KEFS (Delis et al., 2001) represents the first set of executive tests co-normed on a large and representative national sample designed exclusively for the assessment

of executive functions including cognitive flexibility, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity (Homack, Lee, & Riccio, 2005). Three D-KEFS tests were selected for use in this study: Trail Making Test (TMT), Color-Word Interference (CWI) Test, and Verbal Fluency (VF). The TMT contains five conditions. Condition four of the TMT (Number-Letter Switching; similar to TMT, part B) assesses concentration, attention, and cognitive flexibility on a visual-motor sequencing task and is the primary executive function task of the TMT (Homack et al., 2005). The Color-Word Interference Inhibition score assesses the ability to inhibit inappropriate responding (Latzman & Markon, 2010). The Verbal Fluency Category Switching Accuracy score reflects efficient verbal set shifting and speeded lexical production and automatic lexical access (Latzman & Markon, 2010).

The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993; Heaton, 1981) is the most frequently used test to assess EF (Strauss et al., 2006) and is an indicator of task-switching, mental flexibility, non-verbal problem solving, and abstract concept formation (Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004). The number of perseverative errors is the most common measures of executive control (Strauss et al., 2006). Perseverative errors occur when there is a failure to shift categories in response to negative feedback (Goldstein et al., 2004). Patients with damage to the prefrontal cortex seem to be more vulnerable to perseverative errors because they have difficulty shifting mental sets in response to feedback. The number of perseverative errors scores have been used with brain tumor patients to assess EF (Davidson, Gao, Mason, Winocur, & Anderson, 2008; Goldstein et al., 2004). Goldstein et al. (2004) found that the WCST is sensitive to the effect of low-grade brain tumor on EF. D-KEFS and WCST are well known, valid, and reliable measures of EF. However, among brain tumor patients, the TMT, part B and COWA have been most widely used to assess

EF (Day et al., 2016) because of the ease and speed of delivery, especially in comparison to the WCST.

Using multiple measures of EF has been recommended as a way to help alleviate task impurity and low reliability (Strauss et al., 2006). Composite scores are often used to assist with this aim (Gibbons et al., 2012). Furthermore, because EF is composed of a number of different processes that can be impaired singly or in combination in each individual patient, assessment of EF requires multiple measures (Strauss et al., 2006). Composite scores are typically created by averaging standardized scores (e.g., T-scores) of tests that assess the same domains (e.g., Miller et al., 2016; Nguyen et al., 2017).

Executive functioning among patients with brain tumors

Executive dysfunction is often present at diagnosis in many brain tumor patients (Correa, 2010), particulary patients with frontal, left/language-dominant, or very large tumors, which create mass effects (Hendrix et al., 2017; Sacks-Zimmerman, Duggal, & Liberta, 2015). Additionally, deficits in EF are frequently reported in the immediate post-operative phase and often persist beyond three-month follow-up (Day et al., 2016). Furthermore, EF is particularly sensitive to the effects of chemotherapy, steroids, and AED (Correa, 2010). The effects of RT may take longer to affect EF in patients with brain tumors. A cross-sectional study compared 20 low-grade glioma patients treated with RT, 21 low-grade glioma patients who did not receive RT, 19 low-grade hematologic cancer patients, and 19 healthy control participants with regard to cognitive outcomes (Taphoorn et al., 1994). Low-grade glioma patients completed the cognitive evaluation a mean of six years after diagnosis and obtained lower test scores than the cancer control group on tests of EF, but the two low-grade glioma groups (RT versus no RT) did not differ. The authors concluded that the cognitive deficits were due to the brain tumor, not RT

(Correa, 2010). However, a separate study with a larger sample size and more distal follow up (M = 12 years; range = 6 – 28 years) reported that patients who received RT showed a decline in attention, executive function, and information processing speed, regardless of fraction dose, than patients who did not receive RT (Douw et al., 2009). There were no other clinical differences between to the two samples (RT vs. no RT; Douw et al., 2009). The authors hypothesize that RT causes late-delayed (> 6 years) cognitive sequelae; however, note that patients in this study were not randomized and thus, there is a high potential for selection bias. In a recent study of patients with temporal lobe glioma, EF deficits were shown to occur in approximately 40% of patients in the sample and were predictive of decreased occupational and recreational functioning (Day et al., 2016).

2.4 Health-Related Quality of Life and Executive Functioning

Little is known about the relationship between EF and health-related quality of life among brain tumor patients. In a cross-sectional study of newly diagnosed temporal lobe glioma patients (N = 73), Noll, Bradshaw, Weinberg, and Wefel (2017) found that a majority of patients (74%) performed at a clinically significantly impaired level (1.5 standard deviations below the mean) on at least one cognitive functioning test, 36% of the sample was clinical impaired on EF, and 13% of patients exhibited clinically significant levels of depression (as measured by the BDI-II; Beck, Steer, & Brown, 1996). Compared to normative data on healthy control participants, the sample exhibited clinically meaningful reductions in FACT-G EWB (54%) and FWB (24%). Furthermore, health-related quality of life was related to EF. Specifically, the FACT-General total score, and SWB, FWB, and BrCS subscales were all significantly weakly to moderately correlated with TMT, part B scores; worse health-related quality of life was associated with worse EF.

Both brain tumor symptoms and treatment side effects can cause cognitive deficits, including EF impairment, which could potentially diminish patients' health-related quality of life (although this has only been studied cross-sectionally and correlation does not imply causation). Relatedly, brain tumor symptoms, treatment, and the experience and appraisal of having a brain tumor can cause emotional distress, fatigue, and sleep disturbance (Day et al., 2016), components of health-related quality of life that could also potentially affect EF. Depression, in particular, has been reliably associated with objectively assessed deficits in EF in other populations (based on results from a large meta-analysis; Snyder, 2013). Subjective cognitive impairment is a component of health-related quality of life (e.g., "I am able to put thoughts into action," "I am able to concentrate," "I can remember new things," I am able to make decisions and take responsibility"). Yet, notably, subjective measures of cognitive symptoms have only been weakly to moderately associated with objective measures of cognitive functioning (Day et al., 2014). Within the last 10 years, only one study has examined the progression of objectively measured cognitive deficits (including EF) in brain tumor patients, and their relationship to health-related quality of life over time (Kangas et al., 2012).

In a study conducted in Australia, 70 brain tumor patients were assessed for health-related quality of life, EF, mood (POMS depression), social constraints (SCS), and post-traumatic stress symptoms (PCL-S) before RT (T1) and approximately three months after RT (T2; Kangas et al., 2012). Health-related quality of life was assessed using the FACT-Br. EF was assessed using the COWA, TMT part B, and the Weschler Adult Intelligence Scale, third edition (WAIS-III) Similarities subtest, a measure of verbal abstract reasoning. Scores were scaled according to published norms, were converted to percentiles, and were considered separately. The study included both benign (n = 45) and malignant (n = 25) brain tumor patients. The

patients with malignant brain tumor (MBT) were significantly younger and were "recommended to receive multiple medical treatments (including surgery and/or chemotherapy)" (p. 1490; Kangas et al., 2012) compared to the benign brain tumor (BBT) group. Repeated-measures General Linear Model (GLM) analyses were used to test changes from T1 to T2 between groups (BBT vs MBT).

With regard to health-related quality of life, no statistically significant differences were found between the two groups. However, there was a trend toward patients with BBT reporting better emotional well-being at T2 relative to patients with MBTs, controlling for T1, and for patients with MBTs reporting worse social well-being at T2 relative to patients with BBT, controlling for T1. With regard to EF, there were no significant differences between groups (BBT v. MBT). However, on the Similarities test, a significant within-group difference was found over time for patients with MBT, demonstrating an improvement in scores over time. Additionally, all of the patients performed below average on the COWA over time. All patients also scored below average on TMT, part B at T1, but the BBT group improved from T1 to T2. With regard to predictors of health-related quality of life, linear regression was conducted to test which variables at T1 predicted health-related quality of life at T2. Brain tumor status and T1 scores on the PCL-S, FACT-Br, POMS depression, SCS family/friends, and COWA were separately entered into a hierarchical model (there was no discussion of why Similarities and TMT were not included in the model). BBT, higher FACT-G/Br, and lower PCL-S and POMS depression scores at T1 were each found to be significantly associated with better health-related quality of life at T2. In other words, better health-related quality of life (FACT-Br) at T2 was predicted by having a BBT (vs. an MBT), lower post-traumatic symptom and depression scores, and better health-related quality of life (FACT-Br) at T1. Health-related quality of life was not

predicted by verbal fluency (COWA). A major limitation to this study is that there was only one, relatively proximal, follow-up assessment. Additionally, the subgroup samples were uneven and the MBT group was relatively small (n = 22). Furthermore, only predictors of health-related quality of life at T2 were examined/reported. Predictors of EF at T2 were not examined or not reported. Thus, study did not aid in our understanding of predictors of EF over time, such as the influence of distress on EF. Differences on the FACT-Br subscales, not total score, were noted for brain tumor subgroup analyses, but only predictors of the FACT-Br total score at T2 were examined/reported. Lastly, this study was conducted in Australia with primarily Caucasian participants and may not be generalizable to patients in the United States.

The current study will help to broaden our understanding of health-related quality of life and EF over time and elucidate how much changes in EF produce a measurable effect on health-related quality of life and vice versa. It is possible that EF and health-related quality of life could be unrelated (null hypothesis), that EF and health-related quality of life could co-occur, that changes in health-related quality of life could cause changes in EF, or that changes in EF could cause changes in health-related quality of life.

2.5 Summary and Limitations of Prior Research

Brain tumors, treatment of brain tumors, and disease and treatment sequelae can greatly affect both health-related quality of life and EF among patients. Among patients with brain tumors, correlates of health-related quality of life remain elusive (Baker et al., 2015), little is known about the trajectories of health-related quality of life and EF over time, and the relationship between health-related quality of life and EF is largely unknown. Findings have primarily come from cross-sectional studies, and there is a notable paucity of longitudinal descriptive studies of health-related quality of life and EF among brain tumor patients to

elucidate the trajectories of health-related quality of life and EF. When longitudinal studies have been conducted, modern, more sophisticated analytic techniques have been employed infrequently (Baker et al., 2015; Goffaux et al., 2012). Growth curve modeling has been increasingly used to analyze health-related quality of life data over time in cancer research but has rarely been used in the field of neuro-oncology (Goffaux et al., 2012). Furthermore, the relationships between health-related quality of life and EF have been scantly studied, particularly over time.

As noted by Goffaux et al. (2012), "Longitudinal studies, in particular, are needed to better understand the trajectory of change experienced by patients. It is no longer useful to merely quantify the presence of change, but rather, it is important to know why change occurs and what can slow the progression of disease and the decline of patient well-being" (pp. 347). This study aims to address this need by providing information to help better understand the general trajectory of change experienced by patients, and to examine at least one possible reason why change occurs (i.e., the interrelationship between health-related quality of life and EF).

2.6 Specific Aims and Hypotheses of the Present Study

The present study adds to our understanding of: 1) patient, brain tumor, and treatment correlates of health-related quality of life and EF among adults with brain tumors prior to the start of RT (baseline), 2) trajectories of health-related quality of life and EF among adults with brain tumors over time, and 3) causal pathways between health-related quality of life and EF among adults with brain tumors. This study has three specific aims:

Specific Aim 1. To characterize health-related quality of life and EF in adults with brain tumors before RT (baseline) based on patient, tumor, and treatment characteristics.

Hypothesis I. It was hypothesized that patient, tumor, and treatment characteristics would be associated with health-related quality of life and EF at baseline.

Ia. Specifically, for health-related quality of life it was hypothesized that lower KPS, having a high-grade glioma, steroid use, and receiving no surgery or a biopsy only (versus STR or GTR) would be related to worse health-related quality of life at baseline. AED use, seizures, RT type, chemotherapy, tumor side, tumor location, education, marital status, age, gender, and race/ethnicity were not hypothesized to be statistically significantly related to health-related quality of life at baseline.

Ib. For EF, it was hypothesized that less education, receiving no surgery or a biopsy only (versus STR or GTR), steroid use, AED use, seizures, having a high-grade glioma, lower KPS, having a left-sided tumor, or a frontal-lobe tumor (versus other locations) would be significantly related to worse EF at baseline. RT type, chemotherapy, marital status, gender, and race/ethnicity not hypothesized to be statistically significantly related to EF at baseline. Age was not hypothesized to be statistically significantly related to baseline EF because EF scores were adjusted for age prior to analysis.

Specific Aim 2. To characterize health-related quality of life and EF trajectories over time.

Hypothesis II. It was hypothesized that health-related quality of life and EF would change over time. Specifically, controlling for related characteristics identified in Aim 1, linear, quadratic, and cubic time trends of health-related quality of life and EF were examined.

Specific Aim 3. To identify causal pathways between health-related quality of life and EF.

Hypothesis III. It was hypothesized that health-related quality of life and EF would be causally related over time.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Carrie McDonald, Jona Hattangadi-Gluth, and Vanessa L. Malcarne. The dissertation author was the primary investigator and author of this material.

CHAPTER 3: METHODS

3.1 Participants

Data for this study were provided by adults with brain tumors who, at the time of recruitment, were scheduled to undergo RT and who agreed to participate in a larger study that uses quantitative neuroimaging and neurocognitive data to better understand the impact of RT on non-targeted brain tissue. The larger study is a clinical research trial embedded into clinical care. Convenience sampling was utilized and patients were referred to the study through the Radiation Oncology Department at UC San Diego Moores Cancer Center. Potential participants were screened for eligibility by a UC San Diego Health Clinical Trials Research Coordinator. Inclusion criteria for this study included: diagnosis of a primary brain tumor, were expected to undergo fractionated brain RT, age 18 years or older, KPS greater than 70, ability to answer questions and follow commands at the time of consultation and treatment, had the decisional capacity to be able to decide to participate in the study, self-reported ability to speak and read in English, and had an estimated life expectancy greater than one year. Patients who had received prior brain RT were excluded. Recruitment began in 2014 and is ongoing; new patients are still being enrolled in the larger study. The sample for the current study was finalized in March 2019. The Research Coordinator tracked the patients and at each follow-up point the Research Coordinator would make a reasonable attempt to contact patients for scheduling. Patients were not compensated for their participation in the study. See Figure 1 for further screening and enrollment details.

3.2 Measures

Patient, tumor, and treatment variables. The following sociodemographic and medical variables were extracted from patients' medical records: gender, race/ethnicity, age, education,

marital status, seizures (yes/no), KPS, tumor pathology, tumor location, tumor side, surgery type, type of RT, chemotherapy (yes/no), steroid use (yes/no), and AED use (yes/no). Age, education, and KPS were treated as continuous variables. Patients' baseline demographic and KPS scores were used in this study and were not updated for changes. Additionally, seizures, steroids, and AED were considered dichotomous variables and coded as "yes" if they occurred/were prescribed at any point during the study or "no" if they did not occur or were not prescribed during the course of the study. This coding was stable from baseline to 12-months (e.g., if a patient was prescribed steroids at any point during the study, they were coded as "yes" at baseline, and three-month, six-month, and 12-month follow-ups). Chemotherapy was either given concurrent with RT or after RT (i.e., adjuvant); however, it was coded dichotomously (e.g., "yes" at baseline and three-month, six-month, and 12-month follow-ups for concurrent chemotherapy if the patient received concurrent chemotherapy or "no" across time-points if they did not receive concurrent chemotherapy). Any chemotherapy was also coded dichotomously ("yes" for concurrent and/or adjuvant chemotherapy, "no" for no chemotherapy across the study). Two-level variables were dummy coded: gender (categorized as man or woman), race/ethnicity (categorized as Non-Hispanic White or Non-White), marital status (categorized as married or unmarried), seizures (categorized as having reported a seizure(s), yes, or having not reported a seizure(s), no), RT type (categorized as IMRT or protons), any chemotherapy (categorized as yes for either concurrent, adjuvant, or both chemotherapies, or no for not receiving any chemotherapy during the course of this study), steroids (categorized as having received during the course of the study, yes, or having not received during the course of the study, no), and AED (categorized as having received during the course of the study, yes, or having not received during the course of the study, no). Variables with more than two levels

were coded using orthogonal contrast codes: tumor side (categorized as left, right, or central), tumor pathology (categorized as high-grade glioma, low-grade glioma, or other), tumor location (categorized as temporal, frontal, parietal, cerebellar, or other[1]), and surgery type (categorized as no surgery, sub-total resection, gross-total resection/near-total resection, or biopsy/VP shunt). For tumor side, central was compared to left/right, and left was compared to right. For tumor pathology, high-grade glioma was compared to low-grade glioma/other types of tumors, and low-grade glioma was compared to other types of tumors. For tumor location, other was compared to all other locations, frontal was compared to temporal/parietal/cerebellar, cerebellar was compared to temporal/parietal, and temporal was compared to parietal. Finally, for surgery type, no surgery was compared to any surgery (STR/GTR/NTR/Biopsy/VP shunt), GTR/NTR was compared to STR/Biopsy/VP shunt, and STR was compared to Biopsy/VP shunt.

Health-related quality of life. ***Functional Assessment of Cancer Therapy – Brain, Version 4*** (FACT-Br; Cella et al., 1993; Weitzner et al., 1995). As described above, the FACT-Br yields five subscale scores: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and brain tumor-specific additional concern items (Brain Cancer Subscale; BrCS). The five subscales were summed to provide a FACT-Br total score. FACT-Br total scores could range from 0 to 200, PWB scores could range from 0 to 28, SWB scores could range from 0 to 28, EWB scores could range from 0 to 24, FWB scores could range from 0 to 28, and BrCS scores could range from 0 to 92. Higher scores indicated better health-related quality of life. For this sample, internal consistency for the FACT-Br total score, based on the subscale scores, was in the acceptable range, $\alpha = .775$. The FACT-Br has a scoring manual, and normative data have been published for four of its subscale scores

[1] One patient had a thalamic brain tumor, which was not able to be categorized into one of the aforementioned categories and was, therefore, excluded from analyses involving tumor location.

(PWB, EWB, SWB, and FWB) for two reference groups: (a) a sample of the general U.S. adult population (Brucker et al., 2005), and (b) a large, heterogenous sample of adult patients with cancer (Brucker et al., 2005). Normative data for the full FACT-Br have also been published for a sample of adult patients with brain tumors (Weitzner et al., 1995). Based on the percentage of total score method for establishing minimally important differences, two- to three-point changes on the PWB, SWB, EWB, and FWB subscales, six- to ten-point changes on the BrCS subscale, and eight- to 12-point changes on the FACT-Br total score were considered minimally important differences (Yost & Eton, 2005).

Executive Functioning

All EF tests were administered in a standardized fashion by master's-level neuropsychometrists who were supervised by a licensed and board-certified neuropsychologist. Administration was in accordance with published manuals.

Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001). As described above, the D-KEFS is a comprehensive set of tests aimed at assessing many aspects of EF, including cognitive flexibility, inhibition of overlearned response, and verbal response generation. D-KEFS TMT, Color-Word Interference, and Verbal Fluency were administered. From these tests, the primary scores of interest were the TMT Number-Letter Switching (TMT-NL), Color-Word Interference Inhibition (CWI-I), and Verbal Fluency Test Category Switching Accuracy (VF). The raw scores were converted to T-scores and corrected for age using normative data (Delis et al., 2001). T-scores have a mean of 50 and a standard deviation of 10. Thus, in a normal population, 6.68% of the T-scores would be expected to fall at or below a threshold of 35 (i.e., 1.5 standard deviations below the mean). Higher T-scores indicated better functioning.

Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948; Heaton et al., 1993; Heaton, 1981). The WCST is a measure of EF, specifically task-switching, mental flexibility, non-verbal problem solving, and abstract concept formation. It was scored using commercially available software (WCST:CV4 Scoring Program; Heaton & PAR Staff, n.d.). Participants were instructed to choose one of four target cards that match a test card in shape, color, or number of stimuli. Participants were not told how to perform the task, but rather they were given feedback about whether each response is correct or incorrect. Participants sorted cards one at a time until six categories were completed or until all 128 cards were sorted. WCST has been used among brain tumor patients to assess EF and is sensitive to changes in EF (Goldstein et al., 2004). The perseverative errors (WCST-PE) score was used as an indicator of EF. The scoring software provided T-scores corrected for age and education. Higher T-scores indicated better functioning.

EF Composite Score (CS)

A composite score comprised of the three aforementioned D-KEFS subtests and the WCST-PE was created. The WCST has been noted as the most common assessment of EF; however, it should not be used in isolation to assess EF (Strauss et al., 2006). Therefore, consistent with previous studies (Miller et al., 2016; Nguyen et al., 2017), an EF CS was calculated by averaging WCST-PE, D-KEFS TMT-NL, D-KEFS CWI-I, and D-KEFS VF scores. For the present sample, reliability for the EF CS, based on the component T-scores, was in the acceptable range, $\alpha = .768$.

3.3 Procedure

The larger study has been approved by the UC San Diego Institutional Review Board (Protocol # 131457) and is primarily focused on quantitative neuroimaging and neurocognitive assessment to measure radiation-induced brain injury in non-targeted tissue in order to assist

with cognitive preservation. Patients who agreed to participate in this study completed the FACT-Br and a neurocognitive assessment at baseline (pre-RT), and three months, six months, and 12 months after the completion of RT. RT was the standard care for patients in this study. Patients usually had their first medical appointment in the Radiation Oncology Clinic two to three weeks after surgery or diagnosis. Patients typically then began RT two to three weeks after their initial Radiation Oncology appointment. The baseline assessment for patients who agreed to participate in this study was conducted within the two- to three-week window between their initial appointment and the start of RT. Then, patients completed RT five days per week for five to six weeks. The three-month follow-up assessment was conducted approximately three months after the end of RT; the six-month follow-up assessment was conducted three months after that, and the 12-month follow-up assessment was conducted six months after the six-month follow-up assessment (i.e., one year after completing RT). If patients in this study had surgery, it was before their baseline assessment.

3.4 Data Analytic Plan

Alpha was set to 0.05, and all tests were two-tailed, where appropriate. A Bonferroni corrected alpha was also reported for reference. SPSS, version 25, was used for data analyses conducted for Aim 1 (IBM Corp, 2016). R (Team RC, 2013) and RStudio (RStudio, 2018) were used for data analyses conducted for Aim 2. MPlus, version 8, was used for data analyses conducted for Aim 3 (Muthén & Muthén, 1998 - 2017). The sample was characterized at each time point based on baseline (e.g., age) and throughout the study (e.g., steroid use) data using descriptive analyses. Study characteristic means and proportions at each timepoint were compared to subsequent timepoints and from baseline to 12 months to determine if there were differences in the composition of the sample across time and from the start to the completion of

the study. Outlier analyses and assumption checks were performed for each aim. Outlier analyses assisted with further identifying data entry errors, which were corrected; however, no true outliers were identified or removed.

Aim 1: To characterize health-related quality of life and EF in adults with brain tumors before RT based on sociodemographic, tumor, and treatment characteristics.

Analysis for Specific Aim 1: Descriptive statistics and GLM regression with contrast coding were used to characterize health-related quality of life (measured by FACT-Br) and EF (measured by EF CS, which was composed of D-KEFS TMT-NL, D-KEFS CWI-I, D-KEFS VF, and WCST-PE) before RT (i.e., at baseline) based on gender, age at baseline, marital status, race/ethnicity, education at baseline, KPS, seizures, tumor pathology, tumor location, tumor side, type of surgery, type of RT, chemotherapy, AED use, and steroid use. Each of the 15 characteristics was included in its own independent GLM. As noted above, orthogonal contrast codes were created for variables with more than two levels. Orthogonal contrast codes were always run as a set. Primary analyses examined the relationships between the 15 characteristics and FACT-Br total scores and between the 15 characteristics and EF CS. Exploratory analyses examined the relationships between the 15 characteristics and the FACT-Br subscales (PWB, SWB, EWB, FWB, and BrCS) and the individual components of the EF CS (D-KEFS TMT-NL, D-KEFS CWI-I, D-KEFS VF, and WCST-PE). Bivariate correlations among the FACT-Br subscales and with the total score and among the EF CS component T-scores and with the EF CS were examined. For descriptive purposes, FACT-Br total scores that were at or below one standard deviation below the mean of a normative sample (i.e., FACT-Br total scores ≤ 110; Weitzner et al., 1995) were considered below average. EF CS or EF component T scores that were at or below 35 (i.e., 1.5 standard deviations below the population mean, T-scores ≤ 35; Noll

et al., 2017) were considered impaired. The number of patients who fell in the low average range (i.e., T-scores ranging between 36 to 40) was also reported in Table 4. Power analyses were conducted using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007) to assess the power of an independent-samples, two-tailed t-test to detect mean differences between groups, which was appropriate given the statistical approach utilized in Aim 1 (i.e., GLM regression with planned contrast codes and single-degree-of-freedom t-tests). This study was well powered to detect large ($\geq .90$) effects with either balanced or imbalanced groups; 42 patients was sufficient to provide 80% power with a type I error rate of $\alpha = 0.05$ and equal groups, and 54 patients were sufficient to provide 80% power with a type I error rate of $\alpha = 0.05$ and a ratio of 3:1 groups.

Aim 2: To characterize health-related quality of life and executive functioning trajectories over time.

Analysis for Specific Aim 2: LME models were created using lme4 (Bates, Maechler, Bolker, & Walker 2014) in R to characterize, in separate models, the trajectories of health-related quality of life (FACT-Br total score) and EF (composite score) over time (baseline, three months, six months, and 12 months), controlling for significant variables identified in Aim 1. LME models allow for random subject intercepts and account for both within-subject correlation between repeated measures and incomplete outcomes. LME models use maximum likelihood estimation, which is a preferable method for handling missing data in comparison to "classical" techniques, such as deletion and mean imputation (Baraldi & Enders, 2010; Kline, 2011; Little, 2013).

Trend analysis (i.e., linear, quadratic, cubic) was used to model the time points (UCLA: Statistical Consulting Group, n.d.). A stepwise, nested model comparison approach was utilized where the intercept-only model was compared to a covariates model, the covariates model was

compared to a model that included a linear effect, that model was compared to a model that included linear and quadratic effects, and, finally, that model was compared to a model that included linear, quadratic, and cubic effects. Separate models were developed for the FACT-Br total score and for the EF CS. As exploratory analyses, separate models for each of the FACT-Br subscales (PWB, SWB, EWB, FWB, and BrCS) and for the individual components of the EF CS (D-KEFS TMT-NL, D-KEFS CWI-I, D-KEFS VF, and WCST-PE) were also developed. Chi-squared difference tests and associated p-values, AIC, and log-likelihood values were used to determine model fit. If the chi-squared difference test was non-significant, the more parsimonious model was considered the better fitting model. Furthermore, smaller AIC and less negative log-likelihood values indicated better model fit; there is no established cutoff. Significance values for individual fixed effects were also reported.

Here is an example model with linear, quadratic, and cubic variables but without covariates where i = 1, …, *N* participants, j = 0, 1, 2, and 3 (for baseline and three-month, six-month, and 12-month follow-up), and u_i is a different score (overall average or intercept) for each subject, representing inter-individual differences as a random factor in the model:

$$Y_{ji} = \beta_0 + \beta 1 \text{Months}_{ji} + \beta_2 \text{Months}^2_{ji} + \beta_3 \text{Months}^3_{ji} + u_i + \varepsilon_i$$

Compared to between-subjects or cross-sectional designs, within-subjects or longitudinal designs have more power to detect true effects (Judd, McClelland, & Ryan, 2011). Additionally, including appropriate covariates in the model further improved power (Judd et al., 2011). Power analyses for multivariate, longitudinal studies are complex because within-subject correlation, number of repeated assessments, and level of missing data can all affect the estimations of the required sample sizes (Lu et al., 2013), and often require separate statistical modeling studies to estimate the sample size needed to achieve adequate power and obtain unbiased results. Due to

the complexity discussed above, power analyses for the multivariate, longitudinal aspects of this study were beyond the scope of this study.

Aim 3: To evaluate any causal associations between health-related quality of life and EF.

Analysis for Specific Aim 3: Cross-lagged panel model path analysis was used to examine the interrelationships between FACT-Br total scores and EF CS from baseline to three-month follow-up, three-month follow-up to six-month follow-up, and six-month to 12-month follow-up. Path analysis was utilized to specify the structural cross-lagged panel model (Kline, 2011). Generally, a participant-to-parameter ratio of 10:1 provides adequate power for path analyses (Kline, 2011). As noted above, power analyses were beyond the scope of this portion of the study. However, it should be noted that for the original cross-lagged panel model, 14 parameters were estimated, and there are 53 participants in the study (140 participants would be ideal). Auto-regressive pathways between one variable to the same variable at a subsequent time point (e.g., FACT-Br total score at baseline to FACT-Br total score at three-month follow-up) were adjusted for the previous corresponding score (i.e., the subsequent variables represent residualized change in scores based on the preceding level of the same variable; Brown et al., 2013). The model included auto-regressive pathways from baseline to three-month follow-up, from three-month follow-up to six-month follow-up, and six-month follow-up to 12-month follow-up. The model also included synchronous correlations between FACT-Br total scores and EF CS at each timepoint. Correlations between FACT-Br total scores and EF CS scores at baseline were zero-order because these variables are exogenous (i.e., independent). Subsequent synchronous correlations were between the estimated residuals (AKA, “disturbance factors”) of endogenous variables (i.e., residual correlations; Little, 2013). Finally, cross-lagged predictor pathways (e.g., from FACT-Br total score at baseline to EF CS at three-month follow-up) were

also specified. A significant cross-lagged predictor pathway indicated a directional/statistically causal effect.

The analyses were conducted using maximum likelihood estimation. Maximum likelihood is one of the preferred methods for handling missing data (Baraldi & Enders, 2010; Kline, 2011; Little, 2013). Three fit indices were used to determine goodness of fit, per the recommendations of Bentler (2007): (1) Root Mean Square Error of Approximation (RMSEA; Steiger, 1990), an absolute index of overall model fit; (2) Standardized Root Mean Residual (SRMR; Hu & Bentler, 1999), also an absolute index of overall model fit; and (3) Comparative Fit Index (CFI; Bentler, 1990), a relative index of model fit compared to the null model. CFI descriptive index values > .90 were indicative of acceptable model fit and values > .95 were indicative of good model fit. SRMR and RMSEA fit index values < .08 were indicative of acceptable model fit and values < .05 were indicative of good model fit. If at least two of the three descriptive fit indices met acceptable model fit criteria, the model was considered to fit the data (Bentler, 2007). If the model was determined to fit, significant pathways were interpreted. Chi-square was reported for completeness but was not used to assess model fit due to its lack of robustness to sample size (Kelloway, 1995). If the model did not fit the data well, modification indices were consulted, and the model was re-specified, provided that there was a theoretical justification for changing the pathways. Due to the limited sample size, results of the cross-lagged panel model were compared to bivariate, zero-order correlations of the variables included in the cross-lagged panel model to assess model consistency and stability.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Carrie McDonald, Jona Hattangadi-Gluth, and Vanessa L. Malcarne. The dissertation author was the primary investigator and author of this material.

CHAPTER 4: RESULTS

4.1 Descriptive Statistics

Sample characteristics can be found in Table 1. Patients (N = 53) included 31 men (58.5%) and 22 women who were primarily married (73.6%) and Caucasian (81.1%). Patients ranged from 20 to 75 years old (M = 47.0 years, SD = 13.9 years), with an average of 15 years of formal education (SD = 2.6 years). The majority of patients had a KPS of 90 or above (94.3%; M = 92.6, SD = 5.6) and were diagnosed with a glioma (60.4%; high-grade: 43.4%, low-grade: 17.0%) that was likely located on either the right (43.4%) or left (49.1%) side of the brain, with a few tumors that were centrally located (7.5%). The majority of patients had a sub-total resection (54.7%), intensity-modulated radiation therapy (IMRT; 73.6%), chemotherapy (58.5%; concurrent, adjuvant, or both), and received AED (52.8%). Fewer than half of the patients reported seizures (41.5%) or were prescribed steroid medications (49.1%).

At baseline, 53 patients had FACT-Br total scores and EF CS. At three-month follow-up, 39 patients had FACT-Br total scores and 40 patients had EF CS. At six-month follow-up, 39 patients had FACT-Br total scores and 40 patients had EF CS. At 12-month follow-up, 33 patients had FACT-Br total scores and EF CS. Sample characteristic means (e.g., mean age) and proportions (e.g., percentage of men in the sample) did not differ for any of the characteristics from one timepoint to the subsequent timepoint (e.g., baseline to three months) or from start of the study (i.e., baseline) to the end of the study (i.e., 12-month follow-up). Seven patients completed a single assessment (13.2%), 46 patients completed multiple (two or more) assessments (86.8%), and 26 patients completed all four assessments (49.0%). Regarding baseline FACT-Br total scores, patients who completed a single assessment (M = 129.4, SD =

23.2) did not statistically differ from patients who completed multiple assessments (M = 144.9, SD = 23.8), $F_{(1, 51)}$ = 2.6, p = .11. However, they did exhibit statistically significantly worse EF CS (M = 45.2, SD = 16.0) than patients who completed multiple assessments (M = 53.4, SD = 6.9), $F_{(1, 51)}$ = 5.4, p = .03. At baseline, patients reported a mean FACT-Br total score of 142.9 (SD = 24.1), with six patients (11.3%) reporting below average scores (i.e., six patients in this study had FACT-Br total scores below 110, which were one standard deviation below the mean of a published, normative sample of brain tumor patients; Weitzner et al., 1995). At baseline, patients had an average EF CS of 52.27 (SD = 9.1), with two patients in the low average range (3.8%) and two patients (3.8%) in the impaired range. FACT-Br total and subscale and EF CS and individual component test scores for each time point are reported in Tables 2 and 4, respectively. Bivariate correlations between baseline FACT-Br subscale and total scores and baseline EF CS component T-scores and EF CS are reported in Tables 3 and 5, respectively. All correlations were in the moderate to strong range (rs = .3 to .8).

4.2 Correlates of FACT-Br and Executive Functioning at Baseline

FACT-Br. GLM regression with contrast coding revealed that KPS, age, years of education, gender, race/ethnicity, marital status, tumor side, tumor pathology, tumor location, AED, any chemotherapy, and surgery type were not statistically significantly related to baseline FACT-Br total scores, all ps > .05. Conversely, GLM regression with contrast coding revealed that RT type, seizures, and steroids were independently significantly related to baseline FACT-Br total scores. Specifically, patients who would later receive proton beam RT (M = 157.1, SD = 18.3) had significantly higher baseline FACT-Br total scores than patients who would later receive IMRT (M = 137.8, SD = 24.1), $F_{(1, 51)}$ = 7.4, p = .01. Notably, only 14 patients in this study received proton beam RT compared with 39 patients who received IMRT. Patients who did

not report a seizure(s) at any point during the study (M = 148.6, SD = 23.4) reported significantly higher baseline FACT-Br total scores than patients who reported a seizure(s) at some point during the study (M = 134.8, SD = 23.2), $F_{(1, 51)} = 4.5$, $p = .04$. Finally, patients who did not receive steroids during the study (M = 149.9, SD = 19.8) reported significantly higher baseline FACT-Br total scores than patients who received steroids at some point during the study (M = 135.6, SD = 26.3), $F_{(1, 51)} = 5.1$, $p = .03$. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., $\alpha = .05/22 = .002$), then none of the predictors would be considered statistically significantly related to baseline FACT-Br total scores.

Exploratory analyses. The relationships between baseline FACT-Br subscale scores (PWB, SWB, EWB, FWB, and BrCS) and sociodemographic and tumor- and treatment-related characteristics were independently examined.

PWB. Baseline PWB scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor side, tumor pathology, surgery type, RT type, chemotherapy use, steroid use, or AED use, all ps > .05. Conversely, patients with frontal tumors (M = 25.6, SD = 3.2) reported significantly higher baseline PWB scores than patients with temporal, parietal, or cerebellar tumors (combined M = 22.6, SD = 4.4), $F_{(1, 47)} = 6.4$, $p = .02$. The three other tumor location comparisons were not statistically significant). If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., $\alpha = .05/22 = .002$), then tumor location would not be considered statistically significantly related to baseline PWB.

SWB. Baseline SWB scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor side, tumor pathology, surgery type, RT type, chemotherapy use, steroid use, or AED use, all ps > .05. Conversely,

patients with temporal or parietal tumors (combined M = 23.2, SD = 4.3) reported significantly higher baseline SWB scores than patients with cerebellar tumors (M = 16.2, SD = 7.5), $F_{(1, 47)}$ = 5.4, p = .03 (the three other tumor location comparisons were not significant). Of note, only three patients in the sample had cerebellar tumors. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., α =.05/22 = .002), then tumor location would not be considered statistically significantly related to baseline SWB.

EWB. Baseline EWB scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor side, tumor pathology, surgery type, chemotherapy use, steroid use, or AED use, all ps > .05. Conversely, patients who would later receive proton beam RT (M = 20.0, SD = 3.6) reported significantly higher baseline EWB scores than patients who would later receive IMRT (M = 17.0, SD = 4.4), $F_{(1, 51)}$ = 5.2, p = .03. Additionally, patients who had a tumor in an "other" location (i.e., suprasellar, sphenoid wing, cavernous sinus, or base of skull; M = 19.7, SD = 3.3) had significantly higher baseline EWB scores than patients with tumors in all other locations (i.e., frontal, temporal, parietal, or cerebellar; M = 16.8, SD = 4.5), $F_{(1, 47)}$ = 7.2, p = .01. The three other tumor location comparisons were not statistically significant. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., α =.05/22 = .002), then neither of the predictors would be considered statistically significantly related to baseline EWB.

FWB. Baseline FWB scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor side, tumor location, surgery type, chemotherapy use, steroid use, or AED use, all ps > .05. Conversely, patients who would later receive proton beam RT (M = 21.6, SD = 4.5) reported significantly higher baseline FWB scores than patients who would later receive IMRT (M = 17.7, SD = 5.7), $F_{(1, 51)}$ = 5.2, p =

.03. Additionally, patients with low-grade gliomas or other tumors *(M* = 20.0, *SD* = 5.4) had significantly higher baseline FWB scores than patients with high-grade gliomas (*M* = 17.2, *SD* = 5.6), $F_{(1, 50)} = 4.4$, $p = .04$. FWB scores for patients with low-grade gliomas were not statistically significantly different from FWB scores for patients with other tumors. Finally, patients who did not receive steroids at any point during the study (*M* = 20.4, *SD* = 17.0) had significantly higher baseline FWB scores than patients who received steroids at some point during the study (*M* = 17.0, *SD* = 6.2), $F_{(1, 51)} = 5.2$, $p = .03$. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., $\alpha = .05/22 = .002$), then none of the predictors would be considered statistically significantly related to baseline FWB.

BrCS. Baseline BrCS scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor side, tumor location, tumor pathology, surgery type, or AED use, all *p*s > .05. Conversely, patients who would later receive proton beam RT (*M* = 67.0, *SD* = 8.9) reported significantly higher baseline BrCS scores than patients who would later receive IMRT (*M* = 57.5, *SD* = 11.2), $F_{(1, 51)} = 8.2$, $p = .01$. Additionally, patients who did not receive chemotherapy at any point during the study (*M* = 64.1, *SD* = 9.8) had significantly higher baseline BrCS scores than patients who would later receive chemotherapy (*M* = 57.1, *SD* = 11.6), $F_{(1, 51)} = 5.3$, $p = .03$. Patients who did not reported experiencing a seizure(s) at any point during the study (*M* = 63.5, *SD* = 10.7) had significantly higher baseline BrCS scores than patients who reported a seizure(s) at some point during the study (*M* = 55.2, *SD* = 10.6), $F_{(1, 51)} = 7.8$, $p = .01$. Finally, patients who did not receive steroids at any point during the study (*M* = 63.4, *SD* = 10.7) had significantly higher baseline BrCS scores than patients who received steroids at some point during the study (*M* = 56.6, *SD* = 11.2), $F_{(1, 51)} = 5.2$, $p = .03$. If alpha were adjusted to protect against Type I error using a Bonferroni

correction (i.e., α =.05/22 = .002), then none of the predictors would be considered statistically significantly related to baseline BrCS.

Executive Functioning. GLM regression with contrast coding revealed that age at baseline, years of education at baseline, gender, race/ethnicity, KPS, tumor location, tumor pathology, RT type, and surgery type were not statistically significantly related to baseline EF CS, all *p*s > .05. Conversely, marital status, tumor side, seizures, steroids, AED, and chemotherapy were independently significantly related to baseline EF CS. Specifically, unmarried patients (M = 57.3, SD = 8.1) demonstrated better baseline EF CS performance than married patients (M = 50.5, SD = 8.8), $F_{(1, 51)} = 6.6$, $p = .01$. Patients with tumors on the right side (M = 55.5, SD = 4.1) demonstrated better baseline EF CS performance than patients with tumors on the left side (M = 48.2, SD = 10.3), $F_{(1, 50)} = 10.0$, $p = .003$. The difference between baseline EF CS scores for patients with central tumors and patients with left- or right-sided tumors was not statistically significantly different. Patients who did not report a seizure(s) at any point during the study (M = 54.5, SD = 8.9) demonstrated better baseline EF CS performance than patients who reported a seizure(s) at some point during the study (M = 49.1, SD = 8.4), $F_{(1, 51)} = 5.1$, $p = .03$. Patients who did not receive steroids at any point during the study (M = 55.6, SD = 5.9) demonstrated better baseline EF CS performance than patients who received steroids at some point during the study (M = 48.8, SD = 10.5), $F_{(1, 51)} = 8.6$, $p = .01$. Patients who did not receive AED any point during the study (M = 55.8, SD = 6.6) demonstrated better baseline EF CS performance than patients who received AED at some point during the study (M = 49.1, SD = 9.8), $F_{(1, 51)} = 8.3$, $p = .01$. Finally, patients who did not receive chemotherapy during the study (M = 56.0, SD = 6.5) demonstrated better baseline EF CS performance than patients who would later receive chemotherapy (M = 49.7, SD = 9.8), $F_{(1, 51)} = 7.0$, $p = .01$. If alpha were adjusted to

protect against Type I error using a Bonferroni correction (i.e., α =.05/22 = .002), then none of the predictors would be considered statistically significantly related to baseline EF CS.

Exploratory analyses. The relationships between EF CS component scores (i.e., D-KEFS TMT-NL, D-KEFS CWI-I, D-KEFS VF, and WCST-PE) and sociodemographic and tumor- and treatment-related characteristics were independently examined.

D-KEFS TMT-NL. Baseline D-KEFS TMT-NL scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, seizures, tumor pathology, tumor location, surgery type, RT type, or AED use, all *p*s > .05. Conversely, tumor side, chemotherapy use, and steroids were significantly related to baseline D-KEFS TMT-NL scores. Specifically, patients with tumors on the right side (M = 54.43, SD = 4.51) performed significantly better on baseline D-KEFS TMT-NL than patients with tumors on the left side (M = 45.36, SD = 12.05), $F_{(1, 49)} = 12.00$, $p = .001$. The difference between baseline D-KEFS TMT-NL scores for patients with central tumors versus patients with left- or right-sided tumors was not statistically significantly different. Patients who did not receive chemotherapy during the study (M = 53.73, SD = 5.86) performed significantly better on baseline D-KEFS TMT-NL than patients who would later receive chemotherapy (M = 47.37, SD = 11.53), $F_{(1, 50)} = 5.61$, $p = .022$. Patients who did not receive steroids at any point during the study (M = 53.15, SD = 5.94) performed significantly better on baseline D-KEFS TMT-NL than patients who received steroids at some point during the study (M = 46.72, SD = 12.31), $F_{(1, 50)} = 5.89$, $p = .019$. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., α =.05/22 = .0023), then only patients with right-sided tumors would still have statistically significantly higher baseline D-KEFS TMT-NL scores than patients with left-sided tumors.

D-KEFS CWI-I. Baseline D-KEFS CWI-I scores were not statistically significantly related to age, years of education, gender, race/ethnicity, KPS, seizures, tumor pathology, tumor location, surgery type, RT type, chemotherapy use, steroids use, or AED use, all *p*s > .05. Conversely, marital status and tumor side were significantly related to baseline D-KEFS CWI-I scores. Specifically, unmarried patients (M = 58.82, SD = 5.19) performed significantly better on baseline D-KEFS CWI-I than married patients (M = 51.39, SD = 9.76), $F_{(1, 40)} = 5.73$, $p = .021$. Patients with tumors on the right side (M = 56.27, SD = 6.30) performed significantly better on baseline D-KEFS CWI-I than patients with tumors on the left side (M = 53.33, SD = 20.31), $F_{(1, 39)} = 5.41$, $p = .025$. The difference between baseline D-KEFS CWI-I scores for patients with central tumors versus patients with left- or right-sided tumors was not statistically significantly different. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., $\alpha = .05/22 = .0023$), then neither of the predictors would be considered statistically significantly related to baseline D-KEFS CWI-I.

D-KEFS VF. Baseline D-KEFS VF scores were not statistically significantly related to age, years of education, gender, race/ethnicity, marital status, KPS, tumor pathology, tumor location, surgery type, all *p*s > .05. Conversely, tumor side, seizures, RT type, chemotherapy use, steroids use, and AED use were related to baseline D-KEFS VF scores. Specifically, patients with tumors on the right side (M = 59.35, SD = 8.53) performed significantly better on baseline D-KEFS VF than patients with tumors on the left side (M = 52.04, SD = 15.02), $F_{(1, 50)} = 4.23$, $p = .045$. The difference between baseline D-KEFS VF scores for patients with central tumors versus patients with left- or right-sided tumors was not statistically significantly different. Patients who did not report a seizure(s) at any point during the study (M = 59.35, SD = 11.41) performed significantly better on baseline D-KEFS VF than patients who reported a seizure(s) at

some point during the study (M = 51.73, SD = 13.87), $F_{(1, 51)}$ = 4.81, p = .033. Patients who would later receive proton beam RT (M = 62.43, SD = 10.97) performed significantly better on baseline D-KEFS VF than patients who would later receive IMRT (M = 53.95, SD = 12.96), $F_{(1, 51)}$ = 4.75, p = .034. Patients who did not receive chemotherapy during the study (M = 60.41, SD = 8.76) performed significantly better on baseline D-KEFS VF than patients who would later receive chemotherapy during the study (M = 53.19, SD = 14.62), $F_{(1, 51)}$ = 4.26, p = .044. Patients who did not receive steroids at any point during the study (M = 61.59, SD = 9.76) performed significantly better on baseline D-KEFS VF than patients who received steroids at some point during the study (M = 50.58, SD = 13.57), $F_{(1, 51)}$ = 11.57, p = .001. Finally, patients who did not receive AED at any point during the study (M = 59.88, SD = 8.54) performed significantly better on baseline D-KEFS VF than patients who received AED at some point during the study (M = 52.89, SD = 15.27), $F_{(1, 51)}$ = 4.09, p = .048. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., α =.05/22 = .0023), then only steroid use would still be considered statistically significantly related to baseline D-KEFS VF.

WCST-PE. Baseline WCST-PE scores were not statistically significantly related to age, years of education, gender, race/ethnicity, tumor pathology, tumor location, surgery type, or steroids use, all ps > .05. Conversely, marital status, seizures, KPS, tumor side, RT type, chemotherapy use, and AED use were related to baseline WCST-PE performance. Specifically, unmarried patients (M = 57.82, SD = 14.48) performed significantly better on baseline WCST-PE than married patients (M = 47.68, SD = 8.75), $F_{(1, 43)}$ = 7.96, p = .007. Patients who did not report a seizure(s) at any point during the study (M = 53.58, SD = 12.07) performed significantly better on baseline WCST-PE than patients who reported a seizure(s) at some point during the study (M = 46.24, SD = 8.71), $F_{(1, 43)}$ = 5.34, p = .026. Patients' KPS scores were significantly

positively related to baseline WCST-PE performance, $\beta = .70$, $F_{(1, 43)} = 6.05$, $p = .018$; better KPS scores were related to better baseline WCST-PE performance. Patients with centrally located tumors ($M = 67.75$, $SD = 11.44$) performed significantly better on baseline WCST-PE than patients with tumors on either the left or right side ($M = 48.44$, $SD = 9.65$), $F_{(1, 42)} = 14.74$, $p < .001$. The difference between baseline WCST-PE scores for patients with left-sided tumors versus right-sided tumors was not statistically significant; of note, only four patients had centrally located tumors. Patients who would later receive proton beam RT ($M = 55.38$, $SD = 12.22$) performed significantly better on baseline WCST-PE than patients who would later receive IMRT ($M = 48.03$, $SD = 10.13$), $F_{(1, 43)} = 4.32$, $p = .044$. Patients who did not receive chemotherapy at any point during the study ($M = 54.78$, $SD = 13.52$) performed significantly better on baseline WCST-PE than patients who would later receive chemotherapy during the study ($M = 47.07$, $SD = 8.15$), $F_{(1, 43)} = 5.70$, $p = .021$. Finally, patients who did not receive AED at any point during the study ($M = 54.68$, $SD = 13.25$) performed significantly better on baseline WCST-PE than patients who received AED at some point during the study ($M = 46.85$, $SD = 8.10$), $F_{(1, 43)} = 6.04$, $p = .018$. If alpha were adjusted to protect against Type I error using a Bonferroni correction (i.e., $\alpha = .05/22 = .0023$), then only tumor side (central versus left/right) would still be considered statistically significantly related to baseline WCST-PE.

4.3 FACT-Br and Executive Functioning Over Time

FACT-Br. Over the course of the study, FACT-Br total scores ranged from 77 to 189 (possible range: 0 to 200). Table 2 reports the means and standard deviations of FACT-Br total scores and subscale scores as well as the number of patients with below average total scores at each time point. As previously noted, at baseline, six patients had below average FACT-Br total scores (11.3%); at three-month follow-up and six-month follow-up, five patients had below

average scores (5.8%); and at 12-month follow-up, three patients had below average scores (9.1%). The covariates model (model 2) fit the data better than the intercept only model (model 1). However, there was no evidence to suggest a FACT-Br total score trend (linear, quadratic, or cubic) over time, all *p*s > .05, controlling for RT type, seizures, and steroids. See Table 6 for model comparisons. Figure 2 provides multiple visual representations of FACT-BR total scores over time (a. spaghetti plot, b. magnified spaghetti plot, and c. line graph).

Exploratory analyses. Individual LME models were run for each of FACT-Br subscales: PWB, SWB, EWB, FWB, and BrCS. Model comparison results are reported in Tables 7 – 11 respectively, and visual representations of each of the subscale scores over time (a. spaghetti plot and b. line graph) are presented in Figures 3 – 7, respectively.

Over the course of the study, PWB scores ranged from 2 to 28 (possible range: 0 to 28). For the PWB subscale, although tumor location (frontal versus temporal, parietal, or cerebellar tumors) was significantly related to PWB at baseline, LME model comparison between an intercept only model and a model with the full set of orthogonal contrast codes for tumor location revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location was removed from the subsequent LME models predicting PWB scores over time. Allowing for the linear trend, there was a significant quadratic trend of PWB scores over time, simple slope = -0.68 + 2(0.06)Months. PWB scores declined from baseline to three-month follow-up and from three-month follow-up to six-month follow-up but improved from six-month follow-up to 12-month follow-up, on average.

Over the course of the study, SWB scores ranged from 8 to 28 (possible range: 0 to 28). For the SWB LME models, although tumor location (temporal or parietal versus cerebellar tumors) was significantly related to SWB at baseline, LME model comparison between an

intercept only model and a model with the full set of orthogonal contrast codes for tumor location revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location was removed from the subsequent LME models predicting SWB over time. There was no evidence to suggest a SWB trend (linear, quadratic, or cubic) over time, all *p*s > .05.

Over the course of the study, EWB scores ranged from 3 to 24 (possible range: 0 to 24). For the EWB LME models, although tumor location and RT type were significantly related to EWB at baseline, LME model comparisons between an intercept only model and a model with the full set of orthogonal contrast codes for tumor location and a separate LME model with RT type revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location and RT type were removed from the subsequent LME models predicting EWB over time. There was no evidence to suggest a EWB trend (linear, quadratic, or cubic) over time, all *p*s > .05

Over the course of the study, FWB scores ranged from 4 to 28 (possible range: 0 to 28). For the FACT-Br FWB LME models, the initial covariates LME model (including steroids, RT type, and the full set of orthogonal codes for tumor pathology) did not fit the data better than the intercept only model. Individual LME models revealed that only steroid use was a significant predictor of FWB subscale scores over time. Therefore, RT type and tumor pathology were removed from the subsequent LME models predicting FWB over time. There was no evidence to suggest a FWB trend (linear, quadratic, or cubic) over time, all *p*s > .05.

Over the course of the study, BrCS scores ranged from 24 to 89 (possible range: 0 to 92). The covariates model (model 2) fit the data better than the intercept only model (model 1);

however, there was no evidence to suggest a BrCS trend (linear, quadratic, or cubic) over time, all *p*s > .05, controlling for RT type, seizures, steroids, and chemotherapy.

Executive Functioning. EF CS scores ranged from 20 to 69 (possible range: 20 to 80). Table 4 reports the means and standard deviations of EF CS and component scores as well as the number of patients with mildly or moderately impaired EF at each time point. As previously noted, at baseline, two patients had impaired EF (3.78%). At three-month follow-up, three patients had impaired EF (7.5%); at six-month follow-up, one patient had impaired EF (2.5%); and at 12-month follow-up, no patients had impaired EF. The LME model comparisons for EC CS are reported in Table 12. Controlling for marital status, tumor side, seizures, chemotherapy, AED, and steroids use and allowing for the linear and quadratic trends, there was a significant cubic trend of EF CS over time, simple slopes = -1.53 + 2(0.42)Months + 3(-0.03)Months^2. As seen in Figure 8c, initially, the relationship between time and EC CS was negative; however, at three-month follow-up, this relationship became positive, and then between six-month follow-up to 12-month follow-up the relationship became slightly negative/flat, on average, controlling for marital status, tumor side, seizures, chemotherapy, AED, and steroids use.

Exploratory analyses. Individual LME models were run for each of EF CS component scores: D-KEFS TMT-NL, D-KEFS CWI-I, D-KEFS VF, and WSCT-PE. Model comparison results are reported in Tables 13 – 16 respectively, and visual representations of each of the subscale scores over time (a. spaghetti plot and b. line graph) are presented in Figures 9 – 12, respectively.

D-KEFS TMT-NL T-scores ranged from 20 to 70 (possible range: 20 to 80). Controlling for tumor side, chemotherapy, and steroid use and allowing for the linear trend, there was a quadratic trend of D-KEFS TMT-NL T-scores over time, simple slope = 0.85 + 2(-0.06)Months.

As seen in Figure 9c., D-KEFS TMT-NL T-scores improved from baseline to three-month follow-up and from three-month follow-up to six-month follow-up but declined from six-month follow-up to 12-month follow-up, on average, controlling for tumor side, chemotherapy, and steroid use.

D-KEFS CWI-I T-scores ranged from 20 to 67 (possible range: 20 to 80). Controlling for marital status and tumor side and allowing for the linear and quadratic trends, there was a significant cubic trend of D-KEFS CWI-I over time, simple slopes = -2.57 + 2(0.61)Months + 3(-0.3)Months^2. As seen in Figure 10c, initially, the relationship between time and D-KEFS CWI-I T-scores was negative, at 3-month follow-up, this relationship then became positive, and then between 6-month follow-up to 12-month follow-up the relationship became slightly negative/flat, on average, controlling for marital status and tumor side.

D-KEFS VF T-Scores ranged from 20 to 80 (possible range: 20 to 80). The covariates model (model 2) fit the data better than the intercept only model (model 1); however, there was no evidence to suggest a D-KEFS VF T-Score trend (linear, quadratic, or cubic) over time, all *p*s > .05, controlling for RT type, tumor side, seizures, chemotherapy, steroid use, and AED use.

WCST-PE T-Scores ranged from 20 to 80 (possible range: 20 to 80). The covariates model (model 2) fit the data better than the intercept only model (model 1); however, there was no evidence to suggest a WCST-PE T-Scores trend (linear, quadratic, or cubic) over time, all *p*s > .05, on average, controlling for marital status, tumor side, seizures, chemotherapy, RT type, AED use, and KPS scores.

4.4 Causal Pathways between FACT-Br Total Scores and Executive Functioning Composite Scores Over Time

The originally specified cross-lagged panel model did not fit the data well statistically nor descriptively (χ^2 [12, N = 53] = 52.12, p < .001, CFI = .86, RMSEA = .25, SRMR = .21). Modification indices suggested adding second-order auto-regressive paths (e.g., baseline EF CS predicting six-month follow-up EF CS in addition to predicting three-month follow-up EF CS). This cross-lagged panel model did not fit the data well statistically (χ^2 [8, N = 53] = 22.42, p = .004) but did fit the data well descriptively (CFI = .95, RMSEA = .18, SRMR = .06). The final cross-lagged panel model with standardized estimates is presented in Figure 13. Figure 14 presents only the significant pathways, p < .05, with standardized estimates. FACT-Br total scores were relatively stable over time demonstrated by each of the autoregressive paths significantly predicting the next variable. Higher FACT-Br total scores at baseline predicted higher FACT-Br total scores at three months (β = .80, p < .001); higher FACT-Br total scores at three-month follow-up predicted higher FACT-Br total scores at six-month follow-up (β = .81, p < .001); higher FACT-Br total scores at six-month follow-up predicted higher FACT-Br total scores at 12-month follow-up (β = .45, p = .02). The second-order FACT-Br total scores auto-regressive paths were not significant, ps > .05. EF CS scores, however, were less stable. Higher baseline EF CS scores predicted higher EF CS scores at three-month follow-up (β = .84, p < .001) and at six-month follow-up (β = .59, p < .001). Higher EF CS scores at three-month follow-up predicted higher EF CS scores at six-month follow-up (β = .36, p = .002) and at 12-month follow-up (β = .59, p < .001). EF CS scores at six-month follow-up were not predictive of EF SC scores at 12-month follow-up, p = .10. The non-directional, zero-order correlation between FACT-Br total scores and EF CS at baseline was r = .33, p = .007, indicating a moderate, positive correlation. The residual association between FACT-Br total scores and EF SC at three-month follow-up was non-significant, p = .60. The residual associations between

FACT-Br total scores and EF SC at six-month follow-up was $r = .44$, $p = .002$. The residual associations between FACT-Br total scores and EF SC at 12-month follow-up was $r = .43$, $p = .006$. This is consistent with bivariate correlations between FACT-Br total scores and EF CS (see Table 17). In terms of statistically causal (i.e., cross-lagged) pathways, there was one significant pathway between EF CS scores at six-month follow-up to FACT-Br total scores at 12-month follow-up; better EF CS performance at six-month follow-up was predictive of better FACT-Br total scores at 12-month follow-up ($\beta = .24$, $p = .049$). The results of this dissertation are being prepared for publication.

Publications based on this dissertation will be co-authored by Carrie McDonald, Jona Hattangadi-Gluth, and Vanessa L. Malcarne. The dissertation author was the primary investigator and author of this material.

CHAPTER 5: DISCUSSION

Maintaining adequate health-related quality of life has been identified as a top priority when treating patients with brain tumors (NCCN, 2016). However, it has been noted that there is often a difficult tradeoff between extending patients' lives and maintaining their health-related quality of life (Dirven et al., 2014b). Cognitive dysfunction is highly prevalent among patients with brain tumors and has been correlated with lower health-related quality of life, even when the brain tumor has been adequately controlled (Bartolo & Springhetti, 2019). Difficulties with EF are one of the most commonly reported types of cognitive dysfunction, and EF difficulties, in particular, have the potential to negatively impact health-related quality of life.

Yet, among adults with brain tumors, little has been known about what factors influence health-related quality of life (Baker et al., 2015) and EF (Scoccianti et al., 2012), the trajectories of health-related quality of life and EF overtime, and potential causal relationships between health-related quality of life and EF. This lack of information has limited clinical decision making, the delivery of well-timed interventions to the patients who may need them the most, and the ability to provide patients with desired information about their potential trajectories. The present study intended to assist with filling these gaps by addressing three important questions regarding health-related quality of life and EF among adults with brain tumors: 1) What patient, tumor, and treatment characteristics are associated with health-related quality of life and EF prior to the start of RT?, 2) What are the trajectories of health-related quality of life and EF from diagnosis to one year after the completion of RT?, 3) Are health-related quality of life and EF causally related to one another, and if so, when?

5.1 Health-Related Quality of Life and Executive Functioning Prior to Radiation Therapy

Patients' first assessment in this study took place after any surgical intervention that was clinically indicated and before the start of RT. Patients in this study, which was conducted in an urban, National Cancer Institute-designated Comprehensive Cancer Center, were primarily middle-aged, married, well-educated White men and women. On average, they had comparable physical, social, emotional, and functional wellbeing and fewer brain tumor-specific concerns relative to a published sample of patients with brain tumors (Weitzner et al., 1995), with six patients in this study reporting below average health-related quality of life compared to other brain tumor patients (i.e., six patients in this study had FACT-Br total scores below 110, which were one standard deviation below the mean of a published, normative sample of brain tumor patients). Compared to patients with other cancer types and the general population (Brucker et al., 2005), patients in this sample had average physical, social, emotional, and functional wellbeing (using baseline averages for this sample, T-scores ranged from 46 to 55.7 compared to the U.S. general population and 48.4 to 54.5 compared to patients with a variety of cancers).

With regard to EF, on average, patients in this sample performed better than expected on set-shifting, cognitive flexibility, and verbal inhibition as measured by the DKEFS VF and DKEFS CWI-I, compared to what would be expected in the general population (i.e., fewer patients scored in the impaired range than would be expected in the general population). Conversely, more patients in this sample demonstrated impairments in concentration, attention, cognitive flexibility, and executive control, as measured by the DKEFS TMT NL and WCST PE, compared to what would be expected in the general population (i.e., more patients scored in the impaired range than would be expected in the general population). Overall, patients in this sample primarily performed in the average range across measures of EF (EF CS average T-scores at baseline ranged from 50.06 to 56.19).

In sum, this sample was high functioning at baseline, including average reported health-related quality of life and better EF performance than would be expected based on previous research with patients with various types of brain tumors (D'Angelo et al., 2011; Liu et al., 2009; van Kessel et al., 2017). Additionally, at baseline, 94.3% of the sample was capable of normal activity and exhibited few symptoms or signs of disease (KPS score ≥ 90).

5.2 Correlates of Health-Related Quality of Life and Executive Functioning at Baseline

At baseline, patients with different individual, tumor, and treatment characteristics exhibited differences in health-related quality of life and EF. With regard to health-related quality of life, based on previous research (Baker et al., 2015), it was hypothesized that lower KPS, having a high-grade glioma (versus low-grade glioma or other type of tumor; tumor pathology), steroid use, and receiving no surgery or a biopsy only (versus STR or GTR; surgery type) would be related to lower health-related quality of life (as measured by FACT-Br total scores) at baseline. Nearly all of the findings were inconsistent with the hypotheses. Specifically, KPS, surgery type and tumor pathology were not statistically significantly related to health-related quality of life, as measured by FACT-Br total scores. Patients who received steroids reported lower health-related quality of life, as measured by FACT-Br total scores, which was the only fully supported *a priori* hypothesis.

Further examining the subdomains of health-related quality of life, patients who received steroids reported more functional and brain-cancer-specific concerns (e.g., difficulty sleeping, memory and thinking difficulties). Tumor pathology was not statistically significantly related to health-related quality of life as measured by FACT-Br total scores; however, patients with high-grade gliomas reported more functional concerns (lower FWB) than patients with low-grade gliomas or other tumors. Thus, the hypothesis that tumor pathology would be related to health-

related quality of life was partially supported. Furthermore, patients who would later receive IMRT (versus proton beam RT) reported lower overall health-related quality of life (as measured by the FACT-Br total score, EWB, FWB, and BrSC scores). Patients who reported seizures at some point during the study reported lower overall health-related quality of life, which was driven by more brain-cancer-specific concerns. "I have had seizures" and "I am afraid of having a seizure" are items on the BrCS; thus, it is unsurprising that reporting seizures was related to health-related quality of life. The exploratory analyses of the subdomains of health-related quality of life also showed patients who received chemotherapy at some point during the study reported more brain-tumor-specific concerns (e.g., frustration about functional limitations) and patients with tumors in varying locations also had differences in baseline health-related quality of life subdomains. Specifically, patients with temporal, parietal, or cerebellar tumors reported more physical concerns than patients with frontal tumors; patients with cerebellar tumors reported more social concerns than patients with temporal or parietal tumors; and patients with frontal, temporal, parietal, or cerebellar tumors had more emotional concerns (e.g., dissatisfaction with coping, fear of death) than patients with tumors at "other" locations (i.e., suprasellar, sphenoid wing, cavernous sinus, or base of skull). However, given the number of comparisons examined, false positive associations are highly likely; thus, findings should be interpreted with caution. Indeed, when considering a Type I error correction, none of the above findings were considered statistically significant.

Liu et al. (2009) proposed a model of health-related quality of life based on a variety of patient, tumor, and treatment factors. However, based on the findings from this study, support for most of these factors was not established. Indeed, no demographic patient factors were related to health-related quality of life. This finding adds to mixed results in the literature with regard to

the relationships between patient factors (e.g., gender, education, and marital status) and health-related quality of life (Baker et al., 2015; Bergo et al., 2015). The presence of seizures was the only patient factor related to lower health-related quality of life. Interestingly, AED use over the course of the study was not statistically significantly related to health-related quality of life at baseline. All patients who reported seizures received AEDs as well as six patients who did not report seizures and who were prescribed AEDs presumably prophylactically. Tumor factors (i.e., pathology, location, and side) were also not statistically significantly related to overall health-related quality of life. However, in this study, tumor factors may have been better captured by "treatment factor" groupings. For example, the type of RT the patient would later receive was related to baseline health-related quality of life. Because, at baseline, patients had yet to receive RT, this is not actually a treatment factor indicator and likely implies more about tumor characteristics. IMRT is typically used for patients with large malignant tumors or multiple tumors, whereas proton beam RT is typically used for patients with small, deep-seated tumors (American Brain Tumor Association, 2014). In this sample, RT type may have been a better differentiating factor than the tumor pathology or location categories, which were not related to overall health-related quality of life (as measured by the FACT-Br total score). The clinical judgment to decide which RT type a patient should receive likely requires the integration of multiple tumor and patient factors, and, thus, is likely serving as a more sensitive differentiating characteristic than individual patient and tumor factors alone. It should also be noted that brain tumor molecular subtype, which may have provided a more complete understanding of tumor pathology than grade and tissue type, and RT propensity score matching were not examined in this study. (As noted above, tumor pathology and tumor location were related to functional wellbeing, and physical, social, and emotional wellbeing, respectively, but not health-related

quality of life as measured by the FACT-Br total score.) Given the small number of patients who received proton beam RT versus IMRT (14 versus 39, respectively) and the notable imbalance between the two groups, this finding should be interpreted cautiously, and replication studies are needed. However, these findings suggest that although RT is not the cause for the difference in health-related quality of life, patients who are scheduled to receive IMRT may exhibit more health-related quality of life concerns, and, therefore, they may benefit from further health-related quality of life assessment and potentially intervention.

An additional treatment factor that was related to health-related quality of life at baseline was steroid use. Approximately half of the patients in this sample were on steroids at some point during this study. Patients who received steroids were likely on steroids at baseline in order to treat edema caused by the brain tumor and/or surgery. However, some patients may not have been on steroids at baseline. Therefore, steroids, like RT type, could potentially be more of a proxy indicator for another factor or collection of factors, including the reason the steroids were prescribed, often edema. Given the limited number of factors that were related to health-related quality of life at baseline, steroid use may deserve greater attention. Indeed, steroids may serve as a potentially helpful clinical indicator to identify patients with lower health-related quality of life who may be in need of intervention. For example, when a patient is prescribed steroids, that may be a good time to screen for health-related quality of life concerns. Patients prescribed steroids may benefit from being monitored for health-related quality of life concerns and possibly offered health-related quality of life interventions when available and appropriate. Length of time on steroids, steroid dose, and date of initiation of steroids were not collected for this study. A cleaner measure of steroid use, with additional information regarding initiation of

steroids, length of steroid use, and dose, may provide more useful information about the relationship to health-related quality of life.

An additional "treatment" factor that was related to a subcomponent of health-related quality of life was chemotherapy. Again, patients had yet to receive chemotherapy at baseline. Chemotherapy would be administered later, concomitant with RT or adjuvant after RT, and yet was related to more brain-tumor-specific concerns at baseline. Chemotherapy in this analysis likely served at a proxy measure, likely for tumor pathology (glioma versus other type of tumor). Every patient with a glioma (either high-grade or low-grade glioma), except one patient with a low-grade glioma, received chemotherapy in this study; no patients with other tumors received chemotherapy.

Liu et al.'s (2009) model provided a starting place for considering factors than may be related to health-related quality of life; however, the model may be oversimplified and lacking key factors that may be related to health-related quality of life (e.g., environmental factors; Tomey, Diez Roux, Clarke, & Seeman, 2013). Previous research has considered health-related quality of life only as a unitary construct, which may be contributing to the mixed findings in the literature. In the present study, in addition to considering health-related quality of life as a unitary construct, the subdomains of health-related quality of life were considered separately, and yielded different results. Considering health-related quality of life as a unitary construct may lead to overlooking important subdomain differences, which may limit the conclusions that are drawn and the interventions that are offered. For example, a patient with more emotional concerns would likely necessitate a different health-related quality of life intervention than a patient with more physical concerns (e.g., treatment side effects). Future research should consider the subcomponents of health-related quality of life separately. Yet, with regard to this

study and future research, considering a larger number of comparisons, such as considering the health-related quality of life subdomains separately, increases the risk of false positive findings. Further work in theory development should be conducted in order to provide a framework for hypothesis-driven examination of health-related quality of life in its full complexity, and multi-institution studies and data sharing should be utilized to further overcome the limitations related to small samples of patients with brain tumors.

Patient, brain tumor, and treatment factors were also examined in relation to EF. This study hypothesized that less education, receiving no surgery or a biopsy only (versus STR or GTR), steroid use, AED use, seizures, having a high-grade glioma, lower KPS, having a left-sided tumor, or a frontal-lobe tumor (versus other locations) would be significantly related to worse EF at baseline, and RT type, chemotherapy, marital status, gender, and race/ethnicity were not hypothesized to be statistically significantly related to EF at baseline. Age was also not hypothesized to be statistically significantly related to baseline EF because EF scores were adjusted for age prior to analysis. Some of these hypotheses were supported. Indeed, patients who had a tumor on the left side (i.e., likely the language-dominant side), experienced seizures, received AED at some point during the study, and received steroids at some point during the study exhibited worse baseline EF. Receiving chemotherapy at some point during the study and being married were not hypothesized to be related to worse EF performance at baseline; however, receiving chemotherapy at some point during the study and being married were statistically significantly related to worse EF performance at baseline. As noted above, for this baseline analysis, chemotherapy use is likely serving as a proxy for tumor pathology. Unmarried patients demonstrated better baseline EF CS performance than married patients. This finding is contrary to findings among patients with Alzheimer's disease and mild cognitive impairment,

which have linked being married with better cognitive functioning (Cerhan et al., 1998; Hakansson et al., 2009; van Gelder et al., 2006). Of note, only 14 patients in this sample were unmarried at baseline. Thus, given that this finding is opposite of what would be expected based on a related and established literature, this is likely a spurious finding due to lack of stability of the means created by small and unequal subgroup sample sizes and the possibility of capitalizing on chance via multiple comparisons.

Surprisingly, tumor location was not statistically significantly related to EF at baseline. Among the patients in this study, 30% had a frontal brain tumor. Given that EF has been so highly linked to the frontal lobes (Stuss, 2011) and frontal tumor location has been linked to EF impairments among patients with brain tumors (Hendrix et al., 2017), it is surprising that tumor location was unrelated to EF. However, EF impairments have been demonstrated in many illnesses or injuries with primary injuries outside of the frontal lobes (e.g., depression; Stuss, 2011; mild cognitive impairment; Edmonds et al., 2016). Indeed, cancers in entirely other organs have been shown to cause EF deficits (Bergo et al., 2015; Janelsins et al., 2014; Wefel et al., 2011), and EF deficits, and other cognitive dysfunctions, previously attributed to cancer treatments, primarily chemotherapy, have since been identified prior to the start of treatment (Janelsins et al., 2014). The mechanisms of these pre-treatment cognitive impairments are still largely unknown; however, DNA repair mechanisms and oxidative stress that may play a role in the development of both cancer and cognitive impairment have been posited (Janelsins et al., 2014), as well as sociodemographic (e.g., age, socioeconomic status, marital status), lifestyle (e.g., smoking, exercise, diet, sleep hygiene), psychological (e.g., stress, anxiety, depression), physiological (e.g., comorbidities, fatigue), genetic (e.g., ApoE, COMT, BDNF), and allostatic load (e.g., blood pressure, glucose metabolism, lipid metabolism, inflammation; Ahles & Hurria,

2018). Additionally, brain tumors are different from "static" or circumscribed frontal lobe focal brain lesions, where EF impairments have been well documented (e.g., McDonald, Delis, Norman, Wetter, Tecoma, & Iragui, 2005). Although not located in the frontal regions of the brain, large tumors may still exhibit mass effects on other parts of the brain (Hendrix et al., 2017; Sacks-Zimmerman, Duggal, & Liberta, 2015). Additionally, tumor location categorization in this study may not have been specific enough to be related to the type of EF being assessed in this study given that there are several regions with discrete functions within the frontal lobes (Stuss, 2011). Furthermore, slow-growing tumors may have allowed enough time for functional brain reorganization (Duffau, 2008). Moreover, there has been greater attention to distributed networks throughout the brain rather discrete functional regions when considering complex higher cognitive functioning (Catani et al., 2012). Finally, as previously noted, the small subgroup sample sizes necessitate caution when interpreting the findings. Further research is needed to solidify patterns of findings. Nonetheless, these findings suggest that tumor location should not be heavily considered during selection of tests for neuropsychological assessments of patients with brain tumors. In other words, one may reconsider the assumption that a patient with a frontal tumor will have primarily EF difficulties and instead utilize a battery of neuropsychological assessments that covers a broader array of cognitive domains.

When considering the components of the EF CS individually, there were slightly different findings. First, although not related to the EF CS, RT type was related to set-shifting, cognitive flexibility, and executive control, as measured by the D-KEFS VF and WCST-PE. Specifically, at baseline, patients who would later receive IMRT exhibited worse set-shifting, cognitive flexibility, and executive control, as measured by the D-KEFS VF and WCST-PE, than patients who would later receive proton beam RT. As noted above, because at baseline patients

had yet to receive RT, RT type is serving as a proxy measure for, likely a combination of, other characteristics. Second, although RT type was the only variable related to components of the EF CS and not overall EF CS, there was variation in how many variables were related to each component and the strength of the effects. Notably, only two characteristics (marital status and tumor side) were related to inhibition as measured by the D-KEFS CWI-I and only three characteristics (tumor side, chemotherapy use, and steroids) were related to concentration, attention, and cognitive flexibility as measured by the D-KEFS TMT NL. This suggests that the EF CS nearly captured the full range of characteristic differences. Relatedly, the multidimensional nature of EF was highlighted by the fact that each component measure of EF was not uniformly related to the same characteristics.

Interestingly, when considering the results for both Health-related quality of life and EF after a Type I error correction, two findings were particularly prominent: 1) patients who did not receive steroids had statistically significantly higher baseline set-shifting and cognitive flexibility, as measured by the DKEFS VF, than patients who received steroids, and 2) patients with right-sided tumors demonstrated statistically significantly higher baseline concentration, attention, and cognitive flexibility, as measured by the DKEFS TMT NL, than patients with left-sided tumors. Of note, on average, patients who received steroids didn't have impaired scores; their scores were average (M= 50.58, SD= 13.57). Instead, patients who did not receive steroids performed well (M= 61.59, SD= 9.76). It is possible that this was such a high-functioning sample that steroids (and the reasons why people were prescribed steroids in the first place, most often, edema) are actually hindering set-shifting and cognitive flexibility. It is unsurprising that patients with left-sided tumors exhibited EF difficulties given the high language demands of the EF tests employed. Furthermore, tumor side (left versus right, excluding the four

patients who had central tumors) was nearly evenly split in this study (i.e., the subgroups were balanced) and tumor side was not statistically significantly related to any of the other characteristics in this study (e.g., patients who received steroids were equally statistically significantly likely to have a left-sided or right-sided tumor). Thus, there is little to no reason to suspect the tumor side is serving as a proxy factor or that this finding is being influenced by statistical artifacts; tumor side is likely affecting EF.

Of note, to identify the correlates of health-related quality of life and EF at baseline, each variable was analyzed separately as an independent predictor. Yet, there is substantial overlap among predictor variables. As noted above, patients who would later receive chemotherapy all had a glioma. Patients with HHG were more likely to later receive IMRT than proton beam RT. Patients who would later receive IMRT were more likely to also receive steroids. Only one patient with an "other" type tumor reported a seizure and no patients with an "other" type tumor had surgical intervention. Additionally, because this was an observational study without randomization to any of the characteristics, we cannot infer causation. Finally, small sample sizes created unstable means and imprecise estimates. Thus, as noted above, findings should be interpreted with caution and replication studies are needed.

5.2 Health-Related Quality of Life Over Time

Health-related quality of life, on average, did not change over time. However, only 33 people completed the 12-month follow-up assessment. This was true for overall health-related quality of life, as measured by the FACT-Br total score, as well as for all of the subdomains of health-related quality of life, except physical wellbeing, which exhibited a quadratic trend. Thus, on average, patients' health-related quality of life did not fluctuate over the course of the study (i.e., from before the start of RT to 12 months after the completion of RT) from a statistical

standpoint or from a clinically meaningful standpoint (i.e., changes in FACT-Br mean total scores from time point to time point were less than 12 points). Notably, as shown in Figure 2b, some patients did exhibit fluctuations in their health-related quality of life. However, there is no clear pattern of what distinguishes those people from the rest of the sample. The sample of patients who had lower health-related quality of life at baseline relative to the rest of the sample had a mix of characteristics (e.g., age, gender, marital status, tumor type, treatment characteristics). Likewise, the sample of patients who had relatively lower health-related quality of life at the end of the study also had a mix of characteristics. Relatedly, for overall health-related quality of life (as measured by the FACT-Br total score), the study characteristics related to health-related quality of life at baseline (i.e., seizures, RT type, and steroids) improved model fit as a set when compared to the intercept only model; however, none of the characteristics was independently significantly predictive of health-related quality of life across time. In other words, seizures, RT type, and steroids did not significantly predict overall health-related quality of life across the full study. Lastly, patients who completed one assessment did not differ on baseline health-related quality of life (as measured by the FACT-Br total score) from patients who completed multiple assessments.

Of the health-related quality of life domains examined (physical, social, emotional, functional, and brain-cancer specific concerns), physical wellbeing appeared to be the most variable over the course of the study. Patients' physical wellbeing decreased from the start of the study to three-month follow-up and continued to decrease at six-month follow-up, and then at 12-month follow-up, improved beyond their baseline scores. Decline from baseline to six-month follow-up and improvement from six-month follow-up to 12-month follow-up were clinically significant changes (Yost & Eton, 2005), on average. Physical wellbeing, as assessed in this

study, included fatigue, nausea, pain, malaise, being bothered by side effects of treatment, being unable to meet the needs of one's family, and being forced to spend time in bed. Therefore, this finding suggests that patients experience and are bothered by the side effects of their treatment for up to six months following RT (i.e., early delayed effects). This is consistent with previous findings that suggest that patients typically experience early-delayed RT side effects for one to three months following the completion of RT (Butler, Rapp, & Shaw, 2006; Durand et al., 2015). Demyelination-remyelination and edema resorption have been suggested as possible reasons for the transient nature of these effects post RT (Durand et al., 2015). Thus, attention to these issues may be most important from the start of RT to six months after RT, and providers and patients may be reassured to know that, on average, patients in this study who remained in the study at 12-month follow-up, improved and surpass their baseline level of physical wellbeing one-year post RT treatment. Of note, the lowest average physical wellbeing score in this sample (i.e., 21.69 at six-months post RT) was still average compared to a larger adult cancer patient sample (T-score = 51.2) and general U.S. adult population sample (T-score = 48.7). Therefore, patients in this sample exhibited clinically meaningful decline, on average, from baseline to six-months post RT; however, their overall reported physical wellbeing, on average, remained relatively high. Additionally, missing data were considered random and patient dropout for a specific reason such as increased illness severity or death was not modeled in this study. Thus, although this analysis gives as a greater approximation of trends of the full sample over time than only considering patients with complete data, it is still limited in its ability to capture the full experience of patients who dropped out of the study.

Among all of the subdomains, in relation to all of the characteristics that were significantly related to health-related quality of life and its domains at baseline (i.e., RT type,

seizures, steroids, tumor location, tumor pathology, and chemotherapy use), steroids was the only predictor that was also statistically significant over time. Specifically, steroid use was a significant predictor of functional wellbeing over time. Across time, patients who received steroids at some point during the study reported lower functional wellbeing across the course of the study than patients who did not receive steroids during the study. As previously noted, steroid use may not be the cause of lower functional wellbeing, but it does appear to be serving as a good differentiating factor and may assist with identifying patients who may benefit from further health-related quality of life assessment and possibly intervention. Indeed, steroids are typically an immediate treatment (i.e., there is little to no delay between deciding that patient needs steroids and providing them with steroids); thus, if steroids are not the cause for the decline in functional wellbeing, but instead the underlying need for steroids is the cause, steroids may still serve as a good identifying factor for further assessment and intervention. Of note, functional wellbeing, as measured by the FACT-Br FWB subscale, is a broad construct that encompasses work ability and fulfillment, life enjoyment and contentment, illness acceptance, sleep disturbance, and the ability to engage in leisure activities. Whether there are specific aspects of functional wellbeing for patients with brain tumors that are more, or less, affected by steroid use, requires further study.

Overall, with regard to health-related quality of life, this was a high-functioning sample with generally stable average health-related quality of life over the course of the study. However, as previously mentioned, some patients did exhibit lower health-related quality of life. Future directions should assist with identifying patients with brain tumors with health-related quality of life needs throughout the course of their recovery in order to offer interventions. Interventions that have been shown to improve health-related quality of life among patients with brain tumors

include home-based psychosocial intervention and individualized acupuncture with standard rehabilitation (Pan-Weisz et al., 2019). Cognitive training has also been shown to improve health-related quality of life among non-CNS cancer patients (Kesler et al., 2013; Von Ah, Jansen, & Allen, 2014). There is also limited evidence to suggest that Acceptance and Commitment Therapy improves health-related quality of life among patients with brain tumors (Kangas, McDonald, Williams, & Smee, 2015). Given that ACT is a transdiagnostic, values-based, psychosocial treatment (Hayes, 2004), it may be a particularly good intervention to improve broad concerns, such as functional and emotional wellbeing.

5.3 Executive Functioning Over Time

EF, on average, was less stable than health-related quality of life over time. Specifically, EF, as measured by the EF CS, exhibited a cubic trend over time, with a small decrease in performance from baseline to three-month follow-up, a small increase in performance from three-month follow-up to six-month follow-up, and nearly no change from six-month to 12-month follow-up. It is unclear if these changes are clinically meaningful beyond being statistically significant. Clinically meaningful change scores for neurocognitive assessments are lacking and greatly needed (Benedict & Walton, 2012). Indeed, The American Academy of Clinical Neuropsychology has called for more empirical research to identify clinically meaningful change scores (Heilbronner et al., 2010). This work has been started with patients with multiple sclerosis (e.g., Benedict & Walton, 2012), but has yet to be conducted with patients with brain tumors or for cancer-related cognitive impairment more generally. Inhibition, as measured by the D-KEFS CWI-I, also exhibited a cubic trend over time, whereas concentration, attention, and cognitive flexibility, as measured by the D-KEFS TMT NL, exhibited a quadratic trend. Concentration, attention, and cognitive flexibility seemed to follow an inverted-U-shaped

pattern, with improvement in performance from baseline to three-month follow-up, continued improvement at six-month follow-up, and then a small decline in performance at 12-month follow-up. Again, these effects were small, and it is unclear if they would be considered clinically meaningful beyond being statistically significant.

Of the predictors that were related to EF at baseline (i.e., marital status, tumor side, seizures, chemotherapy, steroids, and AED), marital status, tumor side, and chemotherapy use remained significant independent predictors of EF over time. As previously discussed, differences in EF based on marital status may be more of an artifact of methodological issues given that the finding is in the opposite direction of what one would expect based on the well-established cognitive functioning literature and the subgroup imbalance in this study. Regarding chemotherapy use, unlike at baseline when chemotherapy had yet to occur, these findings were for EF over time. Thus, is possible that EF may have been affected by chemotherapy use; however, as discussed above tumor pathology (gliomas versus other) was confounded with chemotherapy use. Therefore, it is unclear from this analysis if EF is related to chemotherapy use, glioma versus non-glioma type tumor or both chemotherapy and tumor pathology. As discussed above, tumor side likely affected EF, both at baseline and across the course of the study. More specifically, patients with left-sided tumors were more likely to have EF difficulties than patients with right-sided tumors from pre-RT to one-year post RT.

5.4 Causal Pathways between Health-Related Quality of Life and Executive Functioning Over Time

Consistent with the patterns of health-related quality of life and EF over time discussed above, results from the cross-lagged panel model showed that health-related quality of life, on average, was relatively stable over time and EF, on average, was less stable. With regard to the

potentially causal relationships between health-related quality of life and EF, only one statistically causal pathway between health-related quality of life and EF was significant; patients' EF at six-month follow-up predicted their health-related quality of life at 12-month follow-up, controlling for previous EF performance and health-related quality of life status. In other words, patients' EF performance at six-month follow-up likely caused patients' self-reported health-related quality of life at 12-month follow-up (however, without randomization, it is not possible to determine causation).

It may be the case that EF at six-month follow-up is an early indicator of overall wellbeing and that patients' self-reported health-related quality of life doesn't reflect this until 12-month follow-up. There is evidence to suggest that the what cancer patients fear the most is diminished cognition (Ahles & Hurria, 2017). Indeed, older cancer patients largely endorse the statement, "it is more important to me to maintain my thinking ability than to live as long as possible" (as cited in Ahles & Hurria, 2017). Six-months post-RT may be a time at which patients with brain tumors are assessing how their EF is affecting their lives. Patients may be willing to accept early and delayed early changes in EF (i.e., during treatment and up-to six months after RT); however, EF difficulties persisting six months after RT may begin to affect their perceptions of their health-related quality of life. This finding provides insight into a potential window of opportunity to improve health-related quality of life via improvement in EF in the first six months after RT.

Pharmacological and non-pharmacological intervention for preserving or improving cognitive functioning among patients with brain tumors have been investigated. There is evidence, albeit limited, that pharmacological interventions (memantine or donepezil) can prevent or improve cognitive functioning among patients with brain tumors treated with RT (Day

et al., 2016; van Lonkhuizen et al., 2019). Lithium has also shown promise for preventing RT-induced cognitive impairments in rat and human brain tumor cell line models (Zhou et al, 2017). Cognitive rehabilitation has also been shown to improve cognitive impairment among adults with primary brain tumors (van Lonkhuizen et al., 2019). Indeed, a recent randomized pilot study of cognitive rehabilitation demonstrated significant improvements in EF among patients with brain tumors (Richard et al., 2019). Of note, this study allowed for patients three-months post treatment to take part in the study; however, most patients who enrolled in the study completed treatments years prior to taking part in this intervention. Thus, more research is needed to determine if cognitive rehabilitation interventions can improve EF earlier in the post-treatment phase. The above studies were not without limitations and more research is needed in the area of interventions for cognitive functioning among patients with brain tumors.

Of note, health-related quality of life and EF tended to covary at each time point, with the exception of three-month follow-up. This suggests that a possible third variable is related to both EF and health-related quality of life at baseline, six-month follow-up, and 12-month follow-up. However, the limited sample size precluded the inclusion of any additional variables, such as steroids, tumor side, or chemotherapy use.

5.5 Study Limitations and Future Directions

Study results should be interpreted in the context of the study limitations. Brain tumors are a rare disease and often leave patients too debilitated to participate in research. Thus, this sample was small and relatively high functioning. The small overall sample size created even smaller subgroups (e.g., 14 patients who received proton beam RT; 14 unmarried patients). Such small subgroups allowed for greater influence from fewer participants (i.e., less stable means). This hindered not only the generalizability of the study, but also limited the statistical analyses

that could be conducted and the power to detect true effects for the analyses that were conducted. It also introduced possible biases in the results created by imbalanced subgroups and patient dropout overtime. Of note, proportions of the characteristics of the sample were not statistically significantly different over time, suggesting a lack of systematic dropout. Yet, based on the known general course of the disease and survival rates, patients with high-grade gliomas likely dropped out due to increased illness severity or death. Additionally, this study lacked power to consider potentially important moderation effects. Furthermore, given that this was a clinically embedded study, recruitment and self-selection bias are more likely than with more formal recruitment methods, such as random sampling. Indeed, this sample lacked diversity in race/ethnicity, education, and marital status, limiting the generalizability of the results. Brain tumor are more prevalent among men and White people than women and minorities (American Cancer Society, 2019; National Cancer Institute, 2017), and this sample was a close match to the U.S. population with regard to gender. However, the sample still lacked racial/ethnic diversity as compared to be what would be expected in the general U.S. population (of note, the racial/ethnic diversity may be somewhat reflective of the specific location in which the study was conducted, i.e., La Jolla, CA, USA, and was likely further limited by the inclusion criterion of proficiency in English). Conversely, the small sample may have included too much diversity in tumor pathology and location. Additionally, as noted above, the large number of tumor types and locations necessitated grouping heterogenous tumor types and locations into groupings that may have averaged over meaningful differences, and the limited sample size precluded examining interactions. Limited sample size among studies with patients with brain tumors is a common problem (see Pan-Weisz et al., 2019).

In part to overcome the challenges of small sample sizes among studies of cognitive functioning in non-CNS cancer patients, Wefel et al. (2011) on behalf of the International Cognition and Cancer Task Force provided recommendations for harmonizing studies of cognitive functioning in patients with non-CNS cancers. These recommendations can also largely be applied to studies with patients with brain tumors. Recommendations include, when available and appropriate to the research question, longitudinal studies with repeat assessment, pretreatment cognitive assessments, the use of multiple control groups (e.g., disease specific, local health controls, and published normative data), careful consideration of inclusion and exclusion criteria, the use of psychometrically reliable and valid objective neuropsychological assessments (including but not limited to Hopkins Verbal Learning Test-Revised, TMT, and the COWA of the Multilingual Aphasia Examination), and reporting results in a way that facilitates cross-study comparisons (Wefel et al.). These recommendations were intended to increase the homogeneity of study methods, improve research design, and facilitate between-study comparisons and meta-analyses (Wefel et al.). Multi-institution collaboration (Chung et al., 2010; Wefel et al.) and home-based data collection (Ownsworth, 2016) have also been suggested as ways to overcome the issue of small sample sizes. Larger sample sizes will allow for application of advanced statistical techniques, such as cross-lagged panel model with covariates and latent profile analysis, to further understand characteristics that contribute to better and worse EF and health-related quality of life.

Conducting more harmonized studies of patients with brain tumors will also assist with the fact that, although randomization is necessary to determine causality, randomization is often not possible for many studies with patients with brain tumors, as was the case with this study. As previously noted, lack of randomization precludes further understanding of causality between

health-related quality of life and EF as well as any of the other characteristics examined (e.g., RT type). One of the primary issues with non-randomized studies is the third variable problem, which was highlighted with regard to several of the baseline findings (e.g., RT type predicting health-related quality of life prior to the start of RT). Epidemiological methods (e.g., longitudinal retrospective, prospective observational, and prospective case-control studies), further study harmonization, and meta-analytic review will allow for great possibility of determining "causality" (Salsburg, 2001).

A strength of this study is that it utilized advanced statistical techniques in order to answer the questions of interest while accounting for dependence in the data and making greater use of the full sample by utilizing maximum likelihood estimation. Yet, these methods are not without limitations. Indeed, although maximum likelihood estimation is one of the preferred methods for handling missing data (Baraldi & Enders, 2010), it still assumes that data are missing at random. The proportions of the sample characteristics from time point to time point were not statistically significantly different from one another, and health-related quality of life for patients with one assessment versus patients with assessments at multiple timepoints was not statistically different at baseline, suggesting that data may have been missing at random. However, EF performance for patients with one timepoint versus patients with multiple timepoints was statistically different at baseline, with patients who only had one assessment preforming statistically significantly worse. Furthermore, based on the known general course of the disease and survival rates, patients with high-grade gliomas likely dropped out due to increased severity of illness or death. Future studies may consider more advanced modeling techniques for missing data, a complex and burgeoning area (Baraldi & Enders, 2010). Furthermore, a general limitation of path analysis is that other path models, in addition to the *a*

priori hypothesized path model considered in the present study, may fit the data equally as well. In other words, although the cross-lagged panel model was testing theory-driven, specific hypotheses about stability of health-related quality of life and EF and about statistically causal relationships between the two constructs, other path models may fit the data as well or better than the cross-lagged panel model examined in this study. Future research should consider other theory-driven cross-lagged panel models and models that include time-varying or time-dependent covariates.

With regard to data dependence, this study chose not to utilize reliable change indices (RCI), which have been suggested to account for practice effects of repeat testing and possibly aid in reliable detection and quantification of longitudinal cognitive change (Wefel et al., 2011). Thus, declines in EF may have been underestimated in this study and observed stability may actually indicate decline. Due to the amount of data missing at various timepoints, statistical modeling methods that utilized maximum likelihood estimation allowed for greater use of data, whereas RCI that require data at each time point would have been quite limiting. Indeed, only 26 patients had complete data; thus, data from approximately half of the sample would have been unusable with the RCI method. Furthermore, LME models (Reynolds, Gatz, & Pedersen, 2002), multiple regression models (Temkin, Heaton, Grant, & Dikmen, 1999), and growth curve models (Wefel et al., 2011) are appropriate for describing patterns of change over time, and some have argued that these statistical methods may be more sensitive than RCI methods to changes in cognitive functioning over time, without the risk of overestimating declines (Wefel et al., 2011). More advanced methods, such as standardized regression-based methods (Cysique et al., 2011), may be utilized in the future.

Longitudinal studies are highly needed yet are challenging to implement. Some of the data for this study were collected in a cross-sectional way (e.g., steroid use) when they could have been collected dynamically (i.e., reassessed for each timepoint) and considered longitudinally, which would add more depth and precision to the study. Furthermore, the data for this study were collected as part of a larger, longitudinal study considering the effects of RT on cognitive functioning and included imaging in addition to neurocognitive assessment and self-report measures. Because health-related quality of life was not the primary focus of the study, health-related quality of life assessment may have been impacted. For example, the FACT-Br was only completed if the patient could complete the full neuropsychological assessment and, even then, may have been forfeited due to time constraints or patient fatigue. Future directions may consider a great focus on health-related quality of life and utilize mHealth technologies, such as ecological momentary assessment (EMA), in order to capture patients' health-related quality of life at various timepoints and in various states. This may provide a broader and more accurate assessment of patients' health-related quality of life over time.

EMA may assist with some of the main methodological issues that have been identified with regard to health-related quality of life, namely timing of assessments, missing data, and possibly selection bias by making the assessment more accessible to more patients. However, health-related quality of life will still be hindered by psychometric issues. Although researchers have agreed that health-related quality of life is an important construct and it has even become a prominent secondary endpoint in clinical trials, the construct itself lacks definition (Haas, 1999; Karimi & Brazier, 2016). Indeed, health-related quality of life patient-reported outcome measures vary greatly in their construct emphasis, with some focusing more on the psychosocial aspects of health-related quality of life (e.g., FACT-Br) and others focusing on physical

symptoms (e.g., EORTC QLQ-C30/BN-20; Mauer, Bottomley, & Taphoorn, 2008). Given this, unsurprisingly, some health-related quality of life patient-reported outcome measures only exhibit small to moderate correlations with each other when large correlations would be expected (e.g., FACT-Br and Powers Quality of Life Index; Weitzner et al., 1995). This further highlights issues with construct validity among measures of health-related quality of life. Furthermore, as new treatments for brain tumors have been created, the health-related quality of life measures have not been updated to reflect new challenges (e.g., eye and skin problems caused by immunotherapy; Dirven et al., 2018). There are also utility issues among health-related quality of life measures. Longer measures can be time consuming and difficult to complete for patients, especially people struggling with cognitive deficits or fatigue. Yet, measures with fewer items, which would be necessary with the use of EMA, are less likely to capture the multidimensional complexity of health-related quality of life (Cheng et al., 2009). Measurement refinement and consensus are of great importance for this population, especially given the difficulty obtaining lager sample sizes. Indeed, an initiative (Response Assessment in Neuro-Oncology [RANO] initiative) has been enacted and a working plan is underway to provide suggested revisions of existing patient-reported outcome measures in neuro-oncology and the development of new patient-reported outcome measures as necessary. The ultimate goal of the initiative is to ensure that high-quality patient-reported outcome evidence is available to inform research, policy, and clinical decisions (Dirven et al., 2018). Indeed, psychometric advances are necessary for moving the field forward.

In additional to the future directions discussed above, future studies should also consider monitoring patients' health-related quality of life and EF for a longer timeframe following RT. Although changes were observed during the time frame of this study, the current timeframe may

have been too short to observe the full impact of the brain tumor and brain tumor treatments on EF and health-related quality of life. Indeed, previous research among patients with low-grade gliomas has shown newly emerging differences in cognitive functioning at 12 years post completion of RT between patients who received RT and patients who did not receive RT (Douw et al., 2009). Future studies should also consider examining other risk factors for cognitive impairment (e.g., genetic risk factors, comorbid medical conditions, and other cancer-related symptoms; Wefel et al., 2011) and other factors (e.g., income, depression) that may be related to both health-related quality of life and cognitive functioning (Cramer et al., 2019).

5.6 Summary and Conclusions

Despite the noted limitations, the current study provides novel and useful information about health-related quality of life and EF in adults with brain tumors. Health-related quality of life among adults with brain tumors remains enigmatic with few study characteristics predicting health-related quality of life at baseline, no patient, treatment, or tumor characteristics independently predicting overall health-related quality of life across time, and no identified trends over time. EF exhibited more change over time; EF initially dipped at three-months post RT and then recovered to pre-RT levels, possibly representing early delayed treatment-related effects that seem to mostly dissipate by six months post-RT. Patients who received chemotherapy and who had left-sided tumors demonstrated worse EF over time than patients who did not receive chemotherapy and who had right-sided tumors. Finally, causal modeling found that EF six months after RT was predictive of health-related quality of life at one-year post RT. This finding suggests a possible window of opportunity to improve health-related quality of life via improvement in EF prior to six months. Further research is necessary to replicate these results given this small and relatively high-functioning sample; however, patients with brain

tumors who experience seizures and receive steroids prior to RT and patients with left-sided tumors should be considered for early EF interventions with the added benefit of potentially improving health-related quality of life.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Carrie McDonald, Jona Hattangadi-Gluth, and Vanessa L. Malcarne. The dissertation author was the primary investigator and author of this material.

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FIGURES

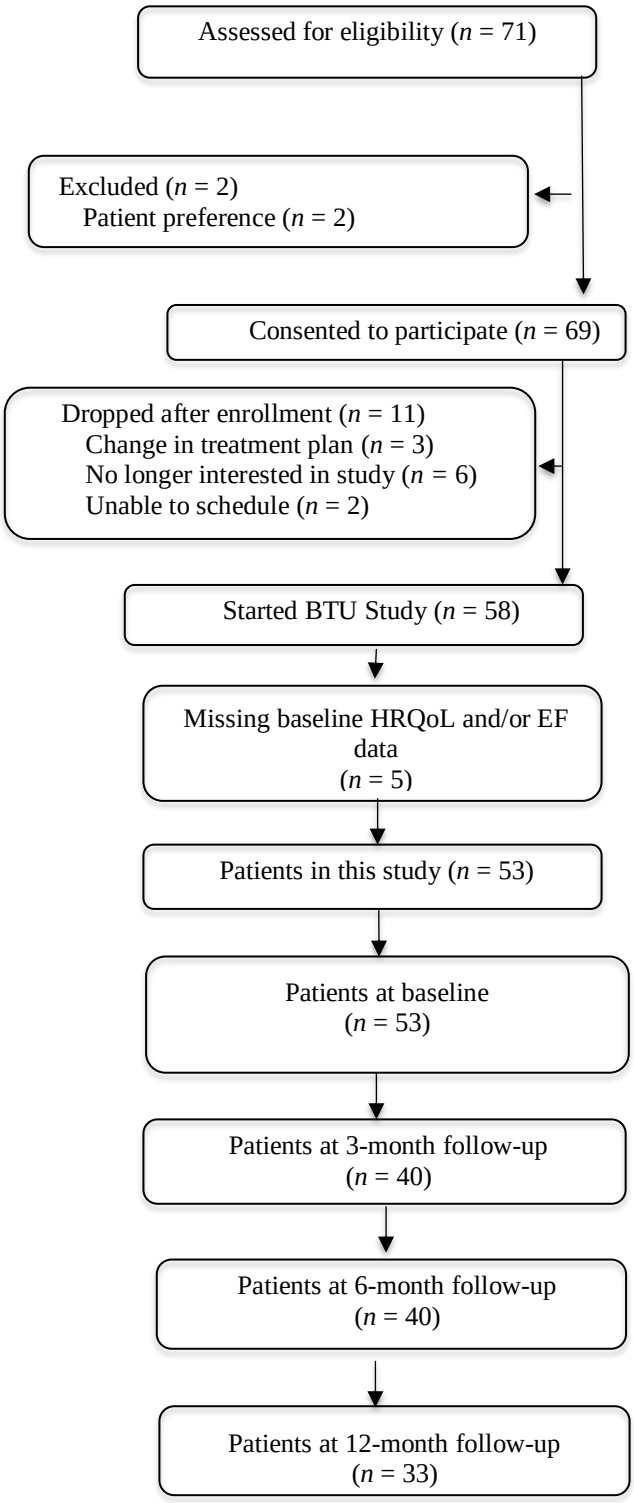


Figure 1. Screening and Enrollment Flowchart

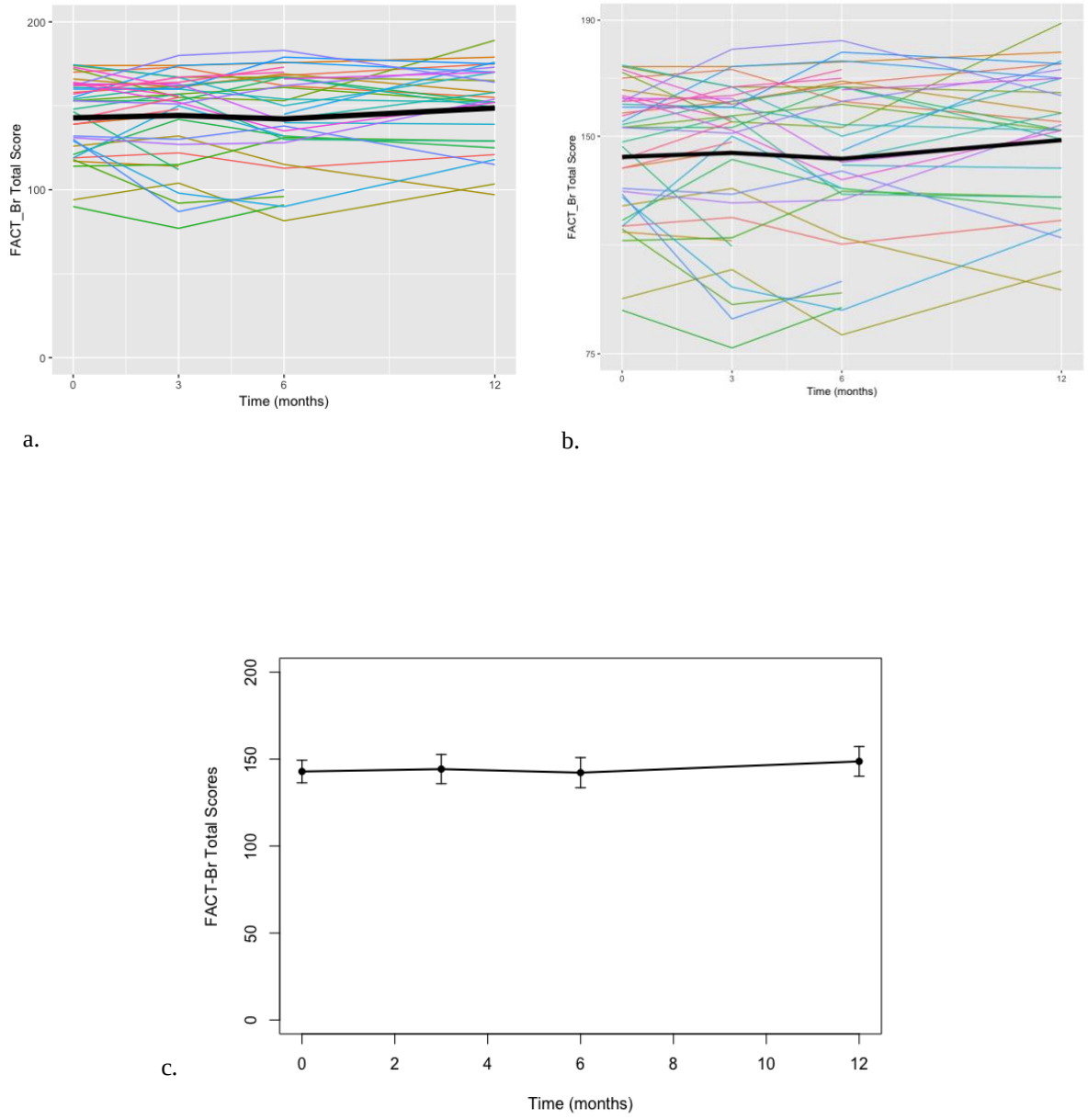
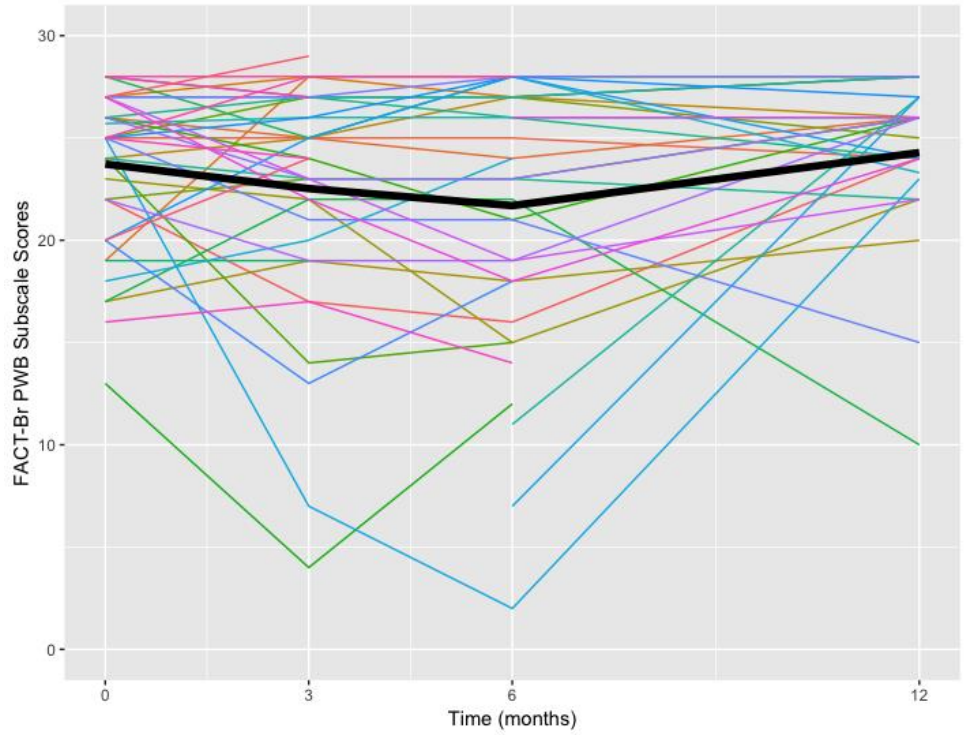


Figure 2. FACT-Br Total Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br Total Scores. b. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale altered to 75 – 200 in order to magnify plot and better represent individual lines. c. Line graph of FACT-Br total score means over time with error bars representing 95% CI.

a.



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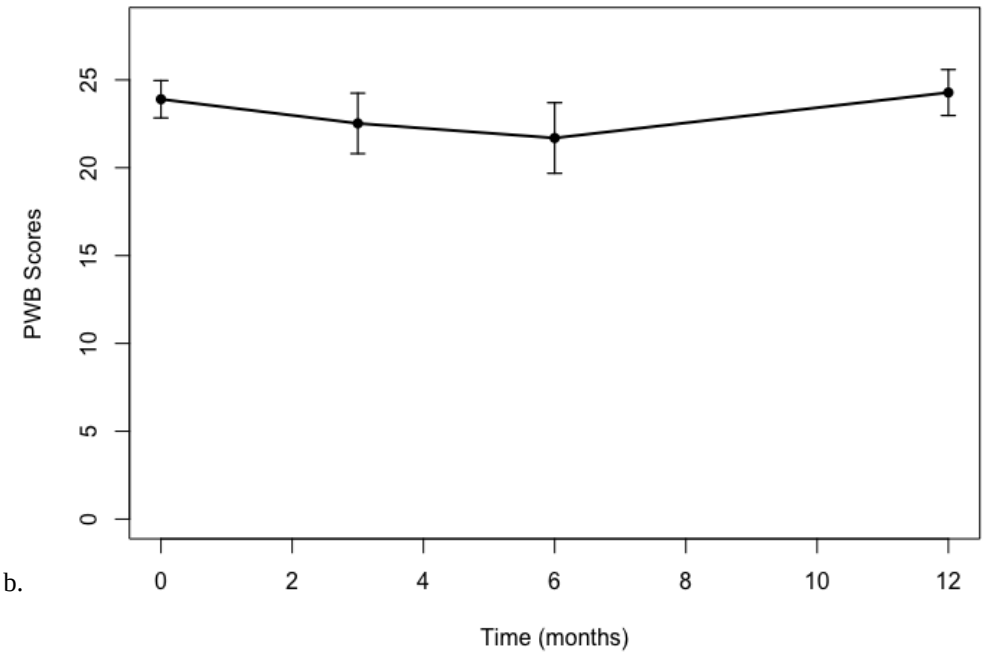
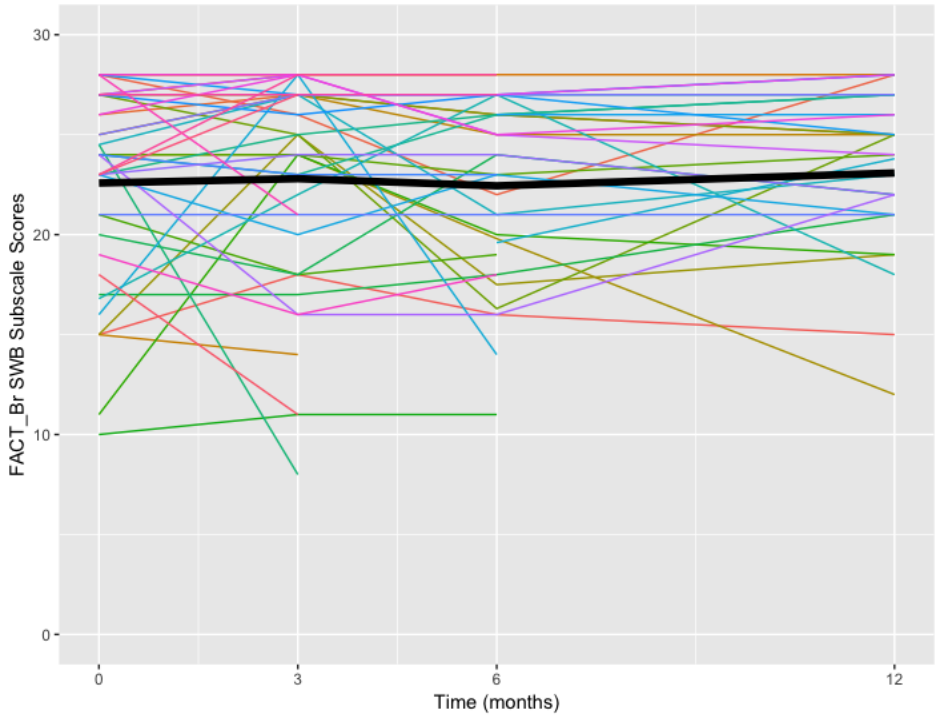


Figure 3. FACT-Br PWB Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br PWB subscale scores. b. Line graph of FACT-Br PWB means over time with error bars representing 95% CI.

a.



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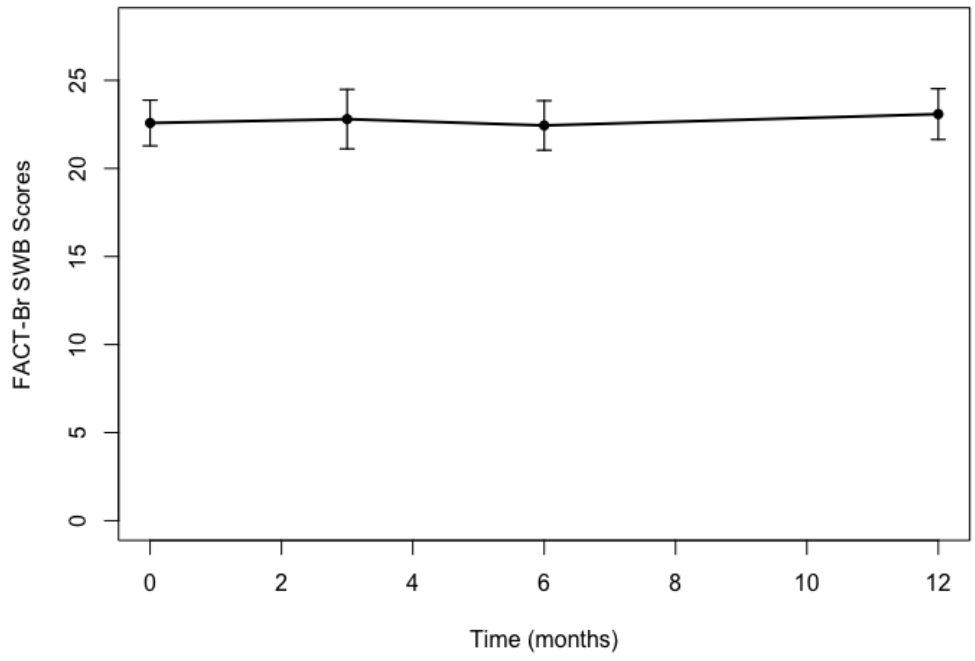


Figure 4. FACT-Br SWB Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br SWB subscale scores. b. Line graph of FACT-Br SWB means over time with error bars representing 95% CI.

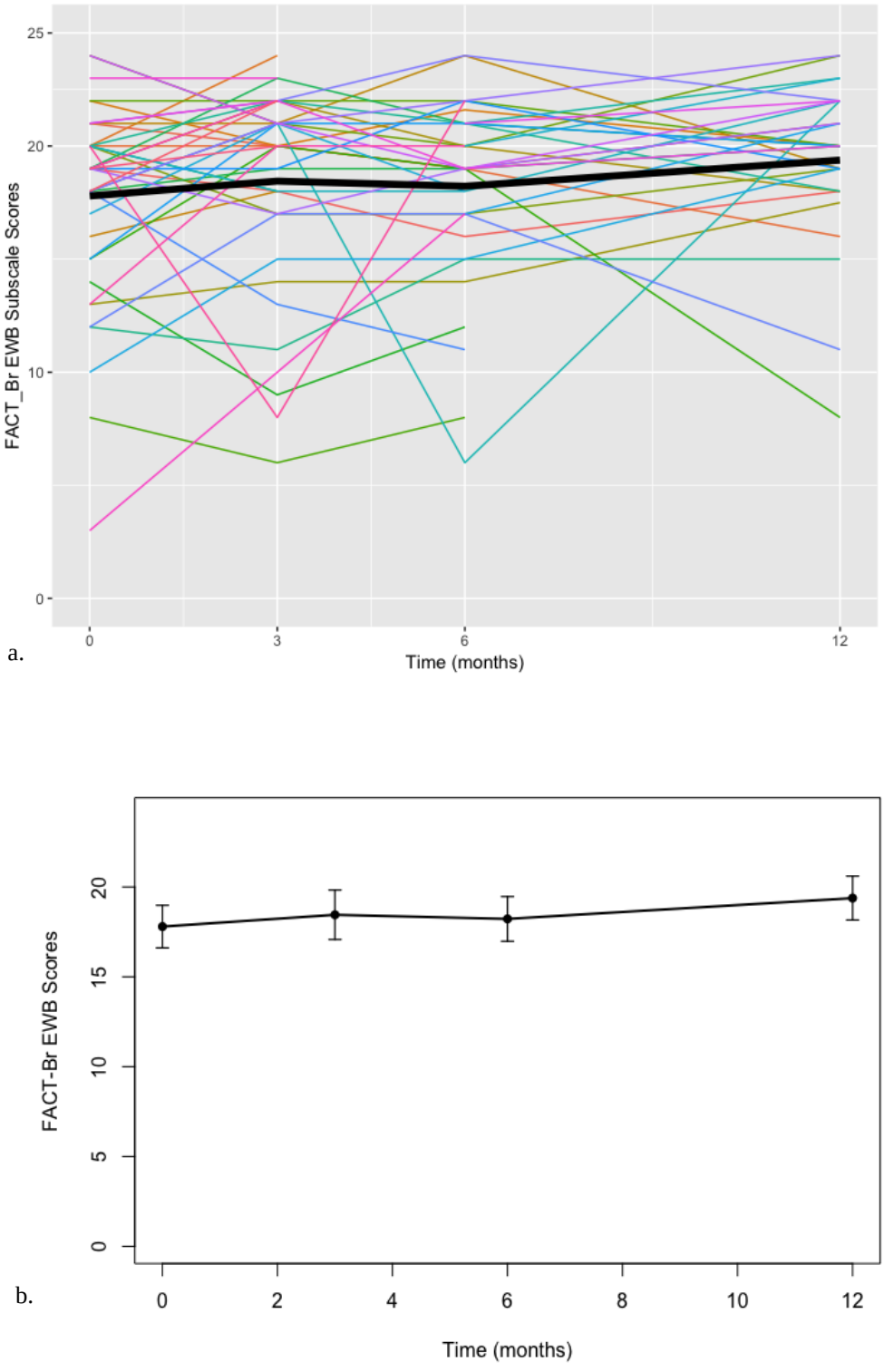
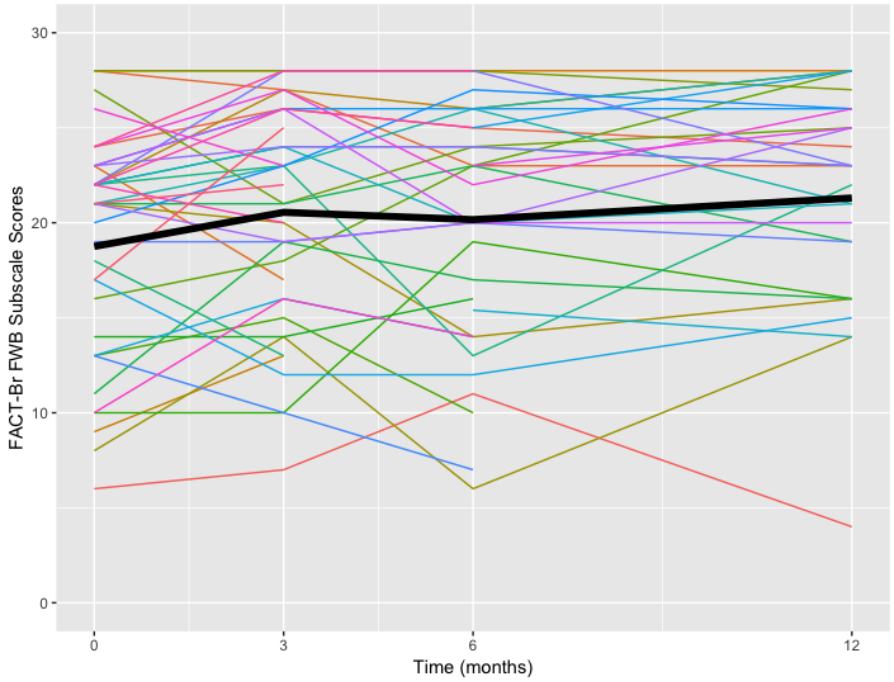


Figure 5. FACT-Br EWB Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br EWB subscale scores. b. Line graph of FACT-Br EWB means over time with error bars representing 95% CI.

a.



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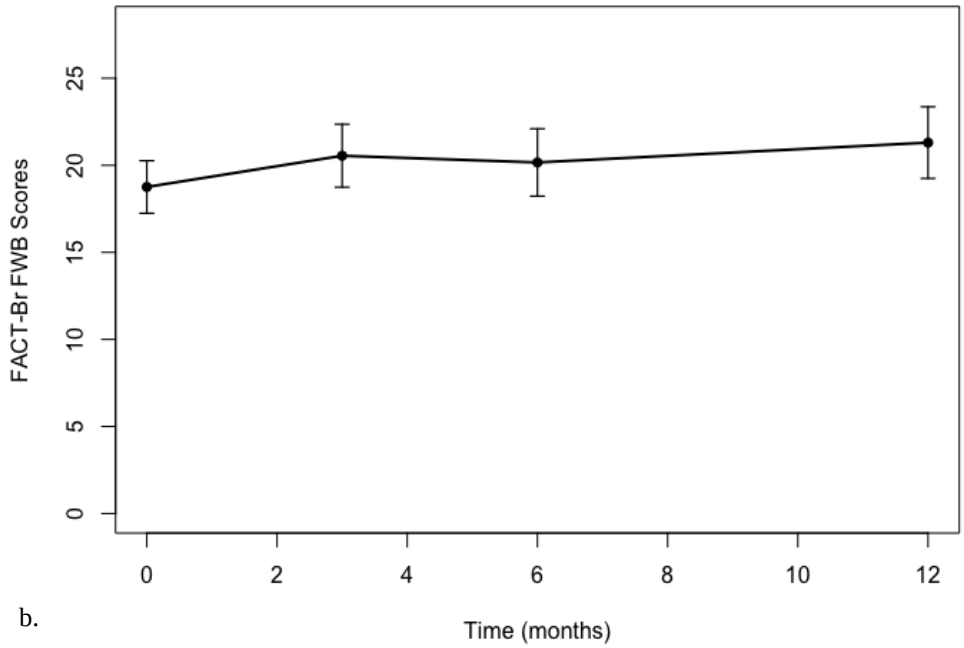
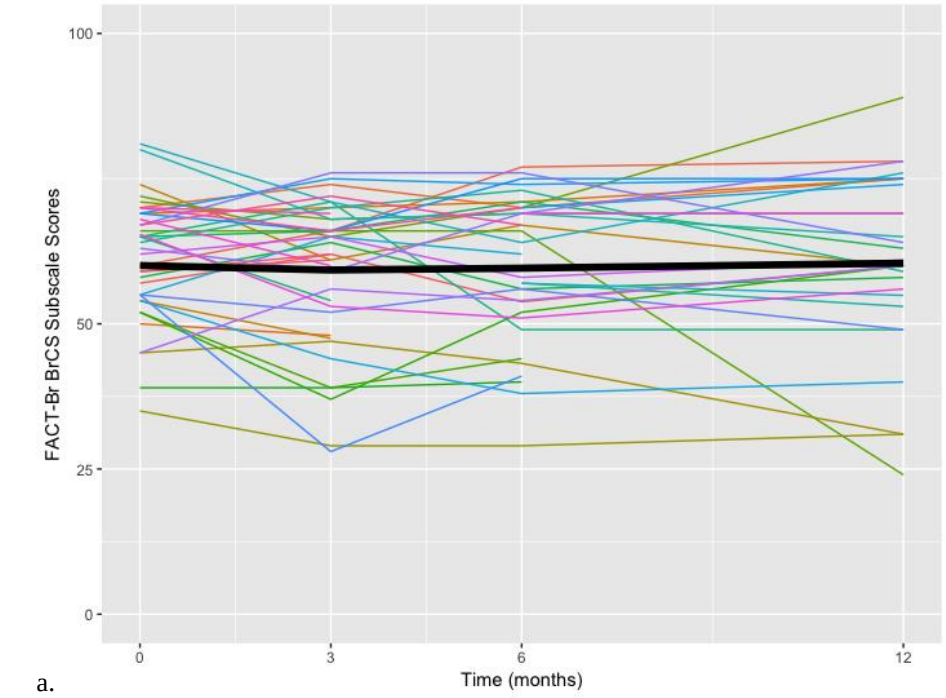


Figure 6. FACT-Br FWB Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br FWB subscale scores. b. Line graph of FACT-Br FWB means over time with error bars representing 95% CI.



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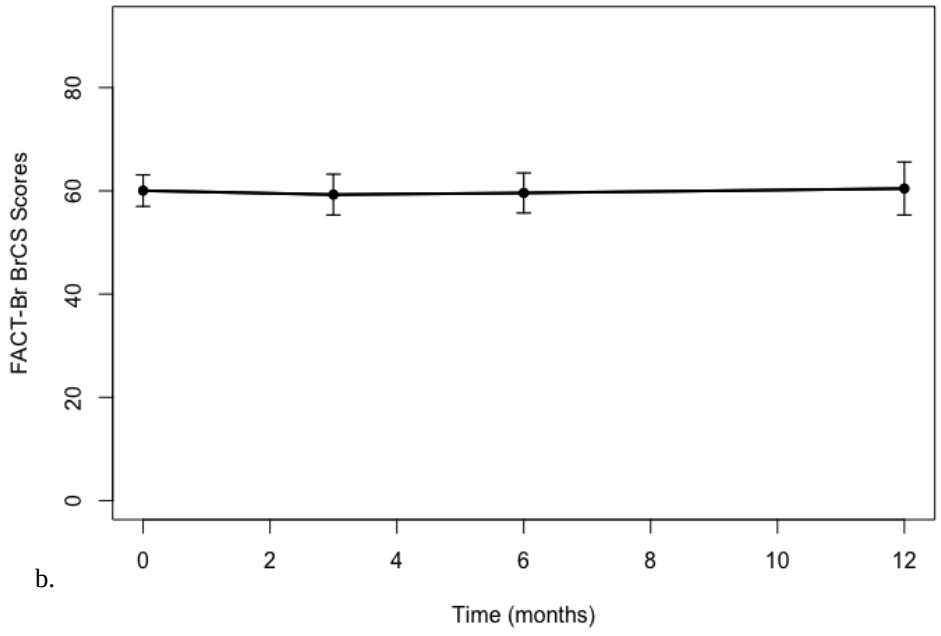
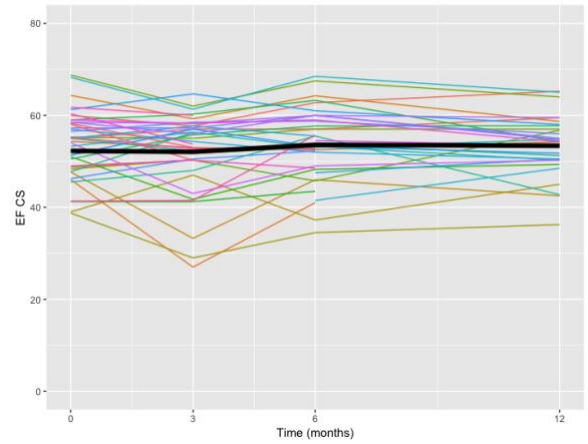


b.

Figure 7. FACT-Br BrCS Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of FACT-Br BrCS subscale scores. b. Line graph of FACT-Br BrCS means over time with error bars representing 95% CI.



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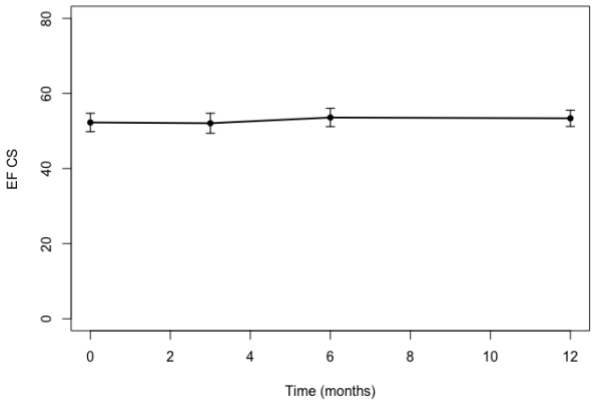

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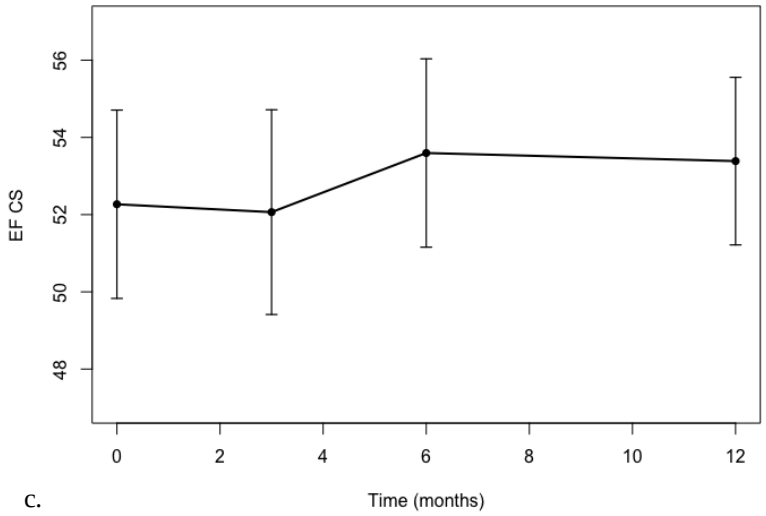
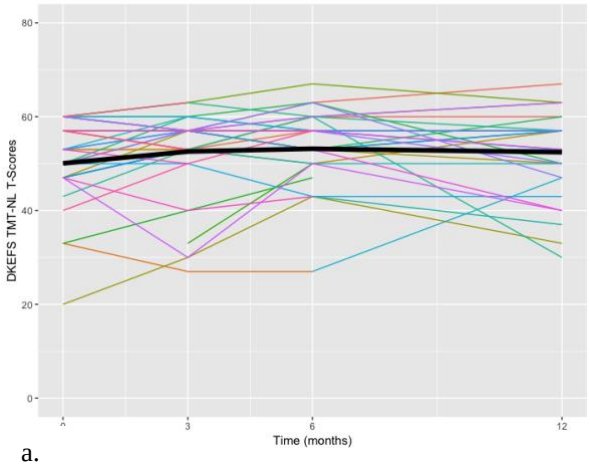


c.

Figure 8. EF CS Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of EF SC. b. Line graph of EF CS means over time with error bars representing 95% CI; y scale is possible range of EF SC. c. Line graph of EF CS means over time with error bars representing 95% CI; y scale altered to 47 - 57 in order to magnify plot and better highlight the cubic trend.



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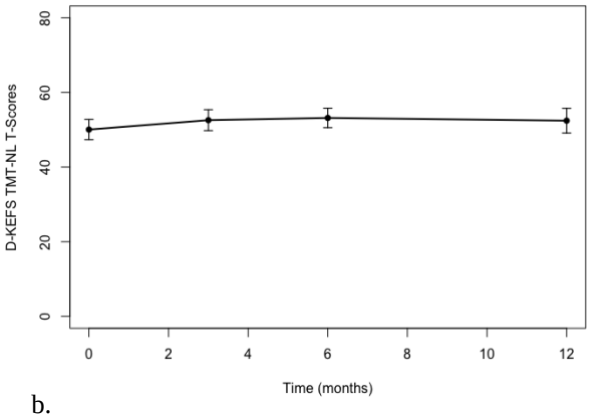

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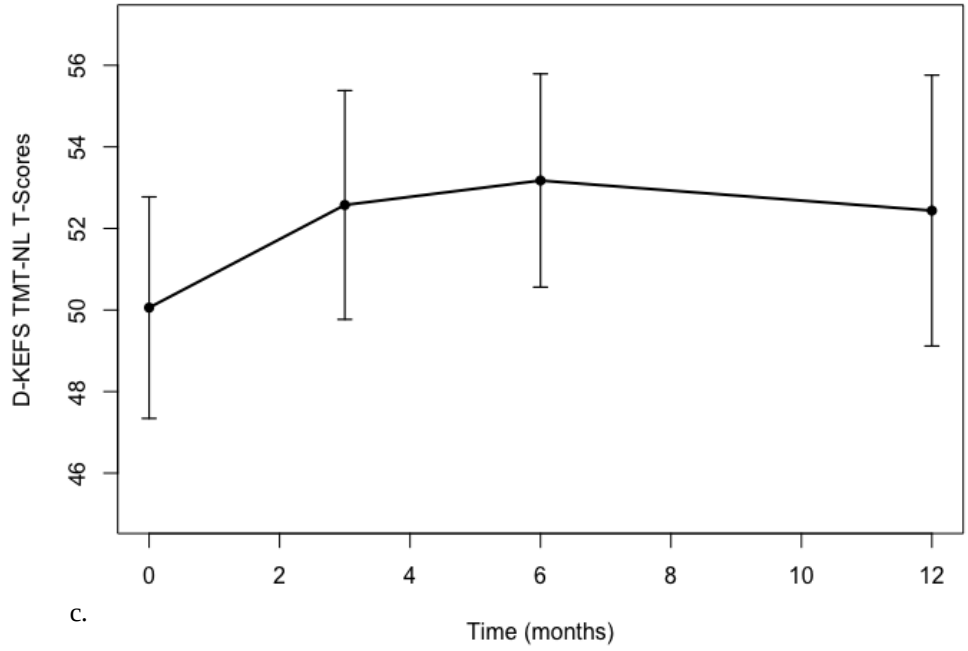
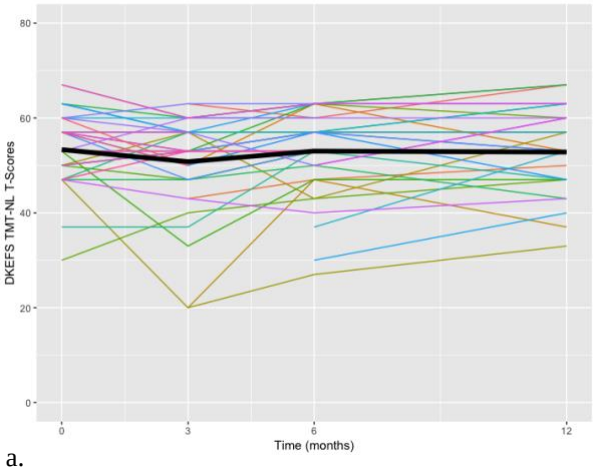


c.

Figure 9. D-KEFS TMT-NL T-Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of D-KEFS TMT-NL T-Scores. b. Line graph of D-KEFS TMT-NL T-Score means over time with error bars representing 95% CI; y scale is possible range of D-KEFS TMT-NL T-Scores. c. Line graph of D-KEFS TMT-NL T-Score means over time with error bars representing 95% CI; y scale altered to 45 - 57 in order to magnify plot and better highlight the quadratic trend.



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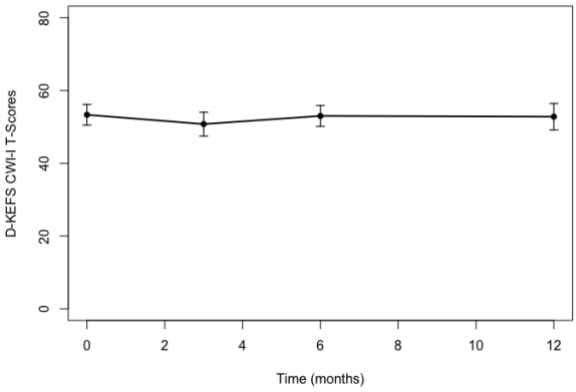

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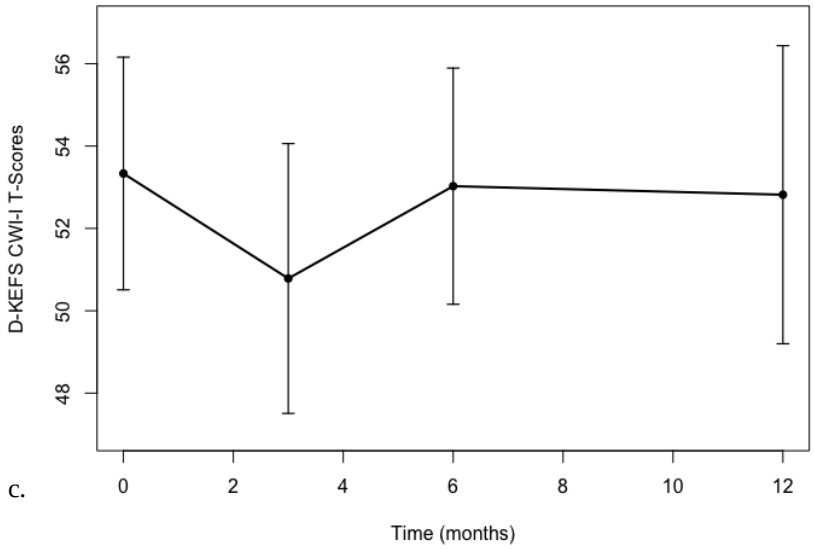
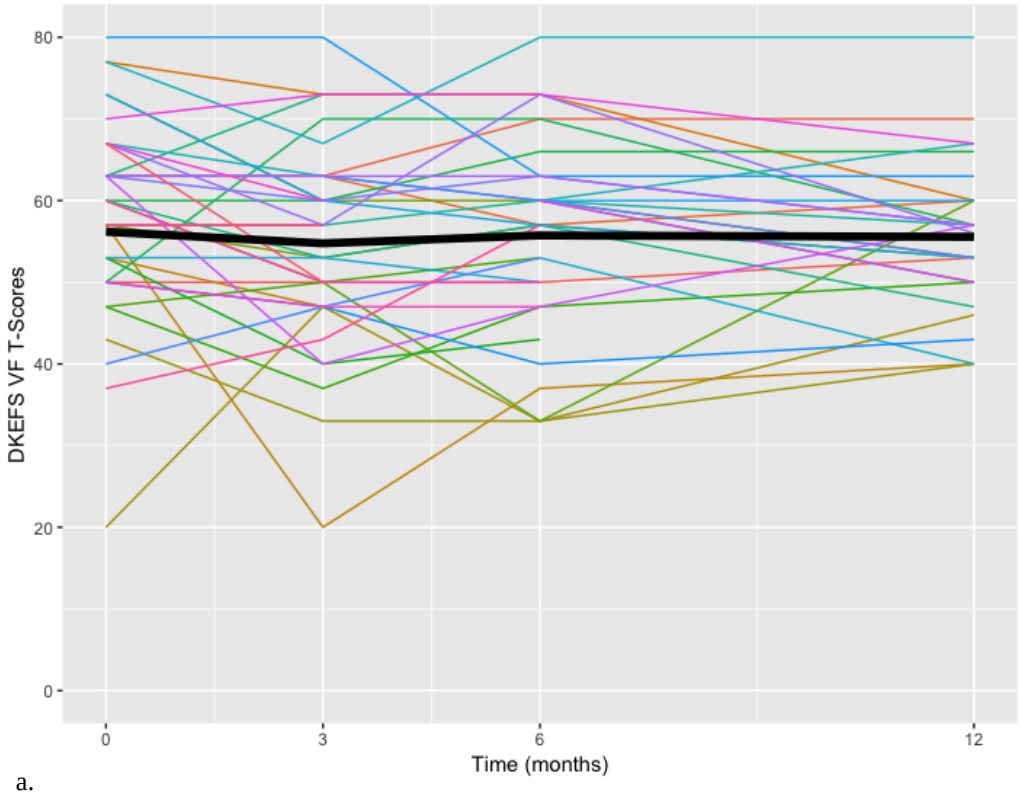


c.

Figure 10. D-KEFS CWI-I T-Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of D-KEFS CWI-I T-Scores. b. Line graph of D-KEFS CWI-I T-Score means over time with error bars representing 95% CI; y scale is range of D-KEFS CWI-I T-Scores. c. Line graph of D-KEFS CWI-I T-Score means over time with error bars representing 95% CI; y scale altered to 47 - 57 in order to magnify plot and better highlight the cubic trend.



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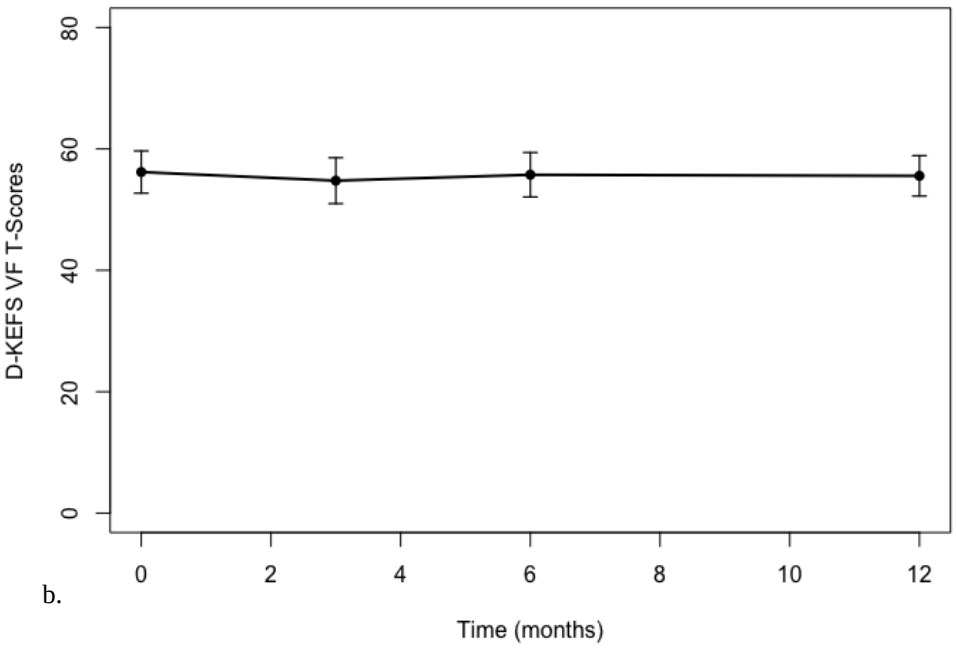
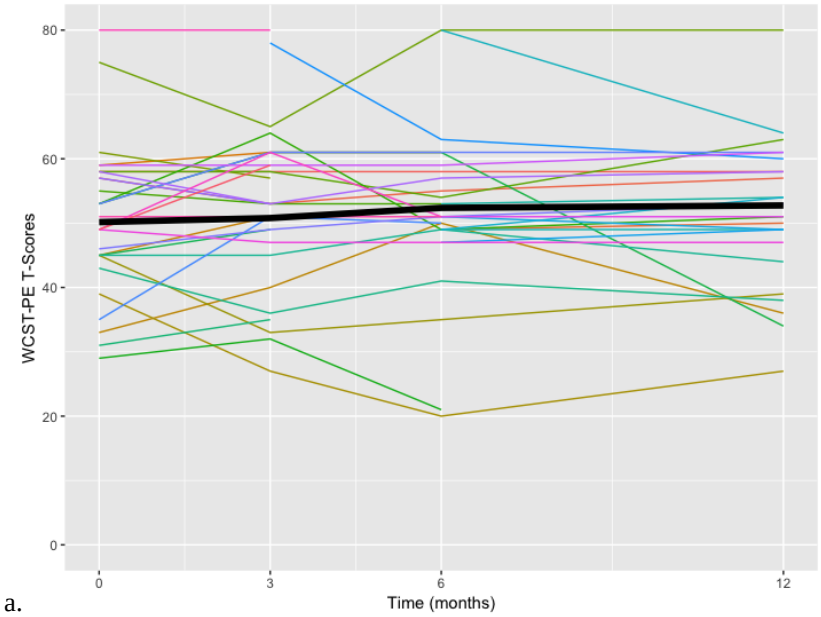
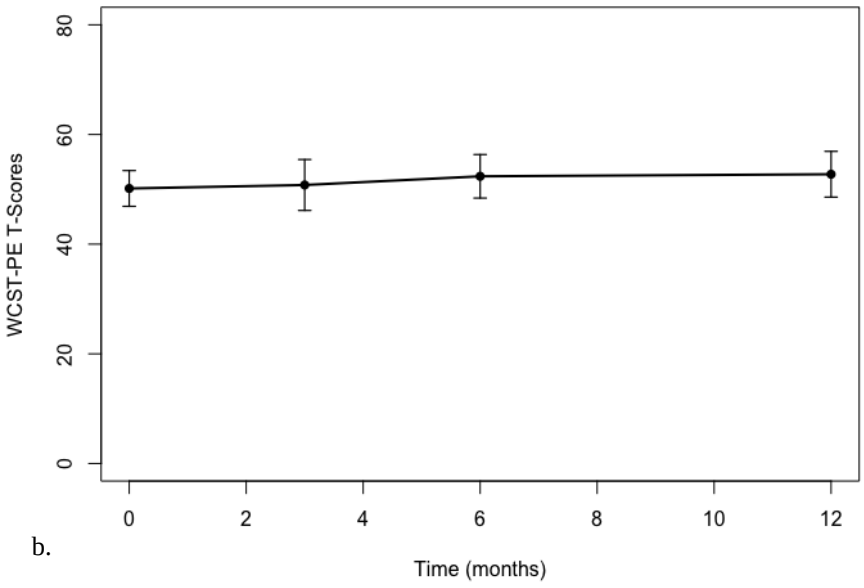


b.

Figure 11. D-KEFS VF T-Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of D-KEFS VF T-Scores. b. Line graph of D-KEFS VF T-Scores means over time with error bars representing 95% CI.



a.



b.

Figure 12. WCST-PE T-Scores Over Time. a. Spaghetti plot with colored lines for each participant and a black best-fit line; rows containing missing values were removed by R; y scale is possible range of WCST-PE T-Scores. b. Line graph of WCST-PE T-Scores means over time with error bars representing 95% CI.

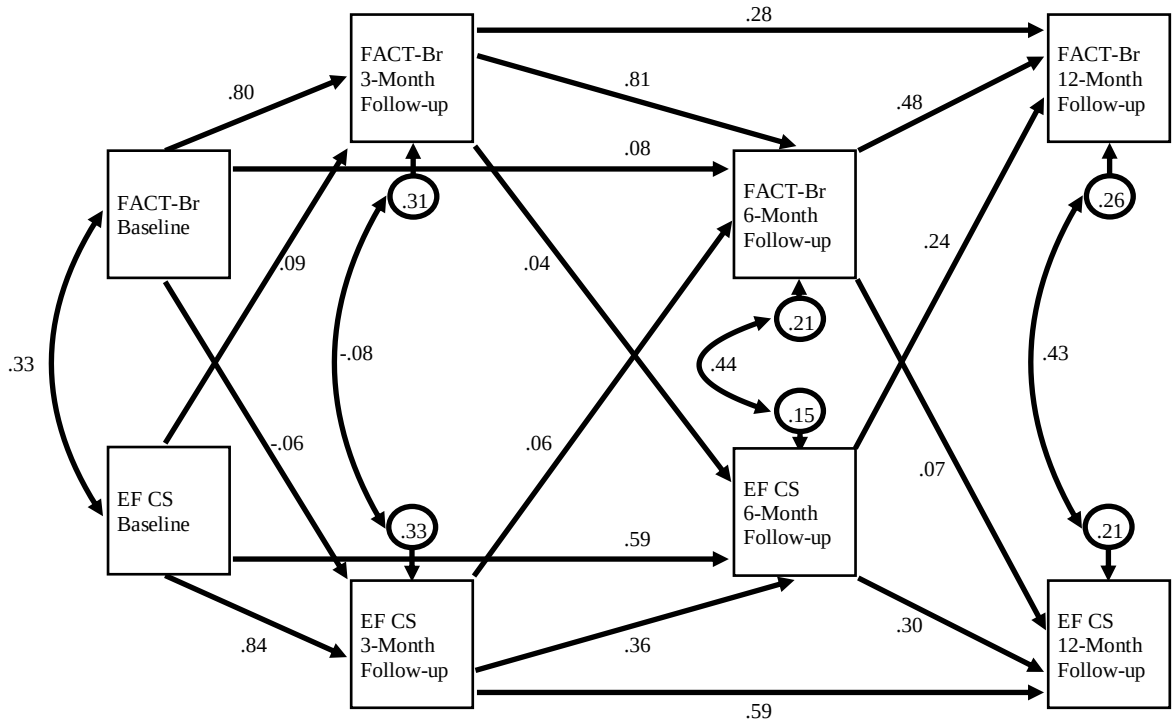


Figure 13. Cross-Lagged Panel Model of FACT-Br Total Scores and EF CS
Estimates are standardized coefficients; the model included auto-regressive pathways from baseline to three-month follow-up, from three-month follow-up to six-month follow-up, and six-month follow-up to 12-month follow-up. The model also includes synchronous correlations between FACT-Br total scores and EF CS at each timepoint. Correlations between FACT-Br total scores and EF CS scores at baseline were zero-order because these variables are exogenous (i.e., independent). Subsequent synchronous correlations were between the estimated residuals (AKA, "disturbance factors") of endogenous variables (i.e., residual correlations). Finally, cross-lagged predictor pathways (e.g., from FACT-Br total score at baseline to EF CS at three-month follow-up) were also specified.

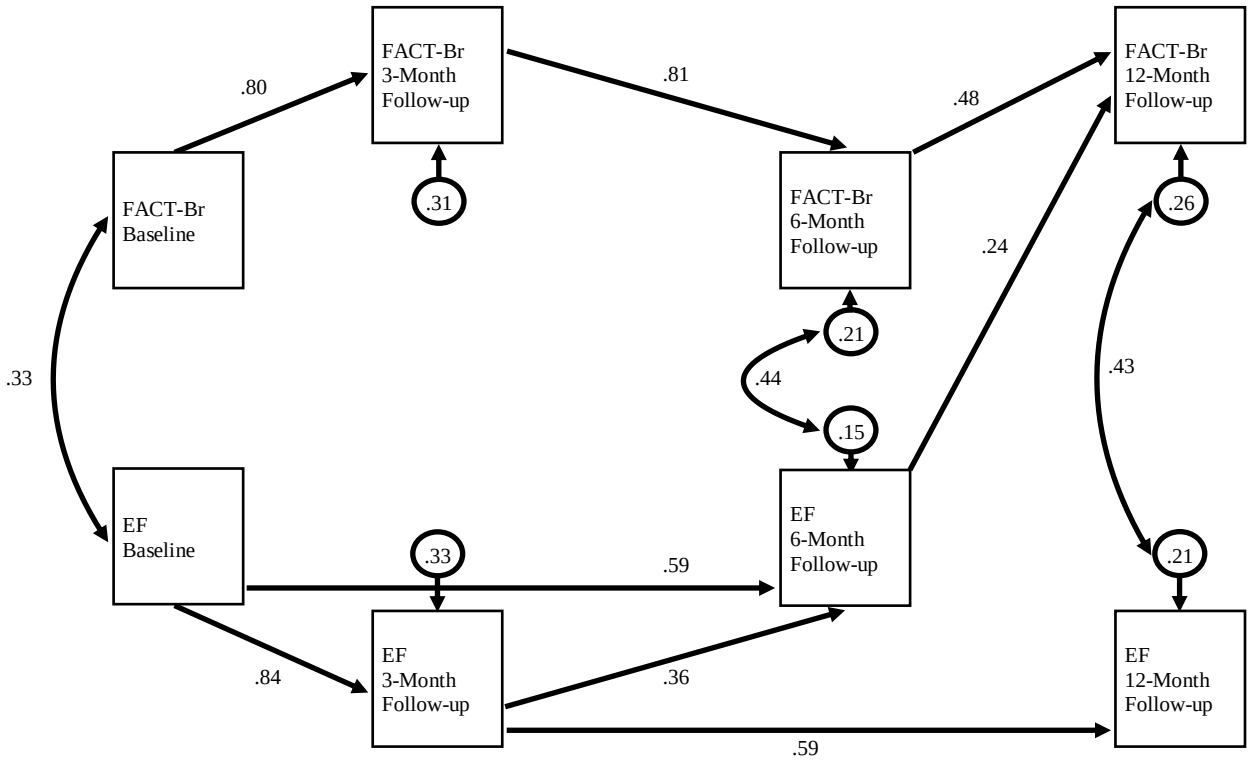


Figure 14. Cross-Lagged Panel Model of FACT-Br Total Scores and EF CS: Significant Pathways
Estimates are standardized coefficients; only significant pathways presented.

TABLES

Table 1. Study Characteristics

	Baseline *n* = 53	3 months *n* = 40	6 months *n* = 40	12 months *n* = 33
Patient characteristics				
Gender				
Men[a]	31 (58.5%)	24 (60%)	22 (55%)	18 (54.5%)
Women[a]	22 (41.5%)	16 (40%)	18 (45%)	15 (45.5%)
Race/ethnicity				
Non-Hispanic White[a]	43 (81.1%)	33 (82.5%)	35 (87.5%)	27 (81.8%)
Non-White[a]	10 (18.9%)	7 (17.5%)	5 (12.5%)	6 (18.2%)
African American	1	0	1	1
Asian	3	3	1	2
Hispanic	6	4	3	3
Age at baseline, years[b]	47.04 (13.9)	46.35 (14.0)	46.9 (14.23)	47.9 (13.8)
Education at baseline, years[b]	15.45 (2.6)	15.63 (2.6)	15.55 (2.7)	15.3 (2.8)
Marital Status				
Married[a]	39 (73.6%)	28 (70.0%)	31 (77.5%)	24 (72.7%)
Unmarried[a]	14 (26.4%)	12 (30.0%)	9 (22.5%)	9 (27.3%)
Single[a]	11	9	8	7
Divorced[a]	3	3	1	2
KPS[b]	92.6 (5.6)	92.5 (5.9)	92.5 (5.9)	92.7 (6.3)
80[a]	3	3	3	3
90[a]	33	24	24	18
100[a]	17	13	13	12
Seizures[a]	22 (41.5%)	18 (45.00%)	18 (45.00%)	13 (39.4%)
Tumor and treatment characteristics				
Tumor pathology				
HGG[a]	23 (43.4%)	15 (37.5%)	16 (40.0%)	12 (36.4%)
LGG[a]	9 (17.0%)	8 (20.0%)	9 (22.5%)	7 (21.2%)
Other[a]	21 (39.6%)	17 (42.5%)	15 (37.5%)	14 (42.4%)
Meningioma	12	10	8	6
Schwannoma	2	2	1	2
Craniopharyngioma	2	2	2	2
Pituitary adenoma	4	3	3	3
Chondrosarcoma	1	0	1	1
Tumor location				
Temporal[a]	11 (20.8%)	9 (22.5%)	10 (25.0%)	8 (24.2%)
Frontal[a]	16 (30.2%)	12 (30.0%)	11 (27.5%)	9 (27.3%)
Parietal[a]	6 (11.3%)	5 (12.5%)	4 (10.0%)	3 (9.1%)
Cerebellar[a]	3 (5.7%)	4 (5.0%)	3 (7.5%)	1 (3.0%)
Thalamic[a]	1 (1.9%)	0	0	0
Other[a]	16 (30.2%)	12 (30%)	12 (30.0%)	12 (36.4%)
Suprasellar[a]	8	7	7	6
Sphenoid wing[a]	1	1	1	1
Cavernous sinus[a]	3	2	2	2
Base of skull[a]	4	2	2	3
Tumor side				
Right[a]	23 (43.4%)	17 (42.5%)	17 (42.5%)	13 (39.4%)
Central[a]	4 (7.5%)	4 (10.0%)	4 (10.0%)	4 (12.1%)
Left[a]	26 (49.1%)	19 (47.5%)	19 (47.5%)	16 (48.5%)

Table 1. Study Characteristics Continued

	Baseline *n* = 53	3 months *n* = 40	6 months *n* = 40	12 months *n* = 33
Surgery type				
GTR or NTR[a]	13 (24.5%)	10 (25.0%)	8 (20%)	8 (24.2%)
STR[a]	29 (54.7%)	23 (57.5%)	25 (62.5%)	19 (57.6%)
Biopsy/VP shunt[a]	4 (7.5%)	2 (5.0%)	3 (7.5%)	2 (6.1%)
None[a]	7 (13.2%)	5 (12.5%)	4 (10.0%)	4 (12.1%)
RT				
IMRT [a]	39 (73.6%)	29 (72.5%)	27 (67.5%)	22 (66.7%)
Proton beam[a]	14 (26.4%)	11 (27.5%)	13 (32.5%)	11 (33.3%)
Chemotherapy				
Concurrent[a]	24 (46.6%)	17 (42.5%)	17 (42.5%)	13 (39.4%)
Adjuvant[a]	30 (57.7%)	22 (55.0%)	24 (60.0%)	18 (54.5%)
Any[a]	31 (58.5%)	22 (22.0%)	24 (60.0%)	18 (54.5%)
Steroids[a]	26 (49.1%)	20 (50.0%)	19 (47.5%)	15 (45.5%)
AED[a]	28 (52.8%)	22 (55.0%)	23 (57.5%)	18 (54.5%)

Note. Composition of the sample at each timepoint based on baseline characteristics or occurrence at any time during the study (e.g., steroids); [a]Count (%), [b]*M (SD);* [a]None of the proportions from one timepoint to the subsequent timepoint or from baseline to 12 months were significantly different from one another; [b]None of the means from one timepoint to the subsequent timepoint or from baseline to 12 months were significantly different from one another; KPS = Karnofsky performance status; HGG = high-grade glioma; LGG = low-grade glioma; GTR = gross-total resection; NRT = near-total resection; SRT = subtotal resection; RT = radiation therapy; IMRT = intensity modulated radiation therapy; AED = antiepileptic drugs.

Table 2. FACT-Br Means, Standard Deviations, and Number of Observations at Each Time Point

	Baseline		3 months		6 months		12 months	
	n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
FACT-Br Total	53	142.9 (24.12)	39	144.3 (26.67)	39	142.2 (27.62)	33	148.7 (25.08)
FACT-Br Total, *n (%)* below average^		6 (11.32%)		5 (12.82%)		5 (12.82%)		3 (9.09%)
FACT-Br Subscales								
PWB	53	23.90 (3.95)	40	22.52 (5.55)	39	21.69 (6.40)	33	24.28 (3.83)
SWB	53	22.58 (4.81)	40	22.80 (5.45)	39	22.44 (4.48)	33	23.08 (4.22)
EWB	53	17.79 (4.40)	40	18.45 (4.44)	39	18.22 (3.96)	33	19.38 (3.58)
FWB	53	18.75 (5.61)	40	20.55 (5.83)	39	20.16 (6.17)	33	21.30 (6.03)
BrCS	53	60.04 (11.34)	39	59.27 (12.59)	39	59.59 (12.36)	33	60.45 (15.05)

Note. ^A score below 110 (1 *SD* below the *M* of a published, normative sample of brain tumor patients) was considered below average

Table 3. Bivariate Correlations among FACT-Br Subscales and Total Score at Baseline

	PWB	SWB	EWB	FWB	BrCS	Total
PWB	—					
SWB	0.43**	—				
EWB	0.29*	0.43**	—			
FWB	0.41**	0.75***	0.48***	—		
BrCS	0.58***	0.61***	0.43**	0.64***	—	
Total	0.66***	0.81***	0.63***	0.84***	0.91***	—

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4. EF Means, Standard Deviations, and Number of Observations and Impaired Patients at Each Time Point

	Baseline		3-Month Follow-up		6-Month Follow-up		12-Month Follow-up	
	n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
EF CS	53	52.27 (9.06)	40	52.06 (8.55)	40	53.60 (7.87)	33	53.39 (6.36)
Low Average, *n (%)*†		2 (3.78%)		0 (0.00%)		1 (2.50%)		1 (3.03%)
Impaired, *n (%)*^		2 (3.78%)		3 (7.5%)		1 (2.50%)		0 (0.0%)
EF CS Components								
DKEFS TMT NL	52	50.06 (9.99)	40	52.58 (9.05)	40	53.17 (8.44)	32	52.44 (9.59)
Low Average, *n (%)*†		1 (1.92%)		2 (5.00%)		0 (0.00%)		3 (9.38%)
Impaired, *n (%)*^		5 (9.61%)		4 (10.00%)		2 (5.00%)		2 (6.25%)
DKEFS CWI-I	42	53.33 (9.34)	37	50.78 (10.17)	39	53.03 (9.14)	33	52.82 (10.61)
Low Average, *n (%)*†		2 (4.76%)		2 (5.13%)		2 (5.13%)		2 (6.06%)
Impaired, *n (%)*^		2 (4.76%)		3 (8.11%)		2 (5.13%)		3 (9.09%)
DKEFS VF	53	56.19 (12.93)	39	54.77 (12.04)	39	55.74 (11.66)	32	55.56 (9.61)
Low Average, *n (%)*†		2 (3.78%)		3 (7.69%)		2 (5.13%)		3 (9.38%)
Impaired, *n (%)*^		3 (5.66%)		2 (5.13%)		3 (7.69%)		0 (0.00%)
WCST PE	45	50.16 (11.15)	33	50.79 (13.61)	35	52.37 (11.98)	32	52.75 (12.04)
Low Average, *n (%)*†		1 (2.22%)		2 (6.06%)		0 (0.00%)		4 (12.5%)
Impaired, *n (%)*^		6 (13.34%)		6 (18.18%)		3 (8.57%)		2 (6.25%)

Note. All scores are T-scores; EF CS is an average of the component scores; †T score of 40 to 36 was considered low average; ^T score of 35 (i.e., 1.5 population *SD* below the population *M* = 50) or below was considered impaired.

Table 5. Bivariate Correlations among EC CS Component T-Scores and EF CS at Baseline

	DKEFS TMT NL	DKEFS CWI-I	DKEFS VF	WCST PE	EF CS
DKEFS TMT NL	—				
DKEFS CWI-I	0.59***	—			
DKEFS VF	0.61***	0.48**	—		
WCST PE	0.34*	0.33	0.46**	—	
EF CS	0.82***	0.76***	0.86***	0.72***	—

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

Table 6. LME Models Predicting FACT-Br Total Scores Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	141.8*	148.2*	148.77*	149.33*	149.15*	3	1401	-698	
	Seizures		-11.67	-11.67	-11.55	-11.55				
2	RT Type		9.51	9.65	9.72	9.73				
	Steroids		-8.22	-8.23	-8.26	-8.26	6	1396	-692	10.6*
3	Months			-0.14	-0.68	0.25	7	1398	-692	0.44
4	Months^2				0.05	-0.21	8	1383	-692	0.64
5	Months^3					0.01	9	1401	-692	0.25

Note. *$p < .05$; b = unstandardized coefficient; LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value

Table 7. LME Models Predicting FACT-Br PWB Longitudinally

Model	Fixed Effects†	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	23.06*	23.16*	23.93*	23.9*	3	972	-483	
2	Months		-0.02	-0.68*	-0.52	4	980	-486	0.11
3	Months^2			0.06*	0.01	5	973	-481	8.84*
4	Months^3				0.002	6	975	-481	0.07

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model, ^significance test based on if intercept is different from 0, which is not a meaningful value; †Although tumor location was significantly related to PWB at baseline, LME model comparison between an intercept only model and a model with the full set of orthogonal contrast codes for tumor location revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location was removed from the subsequent LME models.

Table 8. LME Models Predicting FACT-Br SWB Longitudinally

Model	Fixed Effects†	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	22.49*	22.65*	22.67*	22.58*	3	931	-462	
2	Months		-0.04	-0.06	0.39	4	932	-462	0.44
3	Months^2			0.002	-0.12	5	934	-462	0.02
4	Months^3				0.01	6	935	-462	0.84

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model, ^significance test based on if intercept is different from 0, which is not a meaningful value; †Although tumor location was significantly related to SWB at baseline, LME model comparison between an intercept only model and a model with the full set of orthogonal contrast codes for tumor location revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location was removed from the subsequent LME models.

Table 9. LME Models Predicting FACT-Br EWB Longitudinally

Model	Fixed Effects	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	18.30*	17.99*	17.85*	17.19*	3	905	-449	
2	Months		0.08	0.19	0.49	4	905	-448	1.88
3	Months^2			-0.01	-0.09	5	906	-448	0.43
4	Months^3				0.004	6	908	-448	0.4

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model, ^significance test based on if intercept is different from 0, which is not a meaningful value; †Although tumor location and RT type were significantly related to EWB at baseline, LME model comparison between an intercept only model and a model with the full set of orthogonal contrast codes for tumor location and a separate LME model with RT type revealed that the intercept-only model, the more parsimonious model, was a better fit; therefore, tumor location and RT type were removed from the subsequent LME models.

Table 10. LME Models Predicting FACT-Br FWB Longitudinally

Model	Fixed Effects†	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	19.46*	21.25*	20.90*	20.67*	20.52*	3	937	-466	
2	Steroids		-3.62*	-3.59*	-3.59*	-3.60*	4	933	-463	6.29*
3	Months			0.082	0.28	1.05*	5	933	-461	2.43
4	Months^2				-0.02	-0.23	6	933	-461	1.46
5	Months^3					0.01	7	932	-459	2.94

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model, ^significance test based on if intercept is different from 0, which is not a meaningful value; †the initial covariates LME model (including steroids, RT type, and the full set of orthogonal codes for tumor pathology) did not fit the data better than the intercept only model; individual LME models revealed that only steroids was a significant covariate; therefore, RT type and tumor pathology were removed from the subsequent LME models.

Table 11. LME Models Predicting FACT-Br BrCS Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	58.77*	62.81*	63.58*	63.83*	64.01*	3	1218	-606	
	Seizures		-7.22	-7.14	-7.08	-7.02				
2	RT Type		4.14	4.32	4.34	4.33				
	Steroids		-2.85	-2.85	-2.87	-2.87				
	Chemotherapy		-1.16	-1.23	1.27	-1.34	7	1212	-599	14.2*
3	Months			-0.20	-0.43	-1.18	8	1211	-598	2.25
4	Months^2				0.02	0.22	9	1213	-598	0.3
5	Months^3					-0.01	10	1215	-597	0.41

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model, ^significance test based on if intercept is different from 0, which is not a meaningful value; RT = radiation therapy.

Table 12. LME Models Predicting EF CS Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	51.96*	58.05*	58.10*	58.00*	58.37*	3	1052	-523	
	Marital Status		5.19*	5.19*	5.19*	5.33*				
	Tumor Side CvLR		0.91	0.93	0.92	0.89				
	Tumor Side LvR		-5.43*	-5.93*	-5.42*	-5.46*				
2	Seizures		0.21	0.21	0.19	0.32				
	Chemotherapy		-5.84*	-5.85*	-5.83*	-6.04*				
	Steroids		-3.70	-3.70	-3.70	-3.70				
	AED		0.58	0.59	0.58	-0.61	10	1033	-507	32.63*
3	Months			-0.01	0.07	-1.53*	11	1035	-507	0.04
4	Months^2				-0.01	0.42*	12	1037	-507	0.04
5	Months^3					-0.03*	13	1032	-503	7.23*

Note. *$p < .05$; LL = log-likelihood; $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value; CvLR = centrally located versus either left- or right-sided; LvR = left-sided versus right-sided; AED = antiepileptic drugs.

Table 13. LME Models Predicting D-KEFS TMT-NL Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	51.10*	57.88*	57.42*	56.59*	56.71*	3	1139	-566	
2	Tumor Side CvLR		0.85	0.72	0.63	0.63				
	Tumor Side LvR		-5.63*	-5.62*	-5.59*	-5.60*				
	Chemotherapy		-2.45	-2.41	-2.46	-2.45				
	Steroids		-4.93*	-4.93*	-4.99*	-5.02*	7	1130	-558	16.6*
3	Months			0.11	0.85*	0.34	8	1131	-557	1.06
4	Months^2				-0.06*	0.08	9	1128	-555	5.24*
5	Months^3					-0.01	10	1129	-555	0.33

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value; CvLR = centrally located versus either left- or right-sided; LvR = left-sided versus right-sided.

Table 14. LME Models Predicting D-KEFS CWI-I Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	52.05*	54.01*	53.77*	54.44*	54.94*	3	1052	-523	
	Marital Status		4.43	4.43	4.35	4.40				
2	Tumor Side CvLR		0.14	0.06	0.17	0.28				
	Tumor Side LvR		-7.05*	-7.10*	-7.11*	-7.13*	6	1047	-518	11.1*
3	Months			0.06	-0.45	-2.57*	7	1049	-518	0.26*
4	Months^2				0.04	0.61*	8	1049	-517	2.07
5	Months^3					-0.03*	9	1046	-514	5.1*

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value; CvLR = centrally located versus either left- or right-sided; LvR = left-sided versus right-sided.

Table 15. LME Models Predicting D-KEFS VF Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	54.86*	63.41*	64.12*	64.40*	64.87*	3	1201	-598	
	RT Type		1.20	1.34	1.36	1.30				
	Tumor Side CvLR		-0.72	-0.52	-0.52	-0.48				
	Tumor Side LvR		-5.14*	-5.17*	-5.21*	-5.26*				
2	Seizures		-2.26	-2.28	-2.23	-2.08				
	Chemotherapy		-7.50*	-7.63*	-7.69*	-7.91*				
	Steroids		-7.69*	-7.72*	-7.73*	-7.77*				
	AED		5.21	5.43	5.45	5.48	10	1192	-586	23.5*
3	Months			-0.19	-0.42	-2.20	11	1192	-585	2.06
4	Months^2				0.02	0.50	12	1194	-585	0.31
5	Months^3					-0.03	13	1193	-584	2.45

Note. *$p < .05$, LL = log-likelihood, $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value; CvLR = centrally located versus either left- or right-sided; LvR = left-sided versus right-sided; AED = antiepileptic drugs.

Table 16. LME Models Predicting WCST-PE Longitudinally

Model	Fixed Effects	b	b	b	b	b	df	AIC	LL	$\Delta\chi^2$
1	Intercept^	50.64*	51.74*	51.38*	50.85*	50.84*	3	1037	-515	
2	Marital Status		7.05*	7.05*	6.97*	6.97*				
	Tumor Side CvLR		9.63	9.54	9.58	9.58				
	Tumor Side LvR		-2.12	-2.12	-2.11	-2.11				
	Seizures		-3.04	-2.92	-3.14	-3.14				
	Chemotherapy		-3.24	-3.26	-3.23	-3.22				
	RT Type		0.27	0.25	0.28	0.28				
	AED		0.97	0.88	1.10	1.10				
	KPS_MD		0.56*	0.56*	0.57*	0.57*	11	1028	-503	25.3*
3	Months			0.08	0.50	0.52	12	1029	-502	0.59
4	Months^2				-0.03	-0.04	13	1030	-502	1.34
5	Months^3					0.00	14	1032	-502	0.00

Note. *$p < .05$; MD = mean deviated; LL = log-likelihood; $\Delta\chi^2$ compared to directly preceding model; ^significance test based on if intercept is different from 0, which is not a meaningful value; CvLR = centrally located versus either left- or right-sided; LvR = left-sided versus right-sided; RT = radiation therapy; AED = antiepileptic drugs; KPS_MD = Karnofsky Performance Scale mean deviated.

Table 17. Bivariate correlations between FACT-Br Total Scores and EF CS at Each Time Point

	FACT-Br total score t0	FACT-Br total score t3	FACT-Br total score t6	FACT-Br total score t12	EF CS t0	EF CS t3	EF CS t6	EF CS t12
FACT-Br total score t0	—							
FACT-Br total score t3	0.831 ***	—						
FACT-Br total score t6	0.784 ***	0.906 ***	—					
FACT-Br total score t12	0.790 ***	0.751 ***	0.790 ***	—				
EF CS t0	0.332 *	0.452 **	0.349 *	0.527 **	—			
EF CS t3	0.346 *	0.284	0.329	0.397 *	0.741 ***	—		
EF CS t6	0.398 *	0.425 *	0.442 **	0.557 **	0.841 ***	0.825 ***	—	
EF CS t12	0.387 *	0.387 *	0.374 *	0.540 **	0.810 ***	0.811 ***	0.812 ***	—

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; t0 = baseline, t3 = 3 months, t6 = 6 months, t12 = 12 months; Scores are uncorrected for dependence.