

EXPLORING COGNITIVE RESERVE AND COMPENSATORY BEHAVIORS
USED TO MAINTAIN EXECUTIVE CONTROL FUNCTION
IN ADULTS WITH PRIMARY BRAIN TUMORS

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ABSTRACT

Deborah Dawn Hutchinson Allen: Exploring cognitive reserve and compensatory behaviors used to maintain executive control function in adults with primary brain tumors
(Under the direction of Virginia J. Neelon, PhD, RN)

Technological advances have improved survival in primary brain tumor (PBT) patients, bringing a need to understand the relationship between executive control function (ECF) and self-reported cognitive function (SRCF) in survivors. Neuropsychological testing demonstrates few objective changes in some who report significant cognitive difficulties. To date, little research has explored the discrepancy between objective cognitive performance (OCP) and SRCF. This study describes the congruence of OCP to SRCF in 40 adult PBT survivors. Structured interviews with 7 exemplars describe compensatory behaviors.

Neuropsychological test scores were converted to *z*-scores using age- and education-specific norms. A *z*-score of -1.3 determined cognitive impairment; Everyday Cognitions Scale scores determined SRCF. Analyses include descriptive statistics, graphical plots, correlations, chi-square and *t*-tests.

The study sample (*n*=40) averaged 50 years old (SD 9.7), had high-grade PBT (*n*=35), was at least 1 year beyond completion of treatment, 1.3-25 years since diagnosis, and included 22 women. ECF was impaired in 25% of subjects, memory in 35%, and attention in 27.5%. More than half of subjects self-reported changes in memory and attention. Neither age, time since diagnosis, or tumor/treatment-specific variables were associated with OCP or SRCF scores. Dividing a scatterplot of OCP/SRCF scores into quadrants created four subject groupings.

Analyses focused on the two groups with normal OCP who had normal (congruent) or abnormal (incongruent) SRCF scores. Both groups were mostly female, middle-aged, well-educated, and 6-8 years removed from diagnosis of high-grade PBT. Those with high cognitive reserve (CR) had congruent OCP/SRCF scores and less impact of PBT-specific symptoms on quality of life; those with low CR tended to have incongruent OCP/SRCF scores, more severe symptoms that impacted quality of life, and more depressive symptoms. Low CR exemplars were socially isolated and had curtailed activities since diagnosis. High CR exemplars continued cognitively-engaging activities. During testing, all subjects exhibited similar compensatory behaviors to maintain cognitive function. Those with congruent scores tended to be less aware that they used compensatory strategies.

This study shows that CR and use of compensatory behaviors may explain discrepant relationships between OCP and SRCF, and may lead to development of interventions to minimize cognitive decline and improve quality-of-life.

To my best friend and my love, my husband Scott.
I could not have done this without your love and support.

In memory of those we have lost and
In honor of survivors with primary brain tumors,
as we strive to improve your quality of life.

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LIST OF ABBREVIATIONS

BBL	Biobehavioral Laboratory
CBTRUS	Central Brain Tumor Registry of the United States
CESD-R	Center for Epidemiological Studies Depression-Revised Scale
COWA	Controlled Oral Word Association
CTB	Clinical Trials Battery Composite
DSMT	Digit Symbol Modalities Test
ECF	Executive control function
ECog	Everyday Cognition Scale
EMQ	Everyday Memory Questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-BN20	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire Brain 20
EXIT-25	Executive Interview-25
FACT-BT	Functional Assessment of Cancer Therapy – Brain Tumor Scale
FCAS	Florida Cognitive Activities Scale
FSIQ	Full Scale Intelligence Quotient
HC	Healthy control
HVLT-DR	Hopkins Verbal Learning Test, Revised – Delayed Recall
HVLT-IR	Hopkins Verbal Learning Test, Revised – Immediate Recall
HVLT-RDI	Hopkins Verbal Learning Test, Revised – Recognition Discrimination Index
IRB	Institutional Review Board
Lineberger	Lineberger Cancer Center at University Hospital, Chapel Hill, North Carolina

M	Mean
MDASI-BT	M. D. Anderson Symptom Inventory – Brain Tumor Scale
MMSE	Mini-Mental State Examination
MMX	Extended Mini-Mental State Examination
NAART	North American Adult Reading Test
NIH	National Institutes of Health
OARS	Older Adults Resource Services
PBT	Primary brain tumor
SD	Standard deviation
SON	School of Nursing
TICS	Telephone Interview for Cognitive Status
Tisch	Preston Robert Tisch Brain Tumor Center at Duke, Durham, North Carolina
TMT Diff	Trails Making Test Part B minus A Difference
Trails A	Trails Making Test Part A
Trails B	Trails Making Test Part B
UNC	University of North Carolina at Chapel Hill
VAS	Visual Analog Scale for self-reported effort of study battery

CHAPTER 1: INTRODUCTION

Advancements in cancer treatments have improved survival for patients with primary brain tumors (PBT) (Jemal et al., 2009). As a result, increasing emphasis has been placed on symptom recognition and on lessening symptom impact on the cancer survivor's quality of life (Armstrong, Cohen, Eriksen, & Hickey, 2004; Dodd, Miaskowski, & Paul, 2001). Survivors of PBT experience a variety of distressing symptoms, particularly cognitive impairment, across the trajectory of their illness (Edvardsson & Ahlstrom, 2005; Fox, Lyon, & Farace, 2007). Neuropsychological evaluations of PBT survivors have predominately focused on cognitive function during and immediately after treatment completion, and have demonstrated few changes in cognitive function (Taphoorn & Klein, 2004), but still survivors report significant difficulties in returning to work and other cognitive activities (Fox, Lyon, & Farace, 2007). To date, however, little research has explored the discrepancy between cognitive performance on neuropsychological tests and self-reported cognitive function. A better understanding of this discrepancy may lead to development of cognitive interventions that might lessen or prevent cognitive decline after treatment, and improve quality of life of survivors with PBT.

Background and Significance

Adult survivors of PBT report that dealing with the impact of symptoms presents challenges to their everyday life (Adelbratt & Strang, 2000), and that altered cognitive abilities, particularly regarding functions that require executive control, are the most distressing (Fox, Lyon, & Farace, 2007; Edvardsson & Ahlstrom, 2005; Moretti, Torre, Antonello, Cazzato, Bava, et al., 2005). These cognitive difficulties hamper their ability to return to work or participate in social activities, and result in long-term changes in their daily lives (Correa, 2010; Godbout, Grenier, Braun, & Gagnon, 2005). Survivors of PBT are usually between 45 to 55 years of age, in the prime of their lives, when they are diagnosed, so there is an expectation that they will resume their prior lives after completion of their cancer treatment (Edvardsson & Ahlstrom, 2005; Godbout et al., 2005). Some survivors of PBT may continue to work, but they have to make adaptations to accommodate the effects of illness and treatment (Davies, Hall, & Clarke, 2003; Edvardsson & Ahlstrom, 2005).

Objective findings of cognitive impairment.

The neuropsychological effects of cancer treatment include deficits in memory, attention, concentration, organizational ability, motor skill, language skill, and multi-tasking ability (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003). Even when survivors of PBT report difficulties performing cognitive functions in everyday life, standardized cognitive assessment may not demonstrate significant cognitive impairments when compared standards for age and gender matched healthy individuals (Archibald et al., 1994; Steinbach et al., 2006; Taphoorn & Klein, 2004).

The functional decline related to memory, attention, and executive control function (ECF) is known to impact the quality of life for survivors of PBT (Wefel, et al., 2004). These long-term neuropsychological effects are associated with depression, decreased quality of life, inability to perform normal activities of daily living, and failure to return to work (Anderson-Hanley et al., 2003).

Discrepancy between subjective and objective reports of cognitive impairment.

Few studies have explored the discrepancy between cognitive performance on neuropsychological tests and self-reported cognitive function. Raffa (2010) suggests that this discordance reflects survivor compensation to maintain cognitive performance.

Compensatory strategies comprise techniques or behaviors that individuals use to help perform tasks and maintain function (Tomey & Sowers, 2009; Wilson, 2000). Compensation may occur by adapting the physical environment to reduce the need for a function or by making residual function more effective using functional aids like canes, talking books and voice reminders, or using rehearsal strategies and mnemonics to enhance existing residual function (Tomey & Sowers, 2009; Wilson & Watson, 1997; Wilson, 2000). Survivors with PBT describe their use of storytelling or of taking breaks during neuropsychological testing as typical of the changes they have employed in everyday activities since their diagnosis, even when they were not found to be cognitively impaired on neuropsychological evaluation. The behaviors they used during the present study may have been compensatory means to optimize their performance or to maintain function through pacing themselves. The observation of these behaviors raises questions about how much effort is required of these survivors to completed standardized

neuropsychological assessments, what compensatory behaviors positively and negatively affect their effort, and how these compensatory behaviors are incorporated into their activities.

Similarly, breast cancer survivors with mild post-treatment cognitive decline reported having more difficulty performing work-related tasks (Wefel et al., 2008). They described having to use an increased effort to maintain their functional abilities (Wefel et al., 2008). A better understanding of the type of strategy used to maintain function, and the effort required will help guide future interventions.

Compensation and cognitive reserve.

Compensation after treatment of PBT may occur through recruitment of alternative neural paths or adaptations in existing neural pathways (Goh & Park, 2009). Functional MRI scanning has demonstrated that adaptive neural recruitment is one of the compensatory processes used by elderly subjects while performing cognitive tasks in.

Cognitive reserve refers to resilience of cognitive function to brain damage; it is amassed through educational and occupational activities. Cognitive reserve has been invoked to explain individual variability in cognitive function (Satz, 1993; Stern, 2002; 2003) by postulating that individuals with high cognitive reserve can maintain cognitive function in the face of neuropathology than can individuals with lower reserve. Thus, individuals with high cognitive reserve may adapt more readily and without self-awareness to the cognitive demands after surviving a PBT. Cognitive reserve may also explain the discrepancy between subjective and objective assessments of cognitive function in survivors with PBT.

Overview and Purpose of the Study

The purpose of this study is to describe the relationship of ECF to self-reported cognitive function in 40 adult survivors of PBT. In an exemplar subset of seven subjects who reported cognitive concerns, structured interviews were used to explore any compensatory strategies they use to maintain cognitive function. It is hoped that the results of this study will provide insight into whether cognitive reserve and use of compensatory behaviors may explain the sometimes discordant relationship between measures of cognitive performance and self-reported cognitive function. In addition, the results may provide insight into what components of ECF benefit from compensatory behaviors, how to screen for the use of behaviors in clinical situations, and how to encourage the types of behavior that may be useful in maintaining cognitive function.

CHAPTER 2: REVIEW OF THE LITERATURE

This review of the literature describes the significance of cognitive impairment in adult survivors of PBT with a focus on subjective and objective research findings and the discrepancy between these findings. The use of compensatory strategies and cognitive reserve to explain this discrepancy will be discussed.

Significance of Cognitive Impairment

Cognitive impairments related to cancer or its treatment has been described since the 1980's when the term *chemobrain* was coined by Shilberfarb (1983). While originally proposed to describe the impairments observed during chemotherapy treatments, cognitive impairment may be due to the development of cancer or effects from treatment and can endure beyond treatment administration (Archibald et al, 1994; Wefel, Witgert, & Meyers, 2008).

The cause of cognitive impairment in cancer patients is multifactorial and may be viewed as an interaction of the disease, treatment, and person. Thus the risk of developing cognitive impairment may be dependent on the type, grade, location, and extent of the cancer (Bosma et al., 2006; Kayl & Meyers, 2003; Surma-aho et al., 2001; Taphoorn & Klein, 2004). Treatments that may add to the development of cognitive impairment from that already promoted by the cancer itself include surgery, chemotherapy, radiation therapy, and medications to control cancer-related symptoms (Ahles & Saykin, 2001; Armstrong et al., 2004; Taphoorn & Klein,

2004). Factors pertaining to the person include age, gender, education, socioeconomic status, genetic susceptibility, and immune reactivity may protect or accelerate the development of cognitive impairment (Klein et al., 2003; Taphoorn & Klein, 2004).

One meta-analysis, that included studies up to 2002, examined the neuropsychological effects of varying cancer treatments across different cancers in adult patients (Anderson-Hanley, et al., 2003). The authors reported large effect sizes, $d = -.89$ to $-.90$, for impairment by at least one standard deviation in executive functioning and verbal memory. However all domains were declined in cancer patients receiving systemic therapies by $\frac{1}{3}$ to 1 SD below normative samples or control groups. Most of these studies had small sample sizes and only examined cognitive function the first six months after completing treatment. These results substantiate the existence of cognitive decline during and after completion of cancer-related therapies for persons with non-central nervous system cancers. Thus, the effect of treatment on cognitive function may be more severe or prevalent for those with the additional burden of neuropathology from a PBT.

For those with PBT, all of these multifactorial variables have been demonstrated to impact on the development of cognitive impairment. Adult survivors with PBT are usually diagnosed in their fifth or sixth decade of life (Jemal, Siegel, Ward, Hao, Xu, & Thun, 2009). Prior to the 1990's and due to the low rate of incidence, high rate of mortality, and severity of neurological deficits associated with its invasive nature, cognitive impairment was an expected outcome with diagnosis but not well researched (Taphoorn & Klein, 2004). However, with technological advances, five-year survival rates have increased and cancer is now viewed as a chronic disease. Additionally, cognitive impairment in survivors of PBT at baseline and during the illness trajectory predict survival (Klein et al., 2003), recurrence (Bosma et al., 2006; Meyers & Hess, 2003; Taphoorn & Klein, 2004), and functional outcomes (Hahn et al., 2003, 2009;

Mukand, Blackinton, Crincoli, Lee, & Santos, 2001). Our increased awareness, measurement, and knowledge of cognitive impairment in cancer survivors, particularly those with PBT, has led to improvements in the delivery or dose of therapeutic modalities to protect cognitive function (Ahles & Saykin, 2001; Armstrong et al., 2004; Surma-aho et al., 2001).

Objective Findings of Cognitive Impairment

Cognitive impairment by neuropsychological evaluation has been found to be as high as 89% in samples of survivors with PBT (Imperato, Paleologos, & Vick, 1990; Klein et al., 2001, 2003). Thus, several studies have explored whether tumor specific factors (tumor grade and location) influenced the development of cognitive impairment in survivors of PBT. Klein and colleagues (2003) observed that poorer cognitive function before treatment in older survivors with WHO Grade IV tumors had the shorter survival times. In high grade PBT survivors (WHO Grade III and IV tumors), poorer cognitive function at diagnosis was a predictor for tumor recurrence (Bosma et al., 2006). In addition, they observed that survivors on antiepileptic medications had more impairment in the domains of attention and executive control function. However, Kayl and Meyers (2003) did not find any differences in cognitive function between 24 newly diagnosed survivors with WHO Grade III and WHO Grade IV tumors after surgical resection. Survivors with left hemispheric lesions that involved the survivor's dominant hemisphere had more cognitive dysfunction after radiation therapy (Hahn et al., 2009). Survivors with frontal lesions were more likely to have better cognitive performances (Kaleita et al., 2004). Additionally, Meyers and Hess (2003) observed in longitudinal follow-up with 56 survivors of PBT that declines in cognitive function performances on neuropsychological evaluations preceded tumor progression observed on neurodiagnostic imaging scans. Across all

of these studies, the cognitive domains predominately affected were those of memory, attention, and executive control function.

Treatments involving surgical resection, radiation therapy, and chemotherapy have been shown to have some effects on cognitive function or development of cognitive impairment. The area that has received the most attention has been the short-term and long-term effects of radiation therapy. Several studies have found that survivors of low grade PBT treated with radiotherapy had poorer cognitive function, particularly with memory and attention, than those survivors who did not receive radiation therapy (Douw et al., 2009; Goldstein, Armstrong, John, & Tallenrt, 2003; Klein et al., 2002). In addition, there were no differences on performances of memory three months after completion of radiation therapy only (Lilja, Portin, Hämäläinen, & Salminen, 2001) or when combined with chemotherapy (Hilverda et al., 2010). Laack and colleagues (2005) found that cognitive performances for attention, memory, and verbal fluency were improved 18 months after radiation therapy; however this was not sustained at the 3 year follow-up. Long-term survivors of low grade PBT treated with radiation therapy 1 to 22 years earlier also demonstrated declines in those same domains (Moretti et al., 2005; Klein et al., 2002). Unlike findings with radiation therapy, surgical resection of the tumor has been found to improve cognitive performance (Duffau et al., 2003; Scheibel, Meyers, & Levin, 1996).

Subjective Findings of Cognitive Impairment

While this review has focused primarily on the objective findings of cognitive impairment in survivors of PBT through neuropsychological evaluations thus far, the subjective or patient's perspective of their cognition function is also of importance (Taphoorn & Klein, 2004; Meyers & Hess, 2006; Wefel, Witgert, & Meyers, 2008). Cognitive impairment has been

associated with the presence of other self-reported symptoms in survivors of PBT (Armstrong et al., 2006; Fox, Lyon, & Farace, 2007). Cognitive impairment, depression, fatigue, pain, and sleep disturbance were significantly correlated and were found to explain 62% of the variance in reported quality of life and functional status of long-term survivors with malignant PBT (Fox, Lyon, & Farace, 2007).

There are several qualitative and quantitative studies that found cognitive impairment impacting everyday function in survivors of PBT (Davies, Hall, & Clarke, 2003; Edvardsson & Ahlstrom, 2005; Huang, Wartella, & Kreutzer, 2001; Tang, Rathbone, Park-Dorsay, Jiang, & Harvey, 2008; Wideheim, Edvardsson, Pahlson, & Ahlstrom, 2002). Everyday functioning requires the activation and maintenance of executive control (Lezak, Howieson, & Loring, 2004; Valenzuela & Sachdev, 2006). Executive control function (ECF) is vital to the coordination of activities, decision making, planning, sequencing, correcting error, inhibiting responses and behaviors (Lezak, Howieson, & Loring, 2004), and are necessary for the initiation and organization of goal-directed behaviors (Farias et al., 2008). Everyday functions that include maintaining household functions, performing work-related activities, and engagement in hobbies, recreational, or social activities have been reported as those most affected after diagnosis and treatment for PBT (Davies, et al., 2003; Farias, Mungas, Reed, Harvey, Cahn-Weiner, & DeCarli, 2006; Hanna-Pladdy, 2007; Wideheim, et al., 2002). Davies and colleagues explored the prevalence of disabilities in two year survivors and found that 50% of the participants reported moderate to severe disability in everyday life. There was only one participant still working after completion of treatment. Adults with PBT describing these cognitive impairments emphasize the impact on their everyday functioning and relate these deficits as most distressing (Fox, Lyon, & Farace, 2007; Edvardsson & Ahlstrom, 2005; Moretti, et al., 2005; Godbout,

Grenier, Braun, & Gagnon, 2005; Steinbach, Blaicher, Herrlinger, Wick, Nagele, et al., 2006; Meyers & Brown, 2006). For survivors of PBT, specific cognitive impairments reported on self-reported questionnaires include their forgetfulness, inability to concentrate or feeling distracted, slowed processing and reaction times, difficulty in prioritizing, inability to problem-solve, and lack of motivation (Dietrich, Monje, Wefel, & Meyers, 2008; Brown, Buckner, Uhm, & Shaw, 2003). All are common to ECF dysfunction.

Discrepancy between Objective and Subjective Cognitive Impairment

There were several studies that performed both objective and subjective instruments to measure cognitive impairment in survivors of PBT. Correa and colleagues (2008) found that 9 survivors with low grade PBT who had radiation therapy and concurrent chemotherapy had mild declines in cognitive function as compared to their baseline measures; this was associated with self-reported measures of function. In another study with 24 survivors of low grade PBT, significant changes in psychomotor function was found 4 to 5 years after completing radiation therapy yet self-reported function yielded few cognitive complaints. In a large oncology rehabilitation study with 119 subjects, the researchers found that subjective and objective cognitive function scores were not associated (Poppelreuter et al., 2004). Although 25% of the sample demonstrated some cognitive impairment by objective performance scores, up to 38.7% of the sample reported cognitive complaints of reductions in their ability to process quickly, maintain attention, and get motivated.

Excluding the previous 3 studies, an additional 22 studies exploring cognitive impairment in survivors of cancer from years 1998 to 2010 by cross-sectional or longitudinal designs, 15 studies did not find any association between subjective report of cognitive function and objective

cognitive performance scores (Ahles et al., 2002; Debess, Riis, Engebjerg, & Ewertz, 2010; Castellon et al., 2004; Downie, Mar Fan, Houede-Tchen, Yi, & Tannock, 2006; Fliessback et al., 2005; Harder et al., 2004; Hermelink et al., 2007, 2010; Jenkins et al., 2006; Mallinson, Cella, Cashy, & Holzner, 2006; Mehnert, et al., 2007; Reid-Arndt, Hsieh, & Perry, 2010; Schagen et al., 1999, 2002, 2008; Shilling & Jenkins, 2007; van Dam et al., 1998; Weis et al., 2009). Most of the subjects for these studies were survivors of breast cancer (n=16) but sample size varied across study. The two most commonly used self-report instruments for cognitive function were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the Questionnaire for Self-perceived Deficits in Attention. However, objective measures for cognitive performance varied greatly, as well as the definitions used for cognitive impairment (z score of 1, 1.5, or 2 SD below norm; 1 SD below sample mean; performance below 10th or 5th percentile; and number of impaired tests).

To explain the discrepancy between subjective and objective cognitive function, some have suggested that the instruments of objective cognitive function do not have high enough sensitivity or specificity (Kayl, Wefel, & Meyers, 2006; Middleton, Denney, Lynch, & Parmenter, 2006; Wefel, Witgert, & Meyers, 2008). Others suggest that subjects underestimate their actual performance or tend to be overly sensitive to change in function (Klein et al., 2001; Rabbitt & Abson, 1991; van Gorp et al., 1991). Additional symptoms or mood disorders may factor into the discrepancy between subjective and objective cognitive functions (Rabbitt & Abson, 1991; Sawrie et al., 1999). Some offer that subjective reports of decline in cognitive function may precede that of objective findings in cancer survivors as they may be adapting to their functional demands through compensation (Kayl, Wefel, & Meyers, 2006; Wefel, Witgert, & Meyers, 2008).

Compensatory Strategies

Compensatory strategies are techniques or behaviors that individuals use to perform tasks that are often difficult for them to perform otherwise (Tomey & Sowers, 2009; Wilson, 2000). Compensation may occur by adapting the physical environment to reduce the need for a function or to make residual function easier, using functional aids like canes, talking books and voice reminders, or using rehearsal strategies and mnemonics to enhance existing residual function (Tomey & Sowers, 2009; Wilson & Watson, 1997; Wilson, 2000). Many individuals fail to recognize that they adopt strategies and incorporate behaviors to maintain their function as the compensation has been done subconsciously (Weiss, Hoenig, & Fried, 2007).

Survivors of PBT who have continued to be engaged and active reported fewer physical and cognitive problems (Davies, Hall, & Clarke, 2003). Further, they indicated they had found ways to cope or adapt with their disabilities (Davies, Hall, & Clarke, 2003). Rehabilitation programs focused on functional outcomes have described improvements in self-reported cognitive function in survivors of PBT. Those who sustained cognitive improvements had longer survivorship, thus cognitive improvement predicted overall prognosis (Huang et al., 2001; Tang et al., 2008). As most neurological rehabilitation centers foster engagement in mentally-challenging activities, this latter study suggests that one may be able to restore and sustain function and live longer by active participation in daily activities early in their treatment phase.

Magnetic resonance imaging (MRI) studies of survivors with PBT demonstrate extensive structural neuropathology. Yet neither the presence nor the extent of structural neuropathology relate to the degree of cognitive impairment that exists (Moretti, et al., 2005; Meyers, 2008). In fact, much variability in cognitive function exists for adult survivors of PBT (Gehing et al., 2008). Several functional imaging studies in aging populations have demonstrated activation of

cerebral areas that are normally not used for specific functions until damage has occurred (Ricker, Hillary, & DeLuca, 2001; Scheibel et al., 2007; Scarmeas et al., 2004; Cabeza, Anderson, Locantore, & McIntosh, 2002). It has been suggested that the activation of alternate neural pathways to circumvent damaged areas to maintain function may explain some of the disparity between neuropathology and cognitive function (Wefel, Witgert, & Meyers, 2008). Further functional imaging research is needed to understand if these compensatory mechanisms are observed among survivors with PBT.

Cognitive Reserve

Stern (2003) proposed compensation as the recruitment of alternate neural networks or use of cognitive strategies to maintain cognitive function when neuropathology disrupts normal processes. He further suggests that the efficiency of the brain to process cognitive tasks relates to the level of cognitive reserve one possesses. Cognitive reserve is the accumulation of a lifetime of cognitive achievements and experiences that create the efficient neural networks for processing and compensation (Scarmeas & Stern, 2004). Therefore, lifestyle factors including educational attainment, occupational position, premorbid intelligence, and types of engaging activities, serve to modify the level of cognitive reserve that an individual may have (Hultsch, et al., 1999; Wilson, Mendes de Leon, Barnes, Schneider, Bienias, Evans, & Bennett, 2002; Wilson, Barnes, & Bennett, 2003; Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). It has been observed that those engaged in cognitive activities across their lifespan maintained everyday function as compared to those who participate in few activities (Valenzuela, et al., 2008; Wilson, Barnes, & Bennett, 2003). Two studies demonstrate that the early life activities had a greater effect on maintaining late life cognitive function in aging populations (Dik, Deeg,

& Jonker, 2003; Fritsch, et al., 2007). Engagement in activities in late life can also promote higher levels of cognitive reserve as demonstrated in differences of cognitive function (Wang, et al., 2002; Fratiglioni, et al., 2000) and cerebral blood flow (Scarmeas et al., 2003) in those with mild cognitive impairment or mild dementia. Thus, the continued engagement in cognitive activities throughout the lifespan may protect against cognitive decline (Wilson et al., 2002).

There has been one study with cancer survivors exploring whether cognitive reserve may explain the variability in cognitive impairment (Ahles et al., 2010). Using a longitudinal design, subjective and objective cognitive function was assessed prior to treatment, and 1 month, 6 months, and 18 months after completion of treatment in 60 breast cancer survivors. Survivors treated with chemotherapy who had lower premorbid intelligence had lower performance scores for processing speed as compared to those who did not receive chemotherapy. The subjective and objective reports of cognitive function were not associated although those who received chemotherapy self-reported more cognitive symptoms. Further, younger survivors with higher premorbid intelligence reported the persistence of cognitive symptoms but maintained a normal objective cognitive performance. The authors suggested that they may be more aware of the changes in their cognitive capacity or using compensatory strategies to maintain performance.

Study Purpose and Specific Aims

These results are fundamental to the conceptual framework that compensation and cognitive reserve may be useful for explaining the discrepancy between objective and subjective cognitive function in adults with primary brain tumors. Compensatory strategies that adult survivors with PBT incorporate into everyday function have not been explored, particularly those used to maintain executive control function. Identifying these strategies may help us to learn

what is useful, successful, or requires more effort to maintain cognitive function. Thus, the exploration of compensation may aid in directing future research for the development of intervention and prevention strategies in which to preserve, restore, or diminish the decline of cognitive function. It is hoped that this research will provide essential insights for teaching patients and families cues to discern early cognitive decline and strategies to manage cognitive changes or prevent decline.

Therefore, the purpose of this study was to explore the relationship of ECF and self-reported cognitive function in 40 adult survivors of PBT. In a subset of 7 PBT subjects who reported concerns in ECF, the relationship of ECF and compensatory behaviors was explored through a structured interview using the FCAS. The specific aims are:

Aim 1: To describe executive control function (ECF) and its components in adults following treatment for primary brain tumor (PBT). This aim was addressed by examining subject scores on the following standardized tests of ECF.

- a. Memory was measured by Hopkins Verbal Learning Tests (HVLT) on Immediate Recall (IR), Delayed Recall (DR), and Recognition Discrimination Index (RDI),
- b. Attention was measured by Trails Making Test Parts A (Trails-A) and B (Trails-B) and Symbol Digit Modalities (SDMT),
- c. Verbal Fluency (semantic memory) was measured by Controlled Oral Word Association (COWA), and
- d. ECF was measured by the Clinical Trials Battery (CTB) Composite score, Trails Making Test Parts B-A Difference score (TMT Difference), and Executive Interview-25 scores (EXIT-25).

Aim 2: To describe self-reported cognitive function in adults following treatment for PBT.

This aim was addressed by examining subject self-reported scores on the Everyday Cognitions Test (ECog).

- a. Self-reported cognitive function (ECog total scale score),
- b. Self-reported Memory (ECog memory subscale),
- c. Self-reported Attention (ECog attention subscale),
- d. Self-reported Verbal Fluency (ECog language subscale), and
- e. Self-reported PBT-specific symptom assessment by Functional Assessment of Cancer Therapy-Brain Tumor (FACT-BT) and MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT).

Aim 3: To describe the relationship of ECF performance scores and subject self-report scores. This aim was addressed by exploring the congruence/incongruence:

- a. CTB Composite score and ECog total score,
- b. TMT Difference score and ECog total score, and
- c. EXIT-25 score and ECog total score.

Aim 4: To explore whether cognitive reserve or compensatory behaviors explain the congruence or incongruence between ECF performance scores and subject self-report scores.

This aim was addressed by two items:

- a. Cognitive reserve as measured by the Hollingshead Index, and
- b. Compensatory behaviors as measured by the Florida Cognitive Activities Scale.

CHAPTER 3: REPORT ON FEASIBILITY STUDY

This chapter reports data from a pilot study to determine the feasibility of using a brief neuropsychological battery and self-report questionnaires to identify dysfunctional executive control in survivors of PBT (see Chapter 4, Methods, for descriptions for the instruments used and Appendix A-F for Study Protocol, IRB Approval, and Consents). A secondary goal was to compare executive control function (ECF) in adults with PBT to healthy controls.

Neuropsychological measures used were the Mini-Mental Status Exam (MMSE), Executive Interview (EXIT-25), Trails Making Test-Part B (Trails B), Symbol Digit Modalities Test (SDMT), North American Adult Reading Test (NAART), and the Controlled Oral Word Association Test (COWA). Symptom assessments were derived from a demographic and health history form, Everyday Cognitions Scale (ECog), Everyday Memory Questionnaire (EMQ), Florida Cognitive Activities Scale (FCAS), Functional Assessment of Cancer Therapy-Brain Tumor (FACT-BT), MD Anderson Symptom Assessment-Brain Tumor (MDASI-BT). Scores from 3 survivors of PBT were compared to those from 11 healthy control subjects.

Feedback from subjects was used to modify the instruments used, lessen subject burden, and reduce time for study completion. Study protocols were adjusted to permit questionnaires to be completed at home, and to reduce the number of trials on a touch/vibration recognition and reaction time task. All subjects who opted to take the symptom assessments at home returned

them. Being able to answer the symptom assessments at home allowed the neuropsychological measures to be performed early in the study protocol, thereby reducing subject fatigue.

Preliminary Report of Subject Scores

A total of 14 subjects participated: 3 men and 8 women in the healthy control (HC) group; 1 man and 2 women survivors of PBT. The two female PBT subjects also participated in a structured interview that focused on describing their symptom experience trajectory. Ages for all subjects (listed in Table 3.1) were similar, with healthy controls (HC) averaging 46.5 years [standard deviation (SD) 7.7 years]; PBT subjects averaged 46.0 years (SD 1.0 years). Education, while not matched, was slightly higher for HC group at 13.7 years (SD 2.4 years) compared to the PBT group at 12.3 years (SD 0.6 years). Survivors of PBT all had malignant tumors, diagnosed 9 years (SD 1.4 years) before study enrollment; all three received similar therapies, consisting of gross total resection, radiation, and chemotherapy for at least one year.

Both groups reported a similar global health status (Table 3.1). Several HC subjects were on blood pressure medications, but no subjects took medications for sleep, anxiety, or depression. Protocol enrollment screening MMSE scores were similar: HC group scored 29.9 (SD 0.3) and PBT group scored 29.1 (1.0). Scores on the MMX, a variant of the MMSE global cognitive screening tool that incorporates more ECF and delayed memory items, were slightly higher for the HC group at 49.8 (SD 0.4) than the PBT group at 47.7 (SD 2.5) out of a potential 50 point total. Neither group endorsed depressive symptoms (CESD-R). However, premorbid intelligence as measured by the North American Adult reading Test (NAART) was greater in the HC group; HC subjects read 39.7 words (SD 20.5) compared 23.3 (SD 11.9) words in the PBT group.

Table 3.1.

Comparison of Executive Control Function by Subject Scores.

	Normal Range	PBT #1 Scores	PBT #2 Scores	PBT #3 Scores	Healthy Controls (n=11) Range	Mean	SD
Subject Characteristics							
Age		45	47	46	30-52	46.5	7.7
Education		12	12	13	8-16	13.7	2.4
Global Health Characteristics							
MMSE	0-30	29	28	30	29-30	29.9	0.3
NAART	0-61	18	37	15	10-60	39.7	20.5
CESD-R	0-60	35	27	26	20-33	23.4	3.9
Executive Control Function							
EXIT-25	0-50	4	4	5	0-4	0.91	1.4
COWA Total	Unlimited	54	45	17		48.5	3.9
Letter C	d	22	14	13		16.7	4.1
Letter F		20	17	4		15.7	3.1
Letter L		12	14	0		16.0	4.9
Trails B	0-300	112	120	80	45-109	73.9	21.5
SDMT	0-72	51	2	35	30-56	45.2	9.3
Self-Reported Everyday Function							
OARS: Total	0-28	26	28	28	27-28	27.9	0.3
ADL	0-14	13	14	14		14	
IADL	0-14	13	14	14		13.9	
FCAS: Current	0-100	84	97	87		94.7	
10 years ago		91	120	73		88.3	
Everyday Memory	0-52	38	34	17	14-26	18	3.2
ECogTotal	0-4.0	3.3	1.9	1.1	1.0-1.3	1.3	3.9
Memory	0-4.0	4.0	2.8	1.1		1.3	1.9
Language	0-4.0	3.0	2.0	1.0		1.0	1.9
Visuospatial	0-4.0	2.4	1.4	1.0		1.0	0.0
Planning	0-4.0	2.4	1.2	1.0		1.0	0.4
Organization	0-4.0	3.5	1.3	1.2		1.1	1.7
Divided Attention	0-4.0	4.0	2.0	1.5		1.1	1.0

EXIT-25=Executive Interview-25; COWA=Controlled Word Association Test; SDMT=Symbol Digit Modalities Test; OARS=Older Adults Resource Services Activities of Daily Living and Independent ADL; FCAS=Florida Cognitive Activities Scale; ECog=Everyday Cognitions Questionnaire

On the EXIT-25, HC subjects averaged 0.9 (SD 1.4) points out of 50 while the PBT group averaged 4.3 points (SD 0.5). Items that were consistently missed by the PBT group were design fluency (creating designs with 4 straight lines), a complex Luria hand sequence (three rapidly alternating hand movements), and a visual counting task (number of fish with a

distractor). Subjects in both groups averaged the same number of words on COWA for letter C (HC 16.7, SD 4.1; PBT 16.3, SD 4.9); the second letter F showed more variation, with HC producing 15.7 words (SD 3.1) compared to 13.7 (SD 8.5) in the PBT group. One subject with PBT opted not to continue with the third letter, L; HC group averaged 16.0 words (SD 4.9) and the two PBT subjects averaged 13.0 words (SD 1.4). For the SDMT, the HC group substituted 43.6 items correctly (SD 9.3), compared to PBT group's 29.3 (SD 25.0). One subject with PBT did not follow instructions resulting in a score of 2 although she did substitute 55 items correctly during the timed examination. The HC subjects performed Trails-B in 73.4 seconds (SD 21.5), but subjects with PBT were delayed for an average of 104 seconds (SD 21.2). One subject with PBT had errors and opted not to proceed after corrective instructions.

Assessments of everyday function on the OARS Activities of Daily Living Scale showed that both groups were similarly able to perform activities of daily living, with HC group scoring 27.9 (SD 0.3) and the PBT group, 27.3 (SD 1.1). However, on the Florida Cognitive Activities Scale, subjects with PBT reported performing an average of 7 (SD 1.4) cognitive activities compared to HC group's 13.5 activities (SD 0.7). The PBT group reported that they altered their lifestyles, eliminating an average of 14 activities (SD 2.8) since diagnosis; the HC group had altered 4 activities on average (SD 2.8) in the preceding 10 years. On the Everyday Cognitions Questionnaire, the PBT groups scored all items as consistently worse since diagnosis and the HC reported no change. On the Everyday Memory Scale, subjects with PBT reported more concerns with their memory, averaging 7.5 issues (SD 0.7) compared to HC group averaging 2.5 issues (SD 0.7).

Compensatory Strategies

The compensatory strategies subjects with PBT incorporated into their performance are shown in Table 3.2. Field notes were recorded during study participation. Using constant comparative analysis (Charmaz, 2006; Glaser & Strauss, 1967), the field notes and answers on the FCAS were reviewed to detect recurring behaviors.

Behavioral observation: These types of behaviors were observed during the feasibility study.

1. The survivors of PBT took more time to complete the study battery, ranging of 1.5 to 3.5 hours as compared to 45 minutes for the healthy control group.
2. All 3 survivors of PBT took more breaks during the study. During these breaks they told stories, talked about their families, and asked health-related questions. All of the healthy control subjects attended to the study battery moving from test to test to complete the battery quickly. They did not take any of the breaks offered.
3. All 3 survivors with PBT stayed focused on the testing tasks, especially the timed instruments. Thus, the stories and questionnaires tended to occur during times between tasks or while answering items on the questionnaires. Then, the PI was required to redirect the subject's attention back to the study battery for completion.
4. One survivor with PBT focused on speed for two timed instruments rather than accuracy in completing the task according to directions; this resulted in more errors.
5. Despite the breaks, all of the survivors with PBT reported feeling fatigued at study completion.

Table 3.2.

Characteristics of behaviors exhibited by PBT subjects during testing procedures.

<u>Characteristics of Behaviors</u>	<u>PBT #1</u>	<u>PBT #2</u>	<u>PBT #3</u>
Time to complete in hours	1.5	1.7	3.5
Fatigue	X	X	X
Pacing	X	X	X
Repetition			X
Engagement	X		X
Perfectionism	X	X	
Motivation	X	X	
Effort	X	X	X
Frustration	X	X	
Early Termination		X	X

FCAS: The FCAS provides an opportunity to explore the cognitive activities subjects perform currently, and what activities or behaviors have changed since diagnosis. Using it in an interview format allowed the PI to probe for more information regarding why they changed the behaviors. In general, the healthy control subjects stated they had not changed activities over the past 10 years. The responses from the 3 survivors with PBT are as follows:

- The most common reason that behaviors or activities were stopped was that the subjects did not enjoy it much anymore. Additional reasons included: the activity required too much time, it involved interaction with others, or it was more difficult to perform since their diagnosis.
- Subjects engaged in fewer social activities than before their diagnosis, primarily because they felt others became frustrated with their slower performance.
- Subjects continued to drive, but only to familiar places. Using maps or global positioning devices, and learning new roads were difficult, and they were concerned about getting

lost. Further, none of the survivors with PBT drove on highways because they felt unsafe and distracted by the other vehicles.

- Subjects used lists to remember appointments, conversations, and shop.
- Subjects did not recall when they had started altering behaviors or activities but believed the changes occurred predominately during their chemotherapy treatments. While they did not resume any activities they had stopped during treatment, they continued to reduce their activities over time.

Symptom Experience for 2 Survivors of PBT

Two of the survivors with PBT participated in a structured interview to explore the symptom experience. The questions were open-ended, promoting subject perception of symptoms experienced since diagnosis and the perception of impact on their lives. In these interviews, symptoms of cognitive impairment, fatigue, and sleep disturbance were described as persistent, interfering with quality of life, and causing the most distress in the respective order of severity. Furthermore, the subjects were unaware that these symptoms might persevere after treatment completion and during remission (both survivors had been diagnosed 10 years before the interview). Using constant comparative analysis (Glaser & Strauss, 1967; Charmaz, 2006), differences in symptoms through their trajectory of illness are outlined on Table 3.3.

Specific concerns regarding the progressive worsening of cognitive function and its impact on everyday function were foremost in their descriptions. Particular issues regarding cognitive function were changes in executive control, specifically relating to memory, attention, motivation, ability to multitask (resulting in loss of work), inability to drive distances, and inability to learn new tasks.

Table 3.3.

Matrix of survivorship issues over the illness trajectory in 2 survivors with PBT.

<u>Issue</u>	<u>Diagnosis</u>	<u>Treatment</u>	<u>Survivorship</u>
Health Care Process	Many doctors Throwing fits Demanding scan	Surgery Radiation Chemotherapy	“Fighter” with aggressive therapies Balancing scientific vs. spiritual meaning in their lives
Symptoms	Intense headaches Visual disturbances Projectile vomiting “Something is wrong”	Nausea, Constipation Weak spells or fatigue “Brain cancer is different”	Anxiety, apprehension Memory/cognitive Getting lost, forgetting tasks “Feeling dumb”
Support	Husband on phone, Family flew in, Intensive care	Husband, family, church and community support	Husband, family, children Helping other cancer patients
Life Impact	Frustrating experience	Concern @ hair, Loss of others with cancer	Frustrating disability, loss of work, near bankruptcy, fear of driving, loss of independence, concerns about being safe

Summary of Feasibility and Pilot Findings

Feasibility: By adding measures of psychomotor control to standard measures of ECF and more clinically relevant evaluations of ECF, differences in the relationship of ECF to everyday function were observed in the adult survivors with PBT when compared to healthy control subjects. Feedback from subjects was used to modify battery protocol, instruments used, subject burden, and reduce time for study completion.

Pilot findings: Subjects with PBT had lower performance scores than healthy control subjects. These analyses are consistent with patient and family reported concerns of cognitive dysfunction and its impact on their everyday lives. Additionally, subjects with PBT exhibited several behaviors during testing that were not demonstrated in the healthy control group:

difficulties with shifting attention, eliminating distractions, and speed of processing. These observations of compensatory behaviors used during cognitive performances most likely represent some of the compensatory behaviors PBT survivors incorporate into their everyday function and require further study.

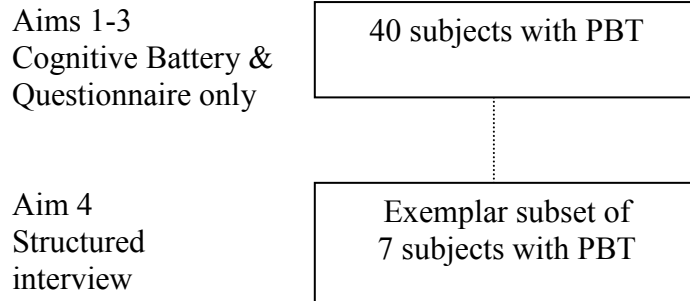
CHAPTER 4: METHODS

The specific aims for this study were to: 1) describe executive control function (ECF) and its components in adult survivors of PBT; 2) describe self-reported cognitive function in those survivors; 3) describe the relationship of ECF performance scores to subject self-report scores, and 4) explore whether cognitive reserve or compensatory behaviors explain the agreement or disagreement between ECF performance scores and subject self-report scores.

Study Design

A cross-sectional, descriptive-exploratory design was used to address the study aims (Figure 4.1). All subjects completed the study testing and questionnaire in one session. Forty survivors of PBT completed a structured, 100-minute battery of neuropsychological and symptom assessment questionnaires. Seven subjects agree to participate in an additional 30-minute structured interview following the cognitive testing. The study protocol was approved by UNC Hospitals and Duke University Health System Institutional Review Boards, and Lineberger and Duke Cancer Center Protocol Review Committees.

Figure 4.1. *Study Design*



Sample

Twenty-two female and 18 male subjects were recruited from UNC and Duke Cancer Centers; all were English-speaking, and between 30 and 65 years old. All participants demonstrated adequate global cognitive function by scoring >30 on the Telephone Interview for Cognitive Status (TICS) (Brandt, Spencer, & Folstein, 1988) and accumulating >24 points (M 28.6, SD 1.6) on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). All subjects had received chemotherapy, radiation therapy, or both for treatment of their PBT, and had completed treatment at least 1 year before their participation in this study. All subjects denied additional neurological, cardiovascular disorders, or psychiatric disorders that might mask treatment-related cognitive impairment. All subjects were determined by their neuro-oncologist to have a stable tumor status within 15 days of study participation. Subjects with epilepsy related to their PBT were medically stable, and had had no change in medications during the 6 months before participation.

Exemplar subset.

Subjects who reported 5 or more cognitive concerns on the Everyday Cognitions Scale (ECog) during telephone screening (described in Telephone Screening Procedures) were eligible to participate in a structured interview following the cognitive battery and questionnaire; 7 of the

40 subjects were eligible and completed the structured interview. This exemplar subset comprised 4 women and 3 men aged 52.3 years old (SD 6.6 years). They had an average of 15 years of education (SD 1.3) and scored an average of 28.3 on the MMSE (SD 0.9). Six subjects were retired but one was still employed; 3 of the subjects lived alone.

Setting and Recruitment

Participants were recruited at two sites: 1) the Lineberger Neuro-Oncology Clinic of University Hospital (Lineberger), University of North Carolina in Chapel Hill, North Carolina, and 2) the Preston Robert Tisch Brain Tumor Center, Duke University Health System (Tisch), Durham, North Carolina. Both clinics are NIH-designated Comprehensive Cancer Centers that provide care to people of varying socio-economic and cultural backgrounds from time of diagnosis through end-of-life. Physician support was provided by Dr. Wu at UNC and Dr. Desjardins at Duke. Recruitment began in December 2011 and was completed in September 2012.

The study was conducted in two locations at the subject's convenience: Duke University Tisch Neuro-Oncology sites or the UNC School of Nursing (SON) Biobehavioral Lab (BBL). Both locations provided a comfortable setting with a convenient bathroom and an area for breaks.

Eligibility and Scheduling

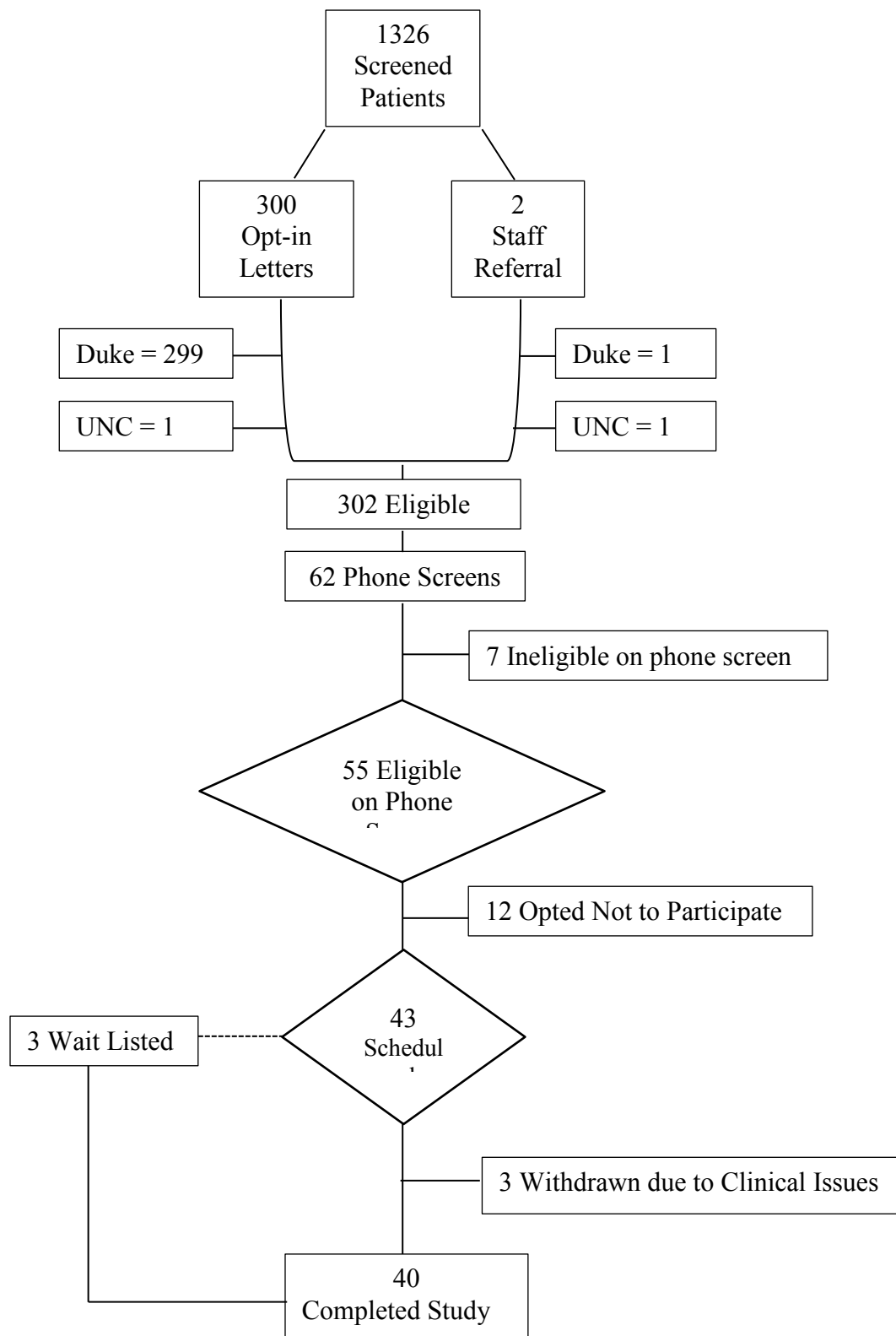
Patients with primary brain tumors (PBT) scheduled for a neuro-oncology clinic visit were screened for recruitment between January and September 2012. Three hundred of 1266 patients scheduled at the Preston Robert Tisch Brain Tumor Center and 2 of 60 patients

scheduled at the UNC Lineberger Neuro-Oncology clinic, met the criteria for study participation (Figure 4.2). Three hundred opt-in recruitment letters were sent, and 60 individuals who expressed interest (a 20% response rate). Another 2 subjects were identified during their clinic visit and referred to the PI for discussion. Both met eligibility criteria and agreed to participate. Although recruiting took place at two sites, 61 of the 62 responders were patients at the Preston Robert Tisch Brain Tumor Center at Duke.

The opt-in letter instructed all responders to leave a voice message on the PI's private office line requesting more study information. All responder phone numbers were correct and all responders were contacted within 24 hours of their initial call or at a time requested by the responder. In 7 cases (11%) an additional call from the PI was needed to arrange the telephone screening.

Of the 62 responders, 7 were not eligible for study due to neurological instability or recent illnesses. Twelve of the remaining 55 had scheduling conflicts and opted not to participate. The first 40 of the remaining 43 responders were scheduled for study participation, and 3 were placed on a wait list. One scheduled subject withdrew prior to participation due to tumor recurrence requiring surgical intervention. Two additional subjects who completed the study battery were excluded from analysis because of tumor recurrence detected by clinical evaluation and MRI review. The three wait-listed individuals were therefore included to give a final sample size of 40 subjects.

Figure 4.2. *Flow diagram of study recruitment.*



Screening and Scheduling Procedures

Subjects were screened in two phases (a telephone screen and a laboratory screen), whose components are listed in Table 4.1.

Table 4.1.
Two Step Screening Procedures

	<u>Telephone Screen</u>	<u>Laboratory Screen</u>	<u>Time to Complete</u>
Phone Recruitment & Description of Study	X		2 minutes
Mini-Consent for Health Screening Questionnaire	X		1 minute
Health Questionnaire, Telephone Cognitive Screen, & Modified ECog Questionnaire	X		8 minutes
Subject Information Packet	X		2 minutes
Subject ID & Scheduling	X		2 minutes
Informed Consent		X	5-10 minutes
Laboratory Health Screen		X	5 minutes
Mini-Mental Status Examination		X	5 minutes
Subject Eligibility Form		X	1 minute

Telephone screening protocol.

The telephone screen determined eligibility based on a few questions about health status, medications, and dementia status. The telephone screen was performed by the PI because it involved medical information with which the research assistant had no experience. On average, this screen took 15 minutes to complete.

Study description & verbal mini-consent.

If responders opted to participate after the initial discussion with the PI about the purpose of the study and its general description, a verbal consent (scripted and IRB approved to assure a standardized approach for all responders) was obtained before assessing their enrollment eligibility.

Eligibility determination.

A health history and medication tool was used to survey all subjects regarding their health history and current medication use. Subjects were excluded if they had neurological or cardiovascular disorders prior to their PBT diagnosis, were taking psychoactive medications, had a history of alcoholism or illegal substance abuse, or if there was a family history of dementia syndromes (Table 4.2).

Table 4.2.
Criteria for eligibility

<u>Eligibility Criteria</u>	<u>Phone Screen</u>	<u>Lab Screen</u>
Age 30 to 65 years old	X	
Read and write English language	X	
Primary Brain Tumor:	X	
Treated with prior chemotherapy or radiation therapy		
No signs of paresis or aphasia.		
Has stable tumor status determined by neuro-oncologist		
Stable seizure status for last six months with no antiepileptic medication changes in the last six months	X	
TICS > 30 points	X	
MMSE > 24 points		X
Signed informed consent		X
* <i>Exclusion Criteria:</i> Exclude subject if yes to any of these		
General anesthesia within the last six months	X	
Paresis or Aphasia	X	
Known neurologic or cardiovascular disorders listed in Health History Screen (Example: Parkinson's disease, multiple sclerosis, Alzheimer's disease, CVA, immune disorders, depression, sleep disorder)	X	
Medications:	X	
Dopaminergics (Pramipexole, Ropinirole, Carbidopa, Levodopa)		
Major anticholinergics (Example: Phenothiazines, Antiparkinson meds)		
Alzheimer's medications (Aricept, Remeril, Exelon, Namenda)		
Chemotherapy: Carmustine, Lomustine (CeeNU), Carboplatin, Temozolomide (Temodar), Etoposide (Vepesid, VP-16), Irinotecan (CPT-11, Camptosar), Procarbazine (Matulane)	X	

The Telephone Interview for Cognitive Status (Brandt, Spencer, & Folstein, 1988) was administered to screen for dementia. This screening tool uses 11 items to assess orientation, immediate and delayed recall, attention, language and verbal fluency, counting and calculating, and nonverbal praxis. Scores range from 0 to 41, with higher scores indicating higher cognitive performance. This screen has 94% sensitivity and 100% specificity for dementia with cutoff scores at 30. Test-retest reliability is .965 and the intra-class correlation coefficient is .99 (Brandt, Spencer, & Folstein, 1988).

Exemplar subset screening.

The Everyday Cognitions Scale (ECog) (Farias et al., 2008), was modified to screen potential subjects for ECF impairment. Individuals with mild, multiple-domain cognitive impairment report difficulties on a third or more items on the ECF subscales (Farias et al., 2008), so it was hypothesized that inability to complete one-third of the 15 items would identify PBT responders with ECF impairments who could be interviewed regarding use of compensatory behaviors and engagement in cognitive activities. Seven subjects were thus identified and agreed to participate in the additional structured interview.

Subject information packet.

Subject information packets were sent to all eligible responders. This packet provided directions to UNC SON Biobehavioral Laboratory or the Tisch neuro-oncology clinic laboratory room in Durham, the date and time they were scheduled, and specific information regarding instructions for the night prior to and morning of the study procedures.

Subject ID assignment.

All individuals who started the telephone screening procedures were assigned a respondent identification number. A subject ID was assigned for those deemed eligible *after*

completion of the telephone screen. These IDs were linked with data collection forms used during study procedures.

Subject scheduling for study participation.

Upon completion of the telephone screen, the PI completed the Scheduling Form, which listed subject study date and time preferences, and served to facilitate the scheduling time in the UNC SON BBL or the Tisch BTC clinic laboratory room. Because many of the subjects come from long distances for their neuro-oncology care, every attempt was made to schedule the study battery at their convenience. Since neuro-oncology clinic visits may be long and stressful and long, and in order to obtain their best cognitive performance, study subjects were encouraged to participate the day before or after their clinic encounter. Responders living near the study sites were offered other scheduling opportunities To promote optimal cognitive performance, study participation was scheduled 10 am and 2 pm.

Laboratory screening protocol.

Laboratory site.

Data collection took place in the same room as the laboratory consent and screening at either the Tisch neuro-oncology clinic or UNC SON BBL. Each subject was escorted by the PI or research assistant to a comfortable room containing all essential study equipment. The room temperature was kept between 70 to 72 degrees to promote a similar and comfortable atmosphere at both facilities.

Laboratory consent.

Upon arrival at the UNC School of Nursing BBL or the Tisch BTC clinic, subjects were made comfortable before beginning the laboratory consent. The PI or research assistant provided the subject with an outline of the study procedures, and answered any questions regarding study

purpose and procedures. The subject was then allowed to read the consent, or to have the PI or research assistant read the consent to them if they preferred. The study purpose, procedures, duration, risks, benefits were explained, as well as the subjects' right to confidentiality and to withdraw from the study at any time without reprisal. Subjects were encouraged to discuss questions or concerns regarding participation in the study and were informed how to contact the PI should they wish to discuss issues after study completion.

Laboratory screen.

After obtaining consent, the research assistant inquired about health or medication changes that might affect eligibility status, and recorded their vital signs. The study was rescheduled if the subject reported any of the following conditions that might interfere with cognitive function: use of "cold" medications within the past week; procedures requiring general anesthesia within the past two weeks; alcohol intake in the last 24 hours; smoking of tobacco products within four hours of testing procedures; use of sedative or hypnotic medications the night prior to study procedures unless routinely taken; or a fever or cold at the time of study procedures. The health and medication answers and vital signs were recorded on the Health Information Survey form.

The Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was administered upon completion of the health eligibility screen. The MMSE takes approximately 10 minutes to complete and has been used extensively as a screening test for global cognitive impairment. The test items assess orientation, short-term memory, attention and calculation, constructional abilities, and language abilities. Total scores range from 0-30; higher scores indicate better cognitive performance. The recommended criterion score of 24 as a threshold for cognitive impairment was used to determine eligibility for study enrollment. The

calculated score and all papers used for drawing were kept with the subject data files. If subjects were to fail to score above 24, data collection would cease and the PI or research assistant would conclude participation by thanking the subject for his or her interest. The protocol also called for the PI to discuss their ineligibility with them due to the low score on the MMSE and urge them to contact a medical provider for appropriate follow-up. The data were not to be retained, but a log indicating that the subject was ineligible due to low MMSE score was developed.

Protection of Human Subjects

Risks to subjects were considered minimal, but include that subjects may perceive that they were either depressed or too cognitively impaired to complete the study. To minimize distress, the PI was available throughout testing procedures to respond to concerns about the procedures. The test batteries were assigned tolerable time intervals (<15 minutes each), performed in a private room, and subjects observed for signs and reports of fatigue. All issues regarding subject responses to any component of the study protocol were discussed in weekly meetings with Dr. Carlson.

Subject numbers were placed on the data collection forms; names were not used. Subject identification and consents are stored in a locked file cabinet separated from subject data. All digitized data, video recordings, and computers are password protected and stored in a locked cabinet; data files will be destroyed after analyses are completed. Backup electronic copies are archived at another site on campus.

Variables and their Measurement

The variables analyzed in this study consist of: 1) executive control function (ECF) with components of attention and working memory; 2) self-reported ECF; 3) cognitive activities; and 4) descriptive factors. Table 4.3 outlines the variables and their measurement. When subjects refused to participate in any measure, the total score was indicated as missing.

Table 4.3.
Variables, their Measurement and Reliability.

Variable	Measurement	Internal Consistency (α)	Test-Retest Reliability (r)
Executive Control Function & components: ECF	EXIT-25 CTB Composite TMT Difference	.83 (Royall et al., 1992)	
Attention	Trail Making Tests, Parts A and B	.96 (Lezak et al., 2004)	.95 (Lezak et al., 2004)
	Symbol Digit Modalities Test	.70 (Smith, 1991)	.74 (Mitrushina et al., 2005)
Verbal Fluency	Controlled Oral Word Association	.83 (Ruff et al., 1996)	.74 (Ruff et al., 1996)
Working Memory	Hopkins Verbal Learning Test	.74 (Mitrushina et al., 2005)	.74 (Mitrushina et al., 2005)
Observed Compensatory Behaviors (from field notes)	Identified during cognitive testing, may include: Taking a break Corrections Starting Over Halting Repeating		
Self-reported cognitive function	Everyday Cognitive Scale	.80 (Farias et al., 2008)	.82 (Farias et al., 2008)
Cognitive reserve	Hollingshead Index NAART	.72 (Blair & Spreen, 1989)	
Self-reported Compensatory Behaviors *	Florida Cognitive Activities Scale	.65 (Schinka et al., 2005)	.55 (Dotson et al., 2008)
Descriptive Measures	Demographics Survey Health Information Survey CESD-R MDASI-BT FACT-BT	.90 (Burnam et al., 1988) .91 (Armstrong et al., 2006) .83 (Weitzner et al., 1995)	.40 (Radloff, 1977) .80 (Armstrong et al., 2005) .78 (Weitzner et al., 1995)

* Subset of 7 survivors with PBT participated in structured interview at end of study battery.

CESD-R=Center for Epidemiologic Studies for Depression, Revised scale; EXIT-25=Executive Interview-25; CTB Composite=Clinical Trials Battery Composite; FACT-BT=Functional Assessment of Cancer Therapy-Brain; MDASI-BT=MD Anderson Symptom Inventory-Brain Tumor; NAART=North American Adult Reading Test; TMT Difference=Trails Making Test Parts B minus A Difference score

Executive control.

Executive control is defined as the capacity to plan, organize, and monitor the performance of goal-directed activities from beginning to end of an activity (NIH, 2010).

Executive control is an everyday function (Valenzuela & Sachdev, 2006). demonstrated by coordinating activities, making decisions, planning and sequencing actions, correcting errors or inhibiting behaviors through the initiation and organization of goal-directed activities (Farias et al., 2008). Executive control dysfunction, defined as impairment in one or several components of function, such as attention or memory, is predictive of inability to perform activities of daily living ([ADL]; Royall, Palmer, Chiodo, & Polk, 2004). Executive control dysfunction was measured by the following instruments and composite scores:

1. The Executive Interview-25 (EXIT-25) (Royall, Mahurin, & Gray, 1992) is a 25-item functional examination developed to elicit responses indicating global executive control function. EXIT-25 assesses verbal and design fluency, motor and impulse control, frontal release signs, imitation behaviors and clinical signs of frontal lobe dysfunction. Each item is scored individually according to subject response: 0 = correct answer, 1 = partially correct (as determined by Royall and colleagues), or 2 = incorrect, failure to complete, or refusal to answer. Response items are summed, with total scores ranging from 0 to 50. Scores of 15 or higher indicate ECF impairment, with higher scores indicating more severe impairment. The EXIT-25 total score correlates well with Trails B ($r=.64$) test, and is predictive of ADL function (Royall et al., 2004). This examination is completed in 30 minutes or less.
2. Clinical Trials Battery Composite (CTB Composite) (Johnson, Sawyer, Meyers, O'Neill, & Wefel; 2012) is a composite score signifying performance on tests of memory, attention, and verbal fluency. This composite score provides a comprehensive determinant of ECF, and is

used as a measure of cognitive function in clinical trials with PBT subjects. In the present study, the difference between raw performance scores for each instrument and the age- and education-specific normed mean for that instrument was calculated. This difference was divided by the normative SD to determine the z-score, and the z-scores for each instrument were averaged to derive the subject's CTB Composite score.

3. Trails Making Test Parts B minus A Difference score (TMT Difference) measures the difference in cognitive demand between the Trails Making Test Parts A and B by controlling for the motor, visual, and speed components required in both tests (Arbuthnott & Frank, 2000; Sánchez-Cubillo et al., 2009). The raw scores from Parts A and B are subtracted to calculate the subject's difference score. This is then subtracted from age- and education-specific normed TMT Difference scores and subsequently divided by the normative SD to determine the TMT Difference z-score.

Components of Executive Control.

As with many cognitive functions, measurement of the components of ECF often overlap, but are considered to have two main subcomponents: attention and working memory.

Attention.

Attention refers to the cognitive capacity to handle environmental stimuli. Attention is described as having three common components: 1) focused attention, also known as selective attention, is defined as the capacity to focus on one or two stimuli while suppressing competing distractions; 2) sustained attention, or vigilance, refers to the capacity to maintain attention over time; and 3) divided attention capacity refers to the ability to perform two tasks simultaneously, which requires the capacity to shift focus in attention (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Lezak, 2004). These components of attention are measured by processing speed,

accuracy and error rates, scanning, set-shifting, and distraction. Dysfunction in attention results in slowed processing, diminished performance accuracy and an increased error rate. Thus this study assessed attention with the following tests: 1) processing speed, or the capacity to perform a function accurately within a specified timeframe, measured by the Trail-Making Test – Part A; 2) set-shifting, the capacity to switch among multiple aspects of a strategy or task, is measured by the Trail-Making Test - Part B; 3) inhibition of automatic response tendencies that interfere with achieving a goal is measured by the Trails Making Tests and Symbol Digit Modalities Test.

1. The Trail Making Tests ([Trails A and B]; Partington & Leiter, 1949) are designed to measure attention, sequencing, and mental flexibility during motor control and visual search tasks (Lezak, 2004). Trails A requires the subject to sequentially connect 25 encircled numbers, and Trails B requires the subject to alternate encircled numbers 1 through 13 with encircled letters A through L. In both tests, the encircled items are randomly distributed on an 8" x 11" page. Subjects are asked to connect the numbers sequentially in Trails A, or the alternating sequence of numbers and letters in Trails B, as quickly and accurately as possible. Subjects are corrected if they make an error between numbers or numbers and letters; errors are not scored, but the mistake and correction prolongs performance time. Total time in seconds to complete the task is the primary outcome, with faster times indicating more efficient visual searching and better selective attention. Maximum time allowed for each test is 5 minutes; subjects were allowed to complete the task but the time score assigned was 5 minutes. Trails A and B correlate only moderately with one another ($r = 0.49$), suggesting each measures slightly different visual search and cognitive set-shifting functions (Lezak, 2004). Both tests correlate highly with caudate atrophy in patients with Huntington's disease, $r_A = 0.72$,

$r_B = .80$ (Starkstein et al., 1988). The Trail Making Tests are a component of the preferred neuropsychology battery developed by Meyers and Brown (2006) for use in adults with PBT.

2. Symbol Digit Modalities Test (SDMT) (Smith, 1991) tests attention through visual search.

The SDMT requires subjects to scan and track 9 symbols that are paired with 9 substitute numbers. The SDMT presents 11 rows containing varying symbols with 110 total blank squares beneath paired responses. The subject is instructed to enter the correct substitute number beneath the symbol, and complete the sequential rows within 90 seconds; accuracy is emphasized over speed. The total number of correct items is counted, and scores range from 0-110, with higher scores indicating better performance in attention. The SDMT correlates highly with the Wechsler Adult Intelligence Scale Revised Digit Symbol test, $r = 0.91$ (Morgan & Wheelock, 1992) in neurology clinic outpatients. This measure is a component of the NIH Toolbox for use in brain-injured patients.

Working memory.

Working memory an updated construct for “short-term memory,” refers to a cognitive storage buffer with limited capacity (Baddley, 2010; Repovš & Baddeley, 2006) and no ability to process beyond the capacity. Working memory is responsible for: 1) processing information across tasks and modalities, 2) storing this information in a short-term buffer, 3) manipulating the information for further cognitive processing, and 4) subsequently storing the outcomes or products (of #3) in the same short-term buffer (Baddley, 2010). Working memory was assessed using the Hopkins Verbal Learning Test.

The Hopkins Verbal Learning Test – Revised (HVLT) (Shapiro, Benedict, Schretlen, & Brandt, 1999) measures new learning, short- and long-term memory, and word recognition. The subject is read 12 words in three successive trials with free recall recorded following each trial.

Total number of correct responses for short-term free recall (HVLT Recall) are recorded and summed to provide a maximum total score of 36. The maximum time allowed for this portion of the test is 5 minutes; at the end of 5 minutes, the total number of words successfully recalled constitutes the HVLT Recall score. Following a delay, the subject is presented with a yes or no recognition test (HVLT Recognition). The subject is read a list of 24 words; 12 of which were not formerly presented but are used as distracters because they are semantically related to the previous words. The total HVLT Recognition score sums correct identifications minus misidentifications; this score may range from -12 to +12. The final portion of this test is a 25-minute delayed free recall (HVLT Delayed) in which the subject is asked to recall the original 12 words; maximum score is 12. The HVLT is a valid measure of memory that is highly correlated with the Brief Visuospatial Memory Test-Revised in patients with non-lateralized brain injuries or psychiatric illness, $r = 0.80$ (Benedict et al., 1996). HVLT is a component of the preferred neuropsychology battery developed by Meyers and Brown (2006) for use in adults with PBT.

Verbal fluency.

Verbal fluency refers to the ability to use one or more strategies to rapidly generate specific exemplars of a response category (e.g., words that begin with specific letters or types of animals) while avoiding response repetition (working memory component). Verbal fluency was measured by the Controlled Oral Word Association Test.

The Multilingual Aphasia Examination - Controlled Oral Word Association (COWA) (Benton, Varney, & Hamsher, 1978) is based on word retrieval to assess verbal fluency. Over a 60-second interval, subjects are instructed to say aloud as many words as they can that begin with a specific letters of the alphabet (either C-F-L or P-R-W, with both selections providing equal difficulty levels). Proper names and multiple forms of the same word are not counted. The

letters are selected based on the known frequency of words in the English language and subsequent letters in each series are more difficult than the preceding letter. The total words produced using all three letters, regardless of early cessation or refusal to continue, are summed for a total score. Duplicate words, multiple word reiterations, and use of proper nouns are summed as errors. The COWA is a valid measure of ECF, particularly attention, and correlates moderately well with ability of individuals with Alzheimer's disease to read a telephone book, $r = 0.40$, or balance a checkbook, $r = 0.45$ (Loewenstein et al., 1992). The COWA is not highly influenced by prior education, and correlates poorly with the Wechsler Adult Intelligence Scale Verbal IQ ($r = .14$) used to measure premorbid intelligence (Yeudall et al., 1986). The COWA is a component of the preferred neuropsychology battery developed by Meyers and Brown (2006) for use in adults with PBT.

Self-reported cognitive function.

Self-reported cognitive function was assessed by the Everyday Cognitive Scale (Ecog) (Farias et al., 2008). The ECog Scale uses a 39-item questionnaire to assess subjects self-rating of current cognitive ability to perform everyday activities. There are a total of 6 subscales: memory, language, visuospatial and perceptual ability, and three ECF subscales. For each item, subjects are asked to compare their current ability to perform activities to their ability before their diagnosis, using the following choices: 1=better or no change, 2=questionable or occasional problems, 3=consistently a little worse, 4=consistently much worse, or 5=don't know. Higher ECog scores indicate the perception of increased problems with cognitive activities.

Cognitive reserve.

Cognitive reserve (CR) refers to the lifetime accumulation of cognitive achievement and experiences that create an efficient neural network that facilitates processing and compensation (Scarmeas & Stern, 2004). Proxies of CR include quantification of premorbid intelligence, occupational, and educational attainment. These were estimated with the North American Adult Reading Test (Blair & Spreen, 1989) and the Hollingshead 2-Factor Index for Social Position.

1. The North American Adult Reading Test (NAART) (Blair & Spreen, 1989) was used as a secondary screen for dementia and has been used to estimate premorbid intelligence. The NAART is a 61 item test that asks subjects to read aloud a list of words chosen because they are pronounced differently they are spelled, thus requiring the subject to be familiar with the word. The total NAART score represents the number of correct responses, with higher scores indicating higher intelligence. Subjects may stop reading words with which they have difficulty or are unfamiliar; however the PI or research assistant encouraged the subject to continue reading the list. Skipped or missed words and early termination of the test results are counted as errors and listed as incorrect responses. The NAART correlates moderately with the Wechsler Adult Intelligence Test Revised IQ subscale, $r = 0.62$, and Full Scale IQ, $r = 0.61$ (Blair & Spreen, 1989).
2. The Hollingshead 2-Factor Index of Social Position (Hollingshead Index) (Hollingshead, 1957) uses educational and occupational attainment to derive a solitary score for CR. Categories of occupations and categories of educational achievements are scored, then weighted for a summation index. Hollingshead Index scores range from 11-77 points; lower scores indicate higher levels of education and occupational attainment, and thus reflect higher CR.

Compensatory behaviors: Exemplar subset.

Compensatory behaviors are actions, or reactions to stimuli, used to achieve an expected outcome when performing tasks outside the range of normal task execution (Tomey & Sowers, 2009; Weiss, Hoenig, & Fried, 2007). These behaviors result from internal or external stimuli, and thus may be conscious or subconscious and overt or covert when used in everyday function. It is assumed that compensatory behaviors are present prior to the determination of clinical disability (Fried et al., 1996), but this may not be the case in persons with neuropathology such as are present in patients with PBT. Persons incorporating compensatory behaviors into everyday function tend to require more effort for task completion, and most underreport their use of compensatory behaviors (Weiss, Hoenig, & Fried, 2007; Fried et al., 1996). Thus, direct observation and structured interviews were used in the present study to detect behaviors used by survivors of PBT for task completion.

To identify compensatory behaviors used to perform daily cognitive activities, a structured interview was administered at the completion of study procedures. This interview incorporated subject responses to the Florida Cognitive Activities Scale (FCAS) (Schinka et al., 2005) and open-ended questions. In addition, field notes recorded during the observation of subjects' study participation were reviewed for identification of compensatory behaviors.

1. The FCAS is a 25-item questionnaire that asks subjects to recall their level of participation in cognitively engaging activities 10 years earlier, as well as their current level of involvement in the same activities. Subjects are asked to rate the level of activities as follows: 1=never did this activity; 2=have not done this in the past year; 3=less than once a month, 4=1-4 times a month; 5=5 times or more a month. "Is this a change?" is asked after every item to facilitate the subjects' reflection on activities they performed prior to diagnosis. Higher

ratings indicate greater participation in cognitively engaging activities. This questionnaire can be completed using pen and paper, but it was read to subjects out loud to prompt discussions regarding their participation in activities and to reflect on when and why changes may have occurred. To facilitate this discussion, the PI described the activity, followed with these statements:

- (1) Tell me more about *the activity you indicated a change in*
- (2) Tell me when you noticed *changes in the activity* occurring?
- (3) Tell me what may have prompted the *changes in the activity*?
- (4) Tell me what have you tried in order to continue performing *the activity*?

Do you think this worked? Tell me more about this. How long did this work for you?

Did you have to start doing it differently again? tell me more about this.

The FCAS correlates with the HVLT, Stroop Color Word Association Test, and Trails B in healthy controls and subjects with neurologic disorders ($r=.33$).

2. The open-ended questions were designed to facilitate subject description of behaviors and included:

- (1) Tell me what activities you found were easy (or difficult) to do?
- (2) Tell me how you maintained your energy to complete the tests?
- (3) Tell me what you did to be more accurate on the tests?

Through a pilot study of the structured interviews, it was learned that subjects were willing to discuss their cognitive performance, strengths, and weaknesses. Therefore, it was expected that these questions and structured interview format would facilitate the intended discussions.

3. Field Notes were recorded during the study procedures and after the subject left. These notes included observations of behaviors, thoughts for future consideration that were provoked during the study procedures, or statements to illuminate subject performances.

Descriptive data.

Descriptive data were collected in order to match patients with healthy controls on key variables, to describe the level of depressive symptoms, functional status, and self-rating of cognitive function, and to describe disease-specific symptoms in subjects with PBT. These measures included:

1. A Health Information Form designed by the PI to assess subject health status. It includes questions about date of birth, handedness to establish cerebral dominance, primary health care information, medications, and specifics regarding the brain tumor diagnosis and treatment regimen.
2. The Older Adults Resource Services Activities of Daily Living Scale (OARS) (Fillenbaum, 1978) is a 14-item questionnaire that elicits subjects' perception of their ability to perform activities of everyday life. Subjects were instructed to recall whether, over the last month, they could perform physical or independent activities without help, with some help, or not do them at all. Items were scored as: 0=completely unable to perform the activity yourself, 1=perform with some help, or 2=perform without help. Scores range from 0-28, with higher scores indicating a greater ability to perform activities of daily living.
3. The Functional Assessment of Cancer Therapy-Brain Tumor (FACT-BT) is a 33-item questionnaire that assesses five domains of well-being (physical, social and family, relationship with physician, emotional, and functional) in survivors of PBT (Weitzner et al., 1995). Item responses range from: 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit,

and 4=very much. Subjects were instructed to answer each item based on how they felt over the preceding week. Higher scores indicate more difficulties and lower quality of life. The FACT-Br had a modest correlation ($r = .47$) with the Ferrans and Powers Quality of Life Index-Cancer Version of (Weitzner et al., 1995).

4. The Center for Epidemiological Studies Depression-Revised Scale ([CESD-R]; Burnam, Wells, Leake, & Landsverk, 1988; Radloff, 1977) is an 8-item questionnaire used to detect depressive symptoms. Subjects were asked to rate symptoms over the preceding 7 days. Item responses range from: 0=rarely (< 1 day), 1=some of the time (1-2 days), 2=occasionally (3-4 days), and 3=most of the time (5-7 days). Higher ratings indicate the presence of depression. CESD-R correlates moderately with Hamilton's Rating Scale, $r = .44$, and Raskin Rating Scale, $r = .54$, for depressed adults admitted to a psychiatric hospital (Radloff, 1977).
5. The MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT) (Armstrong, Cohen, Eriksen, & Cleeland, 2005) is a 22-item questionnaire that measures six domains spanning affective, cognitive, focal neurologic deficits, generalized symptoms, constitutional symptoms, and gastrointestinal symptoms. Subjects were instructed to rate symptom severity and interference they had experienced over the preceding 24 hours. Item responses are based on 0="Not present" to 10="As bad as you can imagine" scale. Higher scores indicate greater symptom severity and problems for the subject.

Data Collection Procedures

All study procedures were performed by the principal investigator (PI) or a trained research assistant; study personnel responsibilities are described in study procedure components.

Cognitive and functional measures.

After obtaining consent and performing the laboratory screen procedures, subjects were asked if they need a bathroom or nourishment break. Opportunities for food and bathroom breaks were offered every 15 minutes to promote subject comfort, ease with testing procedures, and lessen subject fatigue.

All test instructions were scripted to ensure the use of standardized language by the PI or research assistant. All instructions, when appropriate, asked the subject to be as accurate as possible in their responses rather than seeing how fast they could complete the tests. In order to understand the effort required and the subject burden imposed, after each test the subject completed a visual analog scale (VAS; developed by the PI) to estimate the level of difficulty experienced with the test.

The order of administration of the instruments and questionnaires and their administration times were standardized in an attempt to ease subject burden and fatigue. Strict adherence to testing procedures was emphasized and subjects were not permitted to proceed to the next test until the allotted time had elapsed. The order of testing administration, expected times to completion, and transition times to start the next test are listed in Table 4.4.

Table 4.4.

Standardized Schedule: Study Procedures, their components, and time for completion.

<u>Procedure</u>	<u>Components</u>	<u>Recommended Time to Complete for <u>normal</u> subjects</u>	<u>Protocol (including VAS completion time)</u>	<u>Endpoint from Time 0</u>
Ready to administer				0
EXIT-25	EXIT-25	10 minutes	20 minutes	20
<i>Rest Break</i>		5 minutes	5 minutes	25
Neuropsychological	HVLT	4 minutes	10 minutes	35
Battery	NAART	2 minutes	5 minutes	40
	COWA	3 minutes	5 minutes	45
<i>Rest Break</i>		5 minutes	5 minutes	50
Neuropsychological	30 min Delayed Recall	5 minutes	5 minutes	55
Battery continued	HVLT	2 minutes	5 minutes	60
	Trail Making Part A	4 minutes	5 minutes	65
	Trail Making Part B	5 minutes	10 minutes	75
	SDMT	5 minutes	10 minutes	85
<i>Rest Break & Refreshments</i>		5 minutes	10 minutes	95
Structured Interview	Florida Cognitive Activities Scale	15 minutes	30 minutes	125
	Open-ended Questions			
Total Time including breaks		80 minutes	125 minutes	125 minutes

It was uncertain how the proposed structured battery might affect cognitive performance, so all subjects used the VAS to rate testing effort upon completion of the task. The VAS for subject self-rating of effort was based on a 10 cm line with markers from 0= “No Effort” to 10= “Greatest Effort.” After completion of each neuropsychology test (Trails A & B, COWA, HVLT, and SDMT) the subject was instructed to place a mark along the 10 cm line to indicate the perceived effort needed to complete the test. These analyses identified tasks felt by the subject to require more or less effort, and provided guidance for questions posed during the structured interview.

Self-report questionnaires.

All subjects were asked to complete a Subject Packet of self-report questionnaires (OARS, CESD-R, full ECog, MDASI-BT, and FACT-Br). To minimize burden, subjects were allowed to complete the forms at home and return them by mail. This option was used by 8 of 11 healthy control subjects and 1 of 3 subjects with PBT in the pilot study, and there was a 100% return rate.

Exemplar subset for structured interview participation.

The observational room in the UNC SON BBL was used to interview the subsample of 7 survivors with PBT. The room setup was standardized such that subject chair and table positions were marked for room conformity. A break was offered before the structured interview and after completion of the neuropsychological battery.

Study conclusion and payment.

Upon completion of the visit, the subject was thanked for their participation, provided \$25 for completion of the study procedures, provided a paid parking voucher, and given contact information for the PI. The subject was told to contact the PI with questions they may have arisen after completion of the testing. The PI sent a thank you letter to study participants.

Research Training & Fidelity Protocols

Research Assistant training.

A research assistant with experience in administering cognitive tests was hired and trained for all study procedures. While experience with adult survivors of PBT was not necessary, it was preferred that the research assistant have experience at administering tests to persons with cognitive issues.

Multiple training sessions were scheduled to assure consistency of study procedures and test battery administration the first session reviewed the purpose of the study and the reading aloud of study scripts: telephone screening, laboratory procedures, structured interview, and video-recording. This overview also covered data management procedures and the research and ethics training required by both IRBs. All procedures were detailed in a notebook developed by the PI.

Study procedure sessions focused on administration of the laboratory screens, obtaining informed consent, and test administration; these were rehearsed by the research assistant and PI in order to standardize administration procedures, consider ways to minimize subject burden and ease study procedure flow, and maintain consistency in testing procedures. Three sessions devoted to study procedure administration were used for training. Data management procedures were also rehearsed in these practice sessions to ensure that data transcription and maintenance was accurate.

The research assistant was introduced to both recruiting site physician sponsors and clinic staffs to enhance collaboration with the PI and facility staff in identifying, recruiting, and enrolling subjects. The research assistant worked with the PI during staff in-service education regarding study rollout and updates on study recruitment.

Research Assistant fidelity.

The PI monitored research assistant performance of study procedures for the first five subjects and every fifth subject thereafter. All audio-recordings were reviewed for adherence to study scripts, test schedule, and timing adherence. The PI and research assistant met after each review session to discuss procedure adherence, problems or issues encountered with study

procedure, subject concerns, and data management. Drift or deviations from protocols and procedures were corrected and study protocols were reinforced when appropriate.

Research fidelity.

Monthly meetings were held with Dr. Carlson to discuss issues addressed with the RA and ongoing data management and analyses. The PI also addressed any study procedure difficulties with Dr. Raynor in order to improve subject completion of the study battery, help RA performance, and promote subject engagement.

Data Management Procedures

Data were collected by the PI or research assistant and maintained by the PI. At the end of each session or when received from the subject, the neurocognitive battery, EXIT-25, and Subject Packet questionnaires were scored and recorded on paper forms, with all subscales and full scales totaled by hand. These data were entered by the PI twice into an SPSS database and backed up onto compact discs. Data were then compared and any discrepancies resolved by verifying correct responses from original paper forms. The data entry software was programed to perform range checks as data were entered.

Power Analysis

Power analyses were determined by Power and Precision™ software (Biostat Inc., Englewood, NJ) and outlined below for each specific aim. For all power analyses, Type 1 error was restricted to 5%, test-wise, in two-sided tests. The sample size of 40 survivors is based on 80% power necessary to address Aim 3. A sample size of 40 subjects will be sufficient to detect a minimum correlation of 0.41 between neuropsychological measures and self-report of ECF.

For the structure interviews, it was expected that a small sample of PBT survivors would provide an initial exploration for compensatory behaviors. Seven subjects were recruited. While this does not result in saturation, this initial exploration provides a unique contribution to our knowledge of cognitive performance and everyday function in survivors with PBT. This aim provides preliminary data which may warrant future study while also providing the PI essential experience in conducting this proposed study.

Data Analysis

The analyses for each specific aim are as outlined below:

Specific Aim 1. To describe ECF and its components (working memory and attention) in adults following treatment for PBT subjects.

The distribution of subject scores for each neuropsychological measure of executive control, attention, and working memory, and the self-report of ECF function was examined using individual subject scores coded within box plots to visually observe where individual subject scores were positioned in regard to the mean and standard deviations. The box plots and scatterplots served to identify influential cases or outliers.

Analyses for this question were based on the subject's raw performance scores on each instrument in the standardized neuropsychology battery. These scores were compared to mean normative data scores according to age and education (Table 4.5). The difference of the raw performance score and the normed mean was calculated and then divided by the norm SD for determination of a z-score. Cutoff z-scores of -1.3 SD were used to indicate mild impairment and -3.0 SD, severe impairment. For these analyses, impaired function was defined as a raw

score that was -1.3 SD below the age- and education-specific normative data for each instrument and its subscales. The means of the z-scores of the battery instruments were combined into the Clinical Trials Battery (CTB) Composite score for each subject. In addition, subject performance was examined by recording the number of instruments on which they scored -1.3 SD or more below normed expectations. Performance scores of -1.3 SD or more below normed data on more than one instrument indicate mild to severe impairment in that domain (Lezak, Howieson, & Loring, 2004; Johnson et al., 2012). The scores of all 40 subjects were evaluated using age, gender, and when appropriate, education normative data. All of these tests have normative scores which can be used to identify patients who are -1.3 standard deviations or more below normative mean (Lezak, Howieson, & Loring, 2004).

Table 4.5.*Normative data by test and source, stratified for age and years of education levels.*

<u>Cognitive Test</u>	<u>Citation</u>	<u>Age group (years)</u>	<u>N*</u>	<u>Age Only Norms Mean (SD)</u>	<u>< 12 years Mean (SD)</u>	<u>> 12 years Mean (SD)</u>
HVLT-IR	Brandt & Benedict, 2001	25-34	54	28.71 (4.57)	Not Available	Not Available
		35-44	61	28.22 (4.05)		
		45-54	66	27.86 (3.95)		
		55-64	43	27.71 (4.26)		
HVLT-DR	Brandt & Benedict, 2001	25-34	54	10.24 (1.94)	Not Available	Not Available
		35-44	61	10.16 (2.08)		
		45-54	66	10.06 (1.73)		
		55-64	43	9.87 (1.93)		
HVLT-RDI	Brandt & Benedict, 2001	25-34	54	10.84 (1.39)	Not Available	Not Available
		35-44	61	11.15 (1.06)		
		45-54	66	10.74 (1.61)		
		55-64	43	10.70 (1.42)		
Trails A	Tombaugh, 2004	25-34	33	24.40 (8.71)	35.10 (10.94) 33.22 (9.10)	31.72 (10.14) 31.32 (6.96)
		35-44	39	28.54 (10.09)		
		45-54	41	31.78 (9.93)		
		55-59	58/37			
		60-64	55/31			
Trails B	Tombaugh, 2004	25-34	33	50.68 (12.36)	78.84 (19.09) 74.55 (19.55)	68.74 (21.02) 64.58 (18.59)
		35-44	39	58.46 (16.41)		
		45-54	41	63.76 (14.42)		
		55-59	58/37			
		60-64	55/31			
SDMT	Smith, 1982	25-34	477/830**	Not Available	53.30 (7.98)	57.72 (9.08)
		35-44			51.50 (8.03)	54.20 (11.17)
		45-54			47.26 (9.56)	52.27 (8.48)
		55-64			42.80 (9.02)	47.60 (8.31)
COWA	Tombaugh et al., 1999	16-59	268/242	Not Available	40.40 (10.70)	44.70 (11.20)
		60-79	292/185		35.60 (12.50)	42.00 (12.10)

* N=number of subjects in each age group, N/N=number of subjects in each education category for each age group.

** N=number of combined subjects for all education and age groups (i.e., n=477 for age 25-64 with ≤ 12 years of education).

HVLT=Hopkins Verbal Learning Test; IR=Immediate recall; DR=Delayed recall; RDI=Recognition discrimination index; Trails A & B=Trails Making Test Parts A & B; SDMT=Symbol Digit Modality Test; COWA=Controlled Oral Word Association test

Specific Aim 2. To describe self-reported ECF and its components in adults following treatment for PBT.

This aim was explored using three self-reported measures of cognitive function or the presence of brain tumor specific symptoms: the ECog, FACT-BT, and MDASI-BT. The distribution of subject scores for each instrument was examined using box plots and scatterplots to look for influential cases or outliers. To aid in the interpretation of data, ECog subscale scores of 2 or higher were used to identify subject perception of change in cognitive function from “occasional problems” to “consistently much worse.” Subject characteristics, including demographic variables and cancer-related factors, were explored to explain any differences in perception of cognitive function. As the ECog has not been used in this population, ECog scores were compared to PBT-specific symptom assessments (FACT-BT and MDASI-BT) with emphasis on the cognitive items that each scale contained.

Specific Aim 3. To describe the relationship of ECF and its components to self-reported ECF for survivors with PBT.

The relationships between the neuropsychological measures of executive control, attention, and working memory (Exit-25, Trails A and B, COWA, SDMT, HVLT and delayed HVLT) and self-reported ECF (Everyday Cognitive Questionnaire, Everyday Memory Scale) was examined using Pearson-product moment correlations. Type 1 error was restricted to 5%, testwise, in two-sided tests that the correlation is different from zero. Exploratory analyses using normative scores for age, gender, and education level, when available, were used to describe the relationships between neuropsychological measures and self-report in those with PBT compared

to a healthy normative population. The scores from the Clinical Trials Battery Composite (CTB Composite), Trails Making Tests Difference Composite (TMT Difference), and Executive Interview-25 (EXIT-25) were compared to self-reported cognitive function scores on the Everyday Cognitions Test (ECog). Scatterplots of subject scores were used to examine the relationship of cognitive performance (x-axis) and self-reported cognitive function (y-axis). To describe subject patterns observed on the scatterplots, four quadrants were established as shown on Figure 4.3:

- 1) **Group A** subjects report that cognitive function is unchanged since diagnosis (defined as ECog score <2.0) and had ECF performance scores defined as normal (CTB Composite score >-1.3 SD, TMT Difference score >50 , or EXIT-25 score ≤ 5).
- 2) **Group B** subjects report that cognitive function has changed since diagnosis (defined as ECog score ≥ 2.0) but ECF performance was within normal limits (CTB Composite score >-1.3 SD, TMT Difference score >50 , or EXIT-25 score ≤ 5),
- 3) **Group C** subjects report that cognitive function is unchanged since diagnosis (defined as ECog score <2.0) but have poor ECF performance scores (defined as CTB Composite score ≤ -1.3 SD, TMT Difference score >50 , or EXIT-25 score > 5).
- 4) **Group D** subjects report that cognitive function has changed since diagnosis (defined as ECog ≥ 2.0) and have poor ECF performance scores (CTB Composite score ≤ -1.3 SD, TMT Difference score >50 , or EXIT-25 score > 5).

Figure 4.3

Categorization of behaviors according to cognitive function.

	+ NP scores	- NP scores
- SR ECF scores	D: Congruent	B: Incongruent
+ SR ECF scores	C: Incongruent	A: Congruent

SR=self-reported, ECF=executive control function, NP=neuropsychological performance,
+ or – indicates cognitive performance

Specific Aim 4. To explore whether cognitive reserve or compensatory behaviors explain the congruence or incongruence between cognitive performance scores and subject self-reported change in cognitive function scores.

This specific aim explored whether cognitive reserve (CR) might explain the observed congruence or incongruence between self-reported cognitive function and test performance. Analyses for Specific Aim 4 involved examination of: 1) cognitive performance by CR, 2) self-reported change in cognitive function by CR, and 3) congruence-incongruence between performance and self-reported change in cognitive function by CR. Scatterplots, correlations, t-tests and non-parametric statistics were used to explore differences between congruent scores, Group A and C, and incongruent scores, Group B and D, (as described in Specific Aim 3) by CR.

The structured interviews from the *exemplar subset* of 7 subjects are used to describe changes in cognitive activities that might illustrate compensatory behaviors. Neuropsychological test scores and self-reported questionnaires are limited in the identification of compensatory behaviors used to maintain cognitive function.

CHAPTER 5: RESULTS

The first section of this chapter presents sample description with subject characteristics, PBT-specific characteristics, and key medical symptoms and medications. The next four sections focus on the results pertinent to each specific aim.

Sample Description

The sample (Table 5.1) consisted of slightly more women than men, predominately Caucasian, and ranging in age from 30 to 64 years (mean 50.1, SD 9.7 years). These study demographics contrast with national brain tumor registry data (CBTRUS, 2012) showing a 1.1:1 male to female incidence of PBT diagnoses (CBTRUS, 2012), represent. All participants in the present study had at least a high school education; 30% had additional technical or skill education or an associate degree (n=12), and 55% held a bachelor's degree or higher (n=22). The majority (n=29) were living with a spouse.

Table 5.1.
Sample demographics of survivors with PBT (n=40).

<u>Demographics</u>	<u>Frequency</u>	<u>%</u>
Gender		
Female	22	55.0
Male	18	45.0
Race		
Caucasian	37	93.0
African American	3	7.0
Education, number of years		
<12 years	0	-
12 years	6	15.0
Technical Skilled/Associates	12	30.0
Baccalaureate or greater	22	55.0
Living situation		
With spouse/partner	30	75.0
With parents	3	7.5
Alone	7	17.5

Tumor and treatment factors.

Only subjects who had received chemotherapy or radiation therapy for their PBT diagnosis were eligible to participate in this study; this limited participation to those in WHO-PBT grades II to IV tumors. The distribution of WHO-PBT grade at time of study participation was: Grade II (n=5, 12.5%), Grade III (n=25, 62.5%), or Grade IV (n=10, 20%). These distributions conform to national PBT demographics (CBTRUS, 2012).

Hemispheric location of the tumor was split evenly, with 20 on the right and on the left (Table 5.2). No subject had tumors in multiple locations or in the contralateral hemisphere. The most common tumor locations were, as expected, in the frontal (n=19) and temporal lobes (n=10), accounting for 72.5% of this sample. There was no difference in WHO-PBT grade of tumors in various locations, $\chi^2(2)=3.7, p=.18$.

Table 5.2.
Primary brain tumor location at time of diagnosis (n=40).

<u>Location</u>	<u>Frequency</u>	<u>%</u>
Hemispheric location		
Right	20	50.0
Left	20	50.0
Lobe location		
Frontal	19	47.5
Temporal	10	25.0
Parietal	5	12.5
Occipital	2	5.0
Midbrain, including pons and cerebellum	4	10.0

Therapeutic interventions.

Despite differences in tumor pathology, treatment regimens were similar for all three tumor grades with the goals being to control tumor growth by surgical, chemotherapy, and radiation interventions. Most subjects received a combination of treatments during their disease trajectory.

Thirty-four subjects (85%) underwent surgical resection, but six (15%) had tumor locations prohibiting surgical resection, Table 5.3. Thirty-four subjects (85%) received chemotherapy and radiation therapy, 5 (12.5%) received chemotherapy only, and 1 (2.5%) received radiation therapy only. Of the 39 patients who received chemotherapy, 25 (64%) were given multiple agents for a duration of 1 to 3 years.

Table 5.3.

Frequency and percentage of subjects by type of therapeutic intervention (n=40).

<u>Therapeutic Interventions</u>	<u>Frequency</u>	<u>%</u>
Surgery + chemo + radiation	30	75.0
Surgery + chemo	3	7.5
Surgery + radiation	1	2.5
Radiation + chemo	4	10.0
Chemotherapy only	2	5.0

Tumor stability.

All subjects met study criteria of clinical and radiographic stability as determined by their neuro-oncologist, and no longer needed chemotherapy for tumor control. Two thirds of the sample (n=27, 67.5%) never experienced recurrence of their tumor after completion of treatment, Table 5.4. The remaining one third had at least one tumor recurrence following their original diagnosis: 5 subjects (12.5%) had tumor recurrence with transformation from WHO-PBT Grade II to III classification, and 8 subjects (20%) had tumor recurrence without a change in classification.

Table 5.4.

Tumor recurrence by WHO-PBT grade classification (n=40).

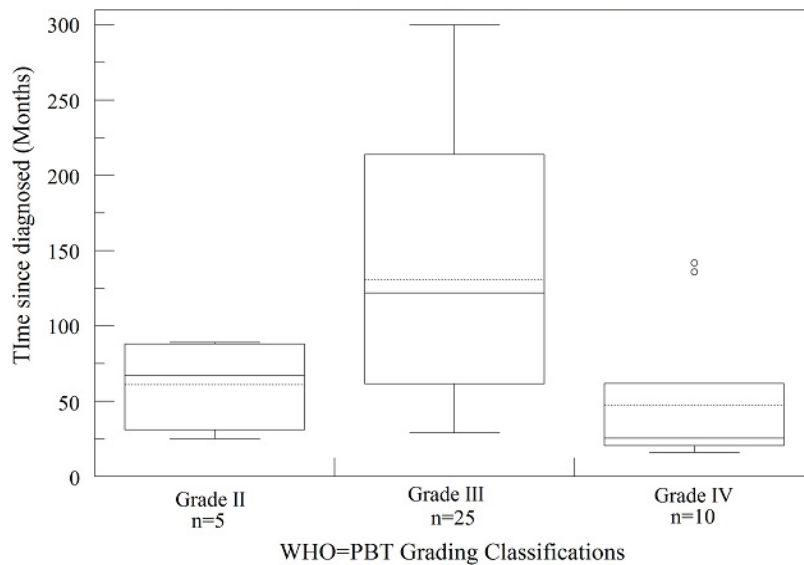
<u>Type of Recurrence</u>	<u>Frequency</u>			<u>%</u>
	<u>Grade II</u>	<u>Grade III</u>	<u>Grade IV</u>	<u>All Grades</u>
No Recurrence	4	14	9	67.5
Recurrence without transformation	1	6	1	20.0
Recurrence with transformation	0	5	0	12.5

Time from diagnosis.

Survival rates vary across and within tumor grades, according to histology and molecular pathology. Time from original diagnosis ranged from 1.3 to 25 years (median 6.7 years) and

averaged 8.4 years (SD 6.0 years). These times vary according to tumor type (Figure 5.1): Grade II tumors averaged 5.1 years (SD 2.4 years), Grade III tumors, 10.9 years (SD 7.0 years), and Grade IV tumors, 3.9 years (SD 4.1 years). The greatest variability was seen with Grade III tumors. Because of unequal variances and group sizes across the three tumor grades (Levene statistic $F(2, 37)=4.92, p=.01$), a Kruskal Wallis test was used to show a significant difference in survival times by tumor grade at time of study participation, $H(2)=12.09, p=.002$.

Figure 5.1. *Time since diagnosis by current tumor grade (n=40).*



Because of active current treatment and study eligibility criteria, recruitment of subjects with Grade II tumors (n=5) was lower than with other tumor grades. Thus, these 5 subjects tended to have a shorter time trajectory since diagnosis (range 2 to 7.4 years; Mean 5.1, SD 2.4 years) than expected from national PBT registry data (CBTRUS, 2012).

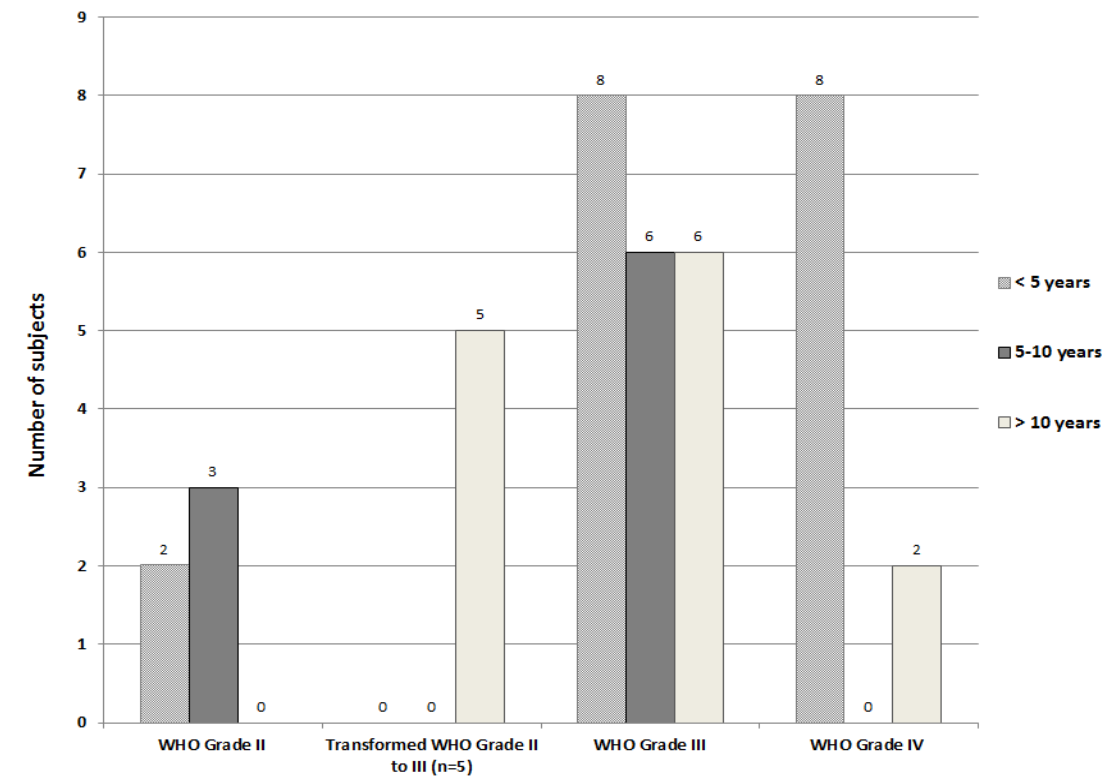
In contrast, more subjects (n=10) with Grade IV tumors were recruited than expected. Consistent with national registry data (CBTRUS, 2012), 8 of these subjects had been diagnosed

within 3 years of study participation. The 2 outliers were long-term survivors of greater than 10 years since diagnosis. Thus the range was 1.3-11.8 years (Mean 3.9, SD 4.1).

The majority of subjects had current diagnoses of Grade III PBT (n=25). As this group had the greatest variability, three subsets were observed: 19 subjects with no tumor recurrence averaged 8.4 ± 5.7 (SD) years since diagnosis, 6 subjects with tumor recurrence averaged 12.7 ± 9.1 years since diagnosis (SD 9.1 years), and 5 subjects with transformation of tumor from Grade II to Grade III pathology averaged 15.8 ± 4.8 years. These differences in survivorship times approached significance, $H(2)=4.6, p=.10$.

Since all of the subjects who experienced tumor transformation had an original diagnosis of Grade II, and since survivorship time may influence cognitive function (Lovely et al., 2013), a transformation tumor category was created and this confirmed significant differences in survival times by tumor categories, $H(3)=15.05, p=.002$. Figure 5.2, demonstrates this point using CBTRUS (2012) survival timeframes of < 5 years, 5-10 years, and > 10 years, $\chi^2(6)= 21.27, p=.002$.

Figure 5.2. *Time since original diagnosis in months by WHO-PBT classification (n=40).*



Self-reported medications.

While most subjects (n=36, 90%) reported taking daily medications, four (10%) denied regular use of any medications, vitamins, supplements, or over the counter medicines. Table 5.5 shows the five classes of medications used. The subjects took 1 to 8 medications per day (average of 3.2 medications daily), the majority of which were used to control neurological symptoms resulting from the PBT or its treatment. Medications used to manage comorbid, non-neurologic conditions were those commonly prescribed for the general US population. There were no significant differences in medication use by tumor grade, recurrence, or other characteristics, but there was a significant relationship between elapsed time since diagnosis and use of medication agents, $\chi^2(2) = 8.52, p = .01$. Those diagnosed less than 5 year prior to study

participation tended to take fewer agents for co-morbid conditions than those diagnosed more than 10 years before.

Table 5.5.
Frequency of daily medications by classifications and tumor grade (n=40).

<u>Classification</u>	<u>Grade II</u>	<u>Grade II to III</u>	<u>Frequency Grade III</u>	<u>Grade IV</u>	<u>All Grades</u>	<u>%</u>
Antiepileptics	4	4	14	3	25	62.5
Psychotropic & hypnotic agents	1	4	9	7	21	52.5
Cardiovascular agents	2	1	11	6	20	50.0
Endocrine/hormone replacement agents	0	1	8	3	12	30.0
Other agents	5	0	9	8	22	55.0
No medications	0	1	2	1	4	10.0

Footnote: Subjects may report medications in multiple categories.

Self-report of health status.

Five self-report surveys were used to assess current health status and to determine whether symptoms interfered with everyday function and quality of life. These were: (1) Key medical events survey, (2) Functional Assessment of Cancer Therapy-Brain Tumor Scale (FACT-BT), (3) the MD Anderson Symptom Inventory-Brain Tumor Scale (MDASI-BT), (4) Older Americans Resources Services Activities of Daily Living Scale (OARS), and (5) Center for Epidemiologic Studies Depression Scale-Revised (CESD-R). If subjects left any items blank, the research assistant attempted to clarify them in order to eliminate missing items.

Key medical events survey.

Subjects reported that their current health status was “the same as” or “better than one month ago” on the Key Medical Events Survey. An average of 2.9 events (SD 1.8) were

reported (Table 5.6); 23 subjects (58%) reported 3 or more total events (Table 5.6). Those with lower grade tumors, Grade II or Grade II to III transformations, reported more events, but the rate was not significantly different from other tumor grades, $F(3,36)=1.4, p=.26$.

Table 5.6.
Key medical events occurring within last 3 months as reported by subjects with PBT (n=40).

Symptom	Frequency				%	
	Grade II	Grade II-III	Grade III	Grade IV	All Grades	
All symptoms, M(SD)	3.6 (1.8)	3.8 (1.6)	2.4 (1.8)	3.2 (1.8)	2.9 (1.8)	
Neurological M (SD)	2.8 (1.3)	3.4 (1.5)	1.8 (1.5)	2.4 (1.0)	2.3 (1.4)	
Headaches	4	3	6	3	16	40.0
Joint pain	3	2	5	4	14	35.0
Dizziness	1	2	7	1	11	27.5
Numbness	0	2	6	3	10	25.0
Weakness	0	4	3	2	9	22.5
Leg swelling	2	0	3	3	8	20.0
Walking	2	0	1	4	7	17.5
Falls	0	2	2	2	6	15.0
Dexterity problems	1	2	2	1	6	15.0
Seizures	1	0	1	1	3	7.5
Other Medical, M (SD)	0.8 (1.1)	0.4 (0.6)	0.6 (0.8)	0.8 (1.2)	0.6 (0.9)	
Cough	2	1	4	4	11	25.0
Cold symptoms	1	0	3	1	5	15.0
Heart racing	1	1	1	2	5	12.5
Short of breath	0	0	2	1	3	7.5
Fever or chills	0	0	1	0	1	2.5
Fainting	0	0	0	0	0	0.0
Chest pain	0	0	0	0	0	0.0
Wheezing	0	0	0	0	0	0.0

Footnote: Subjects may experience more than 1 key event.

Neurologic events, Table 5.7, were more frequent than other medical events; 35 subjects (88%) reported at least one neurologic event (range, 0-5 events; mean, 2.3 events). Fifteen subjects reported general medical events (range, 0-3 events). There were no significant differences across tumor grades in the number of neurologic events, $F(3,36)=2.20, p=.10$, or general medical events reported, $F(3,36)=.30, p=.82$.

Table 5.7.
Summation of Key Medical Events (n=40).

<u>Events</u>	<u>Range</u>	<u>Frequency</u>		
		<u>No events</u>	<u>1-2 events</u>	<u>>3 events</u>
All Key Medical Events	0-7	5	12	23
Neurologic Events	0-5	5	17	18
General Medical Events	0-3	25	13	2

Functional Assessment of Cancer Therapy-Brain Tumor Scale (FACT-BT).

Lower scores on the total and PBT-specific symptoms subscale of the FACT-BT indicate greater symptom impact on quality of life. Five subjects (12.5%) provided no answers on 2-3 items, resulting in a total of 12 missing items across all subjects (0.6%). The FACT-BT total score averaged 139.62 (SD 22.99) and PBT symptom-specific subscale averaged 54.48 (SD 11.42), reflecting a moderate impact on quality of life (Table 5.8). These scores were slightly better than FACT-BT validation scores (total score: M 136.0, SD 26.0; symptom-specific subscale: M 49.0, SD 13.6) in a sample of 101 survivors of PBT (Weitzner et al., 1995). Subject responses to 9 cognitive items pertaining to concentration, new memory, verbal fluency, organization, and planning ranged from 10-32 and averaged 21.05 (SD 6.04). The average is in the upper third of scoring range, indicating a moderate impact on quality of life.

Table 5.8.

Self-reported quality of life and symptom interference for survivors of PBT (n=40).

<u>Scale</u>	<u>Potential Range</u>	<u>Min – Max</u>	<u>Mean (SD)</u>	<u>Median</u>
FACT-BT				
Total Scale	0-184	85-183	139.62 (22.99)	143.5
Brain Tumor Subscale	0-76	31-76	54.58 (11.42)	54.0
Cognitive Items	0-36	10-36	21.05 (6.04)	23.0
MDASI-BT				
Severity Subscale	0-10	0-5.73	1.25 (1.19)	0.8
Interference Subscale	0-10	0-8.67	1.35 (1.93)	0.6
Cognitive Items	0-10	0-8.75	1.83 (2.02)	1.3
OARS				
Total Scale	0-28	23-28	27.08 (1.47)	28.0
Physical Subscale	0-14	12-14	13.85 (0.48)	14.0
Independent Subscale	0-14	11-14	13.23 (1.17)	14.0
CESD-R	0-60	0-39	10.38 (8.41)	9.5

FACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor scale; MDASI-BT=MD Anderson Symptom Inventory-Brain Tumor scale; OARS=Older Americans Resource and Services Instrumental Activities for Daily Living scale; CESD-R=Center for Epidemiology Studies Depression-Revised scale.

MD Anderson Symptom Inventory-Brain Tumor Scale (MDASI-BT).

Higher scores on the MDASI-BT subscales assessing symptom severity and interference indicate greater dysfunction (Armstrong et al., 2006). There were no missing answers on any items. Subjects with PBT reported mean severity scores of 1.25 (SD 1.20) and interference scores of 1.35 (SD 1.95), which reflect minimal symptom burden. These scores may be influenced by the long-term survival and relatively stable health of many of the subjects. These scores are slightly better than the mean severity score of 1.52 and interference score of 2.1 found in 151 survivors of PBT, (Armstrong et al., 2006). The MDASI-BT contains four items assessing cognitive symptom severity (memory, comprehension, verbal fluency, and

concentration). Subjects reported mild cognitive symptom severity, with an average of 1.8 (SD 2.0) and range of 0–8.75.

Older Americans Resources and Services Activities of Daily Living Scale (OARS).

Higher summation scores on the total scale, and on the physical and instrumental subscales, indicate better ability to perform functional activities of daily living. There were no missing items. Only 14 subjects (35%) reported even minimal limitations on the physical or instrumental subscales; total scale scores ranged from 23 to 28 and averaged 27.08 (SD 1.47), Table 5.8.

Center for Epidemiologic Studies Depression –Revised Scale (CESD-R).

Depressive symptoms may influence cognitive function (Johnson et al., 2012), and higher scores on the CESD-R suggest presence of depression. There were no missing items from any subjects. Subject scores averaged 10.38 (SD 8.41), but there was a wide range of scores (0 to 39). Nine subjects (23%) had scores ≥ 16 , but none reported symptoms consistent with depressive categories, and thus represent features consistent with subthreshold depression. No CESD-R scores for subjects with PBT are available for comparison, so it is unclear whether these higher CESD-R scores reflect the presence of significant neuropathology.

Associations between Self-Reported Surveys.

Neurological-associated symptoms on the Key Medical Events Survey were significantly associated with lower scores on the OARS, $r=-.45$, $p=.004$. Total scores on the FACT-BT were significantly associated with MDASI-BT symptom severity ($r= -.62$, $p< .001$), MDASI symptom interference ($r= -.5$, $p< .001$), and OARS ($r=.34$, $p=.03$). CESD-R scores were significantly related to symptom severity (MDASI Severity: $r=.55$, $p<.000$), symptom interference (MDASI

Interference: $r = .41$, $p = .008$), and quality of life (FACT-BT: $r = -.72$, $p < .001$). There were no significant associations between self-reported surveys and tumor grade, recurrence, or time since diagnosis. Subjects who reported greater symptom severity also reported more impact on their daily function and quality of life.

Specific Aim 1

To describe executive control function (ECF) and its components in adults following treatment for primary brain tumor (PBT). This aim will be addressed by examining subject scores on the following standardized tests of ECF:

- a. *Memory* was measured by Hopkins Verbal Learning Tests (HVLT) on Immediate Recall (IR), Delayed Recall (DR), and Recognition Discrimination Index (RDI)
- b. *Attention* was measured by Trails Making Test Parts A (Trails-A) and B (Trails-B) and Symbol Digit Modalities (SDMT)
- c. *Verbal Fluency* (semantic fluency) was measured by Controlled Oral Word Association (COWA)
- d. *ECF* was measured by the Clinical Trials Battery (CTB) Composite score, Trails Making Tests Difference (TMT Difference) score, and Executive Interview-25 scores (EXIT-25)

Memory.

Working memory, which is essential to ECF, was assessed using the Immediate Recall (IR), 25-minute Delayed Recall (DR), and Recognition Discrimination Index (RDI) subscales of the Hopkins Verbal Learning Test (HVLT). Being brief and easily administered, the HVLT subscales allow assessment of new learning, verbal memory, learning efficiency and organization through recall and recognition (Brandt & Benedict, 2002). Table 5.9 shows subject performance scores for the HVLT subscales.

Table 5.9.
Subject scores on HVLT subscales for memory (n=40).

Memory Test	Possible Range	Actual Range	M (SD)	Median	Skewness /Kurtosis	-1.3-2.9 SD Below Norm F (%)	≤-3.0 SD Below Norm F (%)
HVLT-IR	0-36	6-34	23.78 (6.33)	24	-0.65/0.34	9 (22.5)	6 (15.0)
HVLT-DR	0-12	0-12	7.73 (3.15)	8	-0.78/0.25	12 (30.0)	5 (12.5)
HVLT-RDI	0-12	0-12	9.58 (2.31)	10	-1.19/0.73	9 (22.5)	4 (10.0)

HVLT-IR=Hopkins Verbal Learning Test -Immediate Recall; HVLT-DR=Hopkins Verbal Learning Test-Delayed Recall; HVLT-RDI=Hopkins Verbal Learning Test-Recognition Discrimination Index

Immediate recall (IR).

Immediate recall summation scores ranged from 6 to 34 words recalled over three consecutive trials (Table 5.9). Subjects recalled an average of 23.78 words (SD 6.33), which lower than the recall for all normative age groups (Brandt & Benedict, 2002). Most subjects improved their recall during the three trials; only one subject had the best performance on the first trial. No subject scored “0” for any trial. Nine subjects (22.5%) scored 1.3 SD or more below, and 6 (15%) scored 3 SD below means for age-specific normative groups.

Delayed recall (DR).

Possible scores range from 0 to 12. Two subjects could not recall any words on this task. The average number of words recalled was 7.73 (SD 3.15), which is below normed averages across all age groups (Brandt & Benedict, 2002). A total of 17 subjects (42.5%) had performance scores indicating impairment of delayed memory: 12 subjects (30%) scored 1.3 SD or more below normative data, indicating mild impairment; 5 (12.5%) scored 3 SD below, indicating severe impairment. More impairment was seen on the DR task (42.5%) compared to the IR (35%) or RDI (32.5%) tasks (Table 5.9).

Recognition discrimination index (RDI)

The RDI is calculated by subtracting all incorrect answers from the total of correctly recognized nouns. Subject RDI scores ranged from 4 to 12 (average of 9.58. SD 2.31), which was below norm for all ages (Brandt & Benedict, 2002). Seven subjects (17.5%) achieved perfect “12” RDI scores (Table 5.9). Nine subjects (22.5%) scored 1.3-2.9 SD below norm, indicating mild impairment; an additional 4 subjects (10%) scored 3 SD or more below normed data, indicating severe impairment for semantic memory.

Summary of memory performance scores

Seventeen subjects (42.5%) performed at or above normative means on all three HVLT subscales, indicating no impairment in the cognitive domain of memory (Table 5.10). Fourteen subjects (35%) scored 1.3 SD or more below norm on two or more memory tests, indicating mild to severe impairment in the cognitive domain of memory.

Table 5.10.

Frequency of impairment (-1.3 SD or more below norm) on 3 tests of memory (n=40).

	<u>F</u>	<u>%</u>
No impairment on any of 3 tests	17	42.5
Impairment on 1 test	9	22.5
Impairment on 2 tests	6	15.0
Impairment on all 3 tests	8	20.0

Attention.

Selective and sustained attention was assessed by measuring information processing with the Trail Making Tests-Part A (Trails A) and Part B (Trails B), and the Symbol Digits Modalities Test (SDMT). These are timed instruments, which rely on the subject’s cognitive flexibility to

(1) efficiently and rapidly scan the material, and (2) retrieve items from working memory when set shifting between items.

Trail Making Test-Part A.

As shown in Table 5.11, subject performance times ranged from 20 to 185 seconds and averaged 41.08 seconds (SD 26.95), which is below time averages for all age and education level comparison groups. Thirteen subjects (32.5%) performed at or above their comparison group. Three subjects (7.5%) required prompting to correct errors during the task, giving them prolonged performance times ranging from 78 to 185 seconds. These three subjects also had cognitive performance impairments across all tests of attention and memory. Eight subjects (20%) had time performances 1.3 SD or more below age and education-specific normed data and an additional 4 subjects (10%) had time performances more than 3 SD below norm.

Table 5.11.

Subject scores on measures of attention: Trails A, Trails B, and SDMT (n=40).

Attention Tests	Possible Range	Actual Range	M (SD)	Median	Skewness /Kurtosis	-1.3-2.9 SD Below Norm F (%)	≤-3.0 SD Below Norm F (%)
Trails A	0-300	20-185	41.1 (27.0)	35.00	4.18/21.39	8 (20.0)	4 (10.0)
Trails B	0-300	35-300	98.2 (57.5)	75.50	2.29/6.16	7 (17.5)	12 (30.0)
SDMT	0-110	44-61	43.9 (14.1)	46.00	-0.39/0.36	6 (15.0)	5 (12.5)

TRAILS A=Trail Making Test Part A; TRAILS B=Trail Making Test Part B; SDMT=Symbol Digits Modalities Test

Trails Making Test-Part B.

Subject performance times ranged from 35 to 300 seconds (Table 5.11). The average time was 98.15 seconds (SD 57.5), which is longer than performance time averages for normative age groups. Nine subjects (22.5%) performed at or above their comparison group. Nearly half of the sample (n=18, 45%) required prompting to correct errors during the test. Two

subjects (5%) could not complete the task in the maximum time allotment, so their times were capped at 300 seconds; these 2 subjects also had their times capped on the Trails A. Seven subjects (17.5%) had performance times that were 1.3 SD or more below age and education-specific normative comparisons, and a further 12 subjects (30%) were 3 SD or more below norm.

Symbol Digits Modalities Test.

Subject performance on the SDMT ranged from 11 to 73 correct substitutions, with an average of 43.9 (SD 14.1; Table 5.11). Ten subjects (25.0%) performed at or above their comparison group. Eleven subjects (27.5%) had performance scores 1.5 SD or more below age and education-specific norms, and 5 of them (12.5%) had scores 3 SD or more below norm.

Summary for attention performance scores.

As displayed in Table 5.11, more subjects had subnormal performance scores (1.3 SD or more below normative comparisons) on the Trails B (n=15, 37.5%) than on the SDMT (n=13, 32.5%) and Trails A (n=9, 22.5%).

Fifteen subjects (37.5%) scored within normed expectations on all three measures of attention (Table 5.12). Eight subjects (20%) scored 1.3 SD or more below on one measure; 11 subjects (27.5%) had performance scores 1.3 SD or more below on two or more measures of attention (signifying impairment in the cognitive domain of attention). More subjects had difficulties on the Trails B (n=19, 47.5%) than on the other tests of attention. Those who had difficulties on the SDMT tended to have difficulties on the Trails B. The 3 subjects who exceeded time limits on Trails A had impaired cognitive performances on all tests of attention and memory. Six subjects with impaired performances on tests of attention did not have impairments on tests of memory.

Table 5.12.

Frequency of impairment (-1.3 SD or more below norm) on all 3 tests of attention (n=40).

	<u>F</u>	<u>%</u>
No impairment on all 3 tests	21	52.5
Impairment on 1 test	8	20.0
Impairment on 2 tests	6	15.0
Impairment on all 3 tests	5	12.5

Verbal fluency.*Controlled Oral Word Association Test (COWA).*

Subject summation scores on the COWA ranged from 9 to 72 words for an average of 38.07 words (SD 13.65; Table 5.13). Fifteen subjects (37.5%) produced more words than the average of normative comparison groups. Nine subjects (22.5%) had performance scores 1.3 SD or more below normative age and education-specific comparisons, indicating impairment in the domain of verbal fluency.

Table 5.13.

Subject scores on the COWA for verbal fluency (n=40).

						-1.3-2.9 SD	≤-3.0 SD
Verbal	Possible	Actual				Below	Below
Fluency	Range	Range	Mean (SD)	Median	Skewness	Norm	Norm
<u>Test</u>	<u>Range</u>	<u>Range</u>	<u>Mean (SD)</u>	<u>Median</u>	<u>/Kurtosis</u>	<u>F (%)</u>	<u>F (%)</u>
COWA	Unlimited	9-72	38.1 (13.65)	40.50	0.03/0.03	8 (20%)	1 (2.5%)

COWA=Controlled Oral Word Association Test

Summary of performance scores across all instruments.

Global cognitive impairment may be determined by impaired performance scores on four or more tests on the neuropsychological battery (Lezak, Howieson, Bigler, & Tranel, 2012). Six subjects (15%) performed at or above normed expected scores on all seven instruments. Eleven subjects (22.5%) performed 1.3 SD or more below normative values on a single instrument (Table 5.14). The performance scores for 17 subjects across all 7 instruments showed no

evidence of global cognitive impairment. The remaining 23 subjects scored 1.3 SD or more below norm on 2-3 instruments, n=13 or 4-7 instruments, n=10, indicating the presence of mild to severe cognitive impairment.

Table 5.14.
Frequency of subject performance impairment (1.3 SD or more below norm) across all seven tests (n=40).

	<u>F</u>	<u>%</u>
No impairment on all 7 tests	6	15.0
Impairment on 1 test	11	22.5
Impairment on 2-3 tests	13	32.5
Impairment on 4-7 tests	10	25.0

Shared Variance between ECF, Memory, and Attention.

Principal components analysis (PCA) was performed to assess the shared variance of the ECF construct and it's components of memory and attention. Subject performance scores on the EXIT-25 and standardized neuropsychological battery for memory (HVLT-IR and HVLT-DR), attention (TMT-A, TMT-B, and SDMT), and language (COWA) were used.

Sampling adequacy to determine if data were likely to factor well was assessed by the Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity (Pett, Lackey, & Sullivan, 2003). Adequate sampling is indicated by a KMO >.7 and significant Bartlett's test. The KMO for this sample was .80 and the Bartlett's test was significant $p>.001$.

An unrotated PCA maximizes the sum of squared factor loadings to explain all item variance and assumes there is: 1) no shared variance, 2) all items measure the latent variable, and 3) there is no error (DeVellis, 2003). Using the Kaiser criterion rule, only one factor had an eigenvalue >1.0 and explained 59.44% of the total variance. Further, the Cattell scree plot test

suggested the presence of 2 or less factors. Thus PCA extraction produced only one component to explain the variance in scores (Table 5.15).

Table 5.15. *Component extraction matrix using PCA.*

<u>Scale</u>	<u>Component</u>
HVLT-IR	.81
HVLT-DR	.82
TMT-A	-.74
TMT-B	-.84
SDMT	.76
COWA	.66
EXIT-25	-.75

Correlations between cognitive performance scores and subject characteristics.

No significant associations were observed between age, education, gender, time since diagnosis, tumor characteristics (hemisphere, location, grade, or treatment type), self-reported physical functioning, depressive symptoms, or PBT-specific symptoms and performance scores for memory subscales (HVLT subscales) or verbal fluency (COWA). The HVLT-DR subscale was associated with the MDASI Severity subscale, $r = -.32$, $p = .04$. Thus, impairments in delayed recall were associated with more severe symptoms.

Performance scores for tests of attention were significantly associated with subject self-report of PBT-specific symptoms on the MDASI and FACT-BT. The MDASI Symptom subscale was associated with the Trails A ($r = .55$, $p > .001$), Trails B ($r = .47$, $p = .002$), and SDMT ($r = -.43$, $p = .005$). Thus, impaired performance on any of the three tests of attention was associated with severity of PBT-specific symptoms. The FACT-BT Total scale score was associated with the Trails A ($r = -.31$, $p = .05$) and Trails B ($r = -.39$, $p = .01$). Thus, impaired performance on either Trails test was associated with presence of more PBT-specific symptoms.

Age was significantly associated with performance on the SDMT, $r=-.52$, $p<.001$, indicating that older subjects produced fewer correct substitutions than younger subjects; the association was limited to this single test of attention. Education, time since diagnosis, tumor characteristics, self-reported physical function and depressive symptoms were not associated with attention performance scores.

Executive control function.

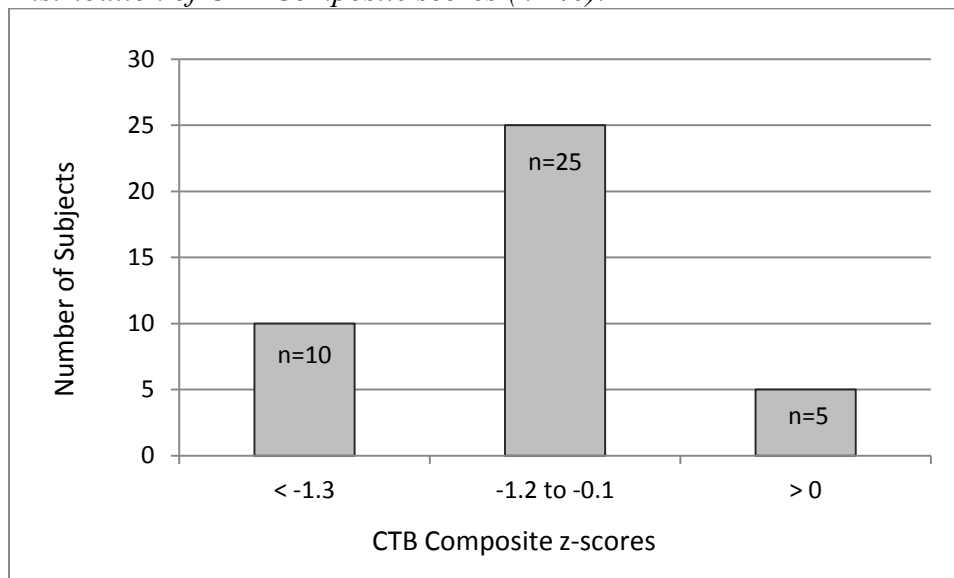
Executive control function was measured by calculating the Clinical Trials Battery Composite score (CTB Composite), the Trails Making Test Part B minus A Difference score (TMT Difference), and the Executive Interview-25 (EXIT-25).

Clinical Trials Battery (CTB) Composite.

The CTB is a z-score composite of performance scores for test of memory (HVLT subscales), attention (Trails A and B), and verbal fluency (COWA). It has been used as an index of global cognitive impairment (Johnson et al., 2012). AS the PCA demonstrated only one factor for all tests in the neuropsychological battery, the CTB Composite scores may be used to indicate subject performance for ECF. The CTB Composite score ranged from 0.8 to -8.1 and averaged -1.2 (SD 1.6). Since the CBT is derived from the z-scores on each neuropsychological instrument, scores ≥ 0 indicate better cognitive function, and lower scores indicate cognitive impairment. Five subjects (12.5%) had CTB Composite scores of 0 or higher (Figure 5.3). Twenty-five subjects (62.5%) had CTB Composite performance scores between -0.1 and -1.4 SD. Seven subjects (17.5%) had CTB Composite scores of -1.3 – 3.0, indicating mild to moderate impairment, and 3 scored below -3, indicating severe impairment. The bar graph in Figure 1 shows that most subject composite scores were below 0 (skewness -2.6 and

kurtosis 8.6). Age, education, tumor characteristics, self-reported physical function, and PBT-specific symptoms were not associated with CTB Composite scores.

Figure 5.3.
Distribution of CTB Composite scores (n=40).

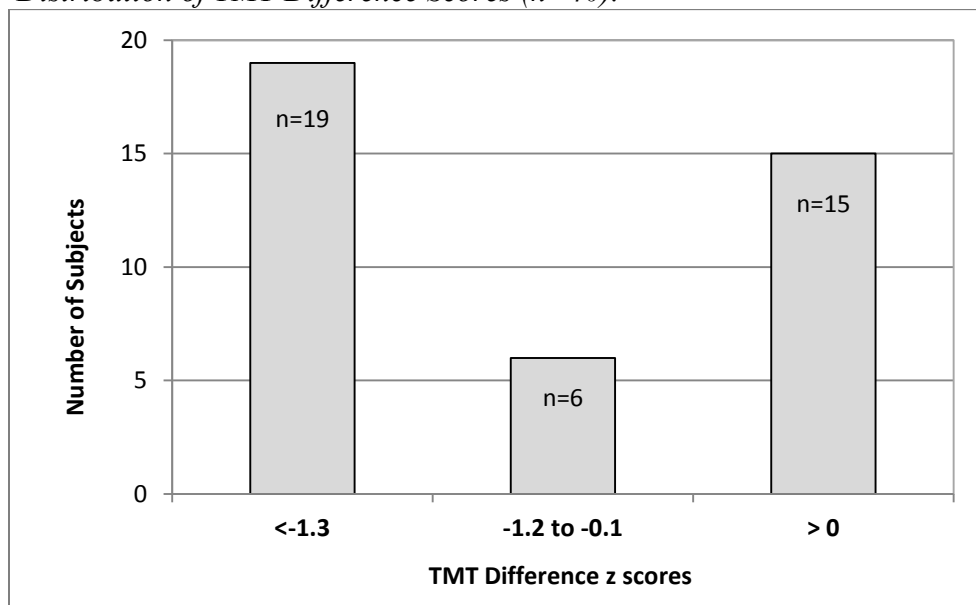


Trails Making Tests Difference score.

The Trails Making Tests Difference z-score (TMT Difference) has been considered an indicator of impaired ECF because it controls for speed, motor control, and visual scanning. The TMT Difference ranged from 0 to 222 seconds, with a median of 45 seconds and an average of 57.1 seconds (SD 41.8). Age and education specific normative scores for the Trails-A and Trails-B were used to calculate z-scores for the TMT Difference score, with z-scores ≥ 0 indicating better cognitive function and scores < 0 indicating cognitive impairment. Fifteen subjects (37.5%) had TMT Difference scores ≥ 0 , indicating that their mean performance scores were at normed comparison levels or higher (Figure 5.4). Six subjects (15%) had TMT Difference scores of -0.1 to -1.3. Five subjects (12.5%) had CTB Composite scores between -1.3

to -3.0, indicating mild to moderate executive control dysfunction. Fourteen subjects (30%) scored below -3 SD, indicating severe impairment. Figure 5.4 shows that the majority of TMT Difference scores were below 0 (skewness -1.10 and kurtosis 0.6). Age, education, tumor characteristics, self-reported physical function, or PBT-specific symptoms were not associated with TMT Difference scores.

Figure 5.4.
Distribution of TMT Difference Scores (n=40).



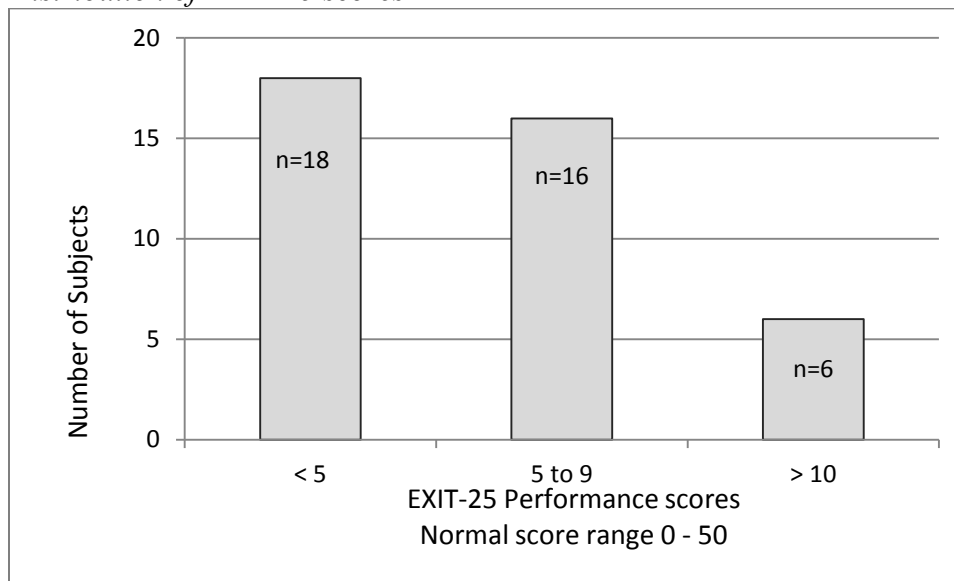
Executive Interview-25.

Executive Interview-25 (EXIT-25) scores ranged from 1 to 17 with a median score of 5 and a mean of 5.93 (SD 3.58). No subject scored 0 indicating that every subject had at least one item error on the EXIT-25. Eighteen subjects (45%) had performance scores of less than 5 points, indicating no evidence of ECF impairment. The majority of subjects accumulated 5 or more points (n=22, 55%), but only one subject (2.5%) had a performance score above 15. The

scores for these 22 subjects indicate mild ECF impairment in 16 (40%) and severe in 6 (15%).

Figure 5.5 shows the distribution of EXIT-25 scores with a skewness of 1.2 (kurtosis 1.3).

Figure 5.5.
Distribution of EXIT-25 scores



Subject age correlated moderately with performance on the EXIT-25, $r=.48$, $p=.002$, with older subjects tending to have worse performance scores on the EXIT-25. There were no significant relationships between education, time since diagnosis, tumor characteristics, self-reported physical function, depression, or PBT-related symptoms with EXIT-25 performance.

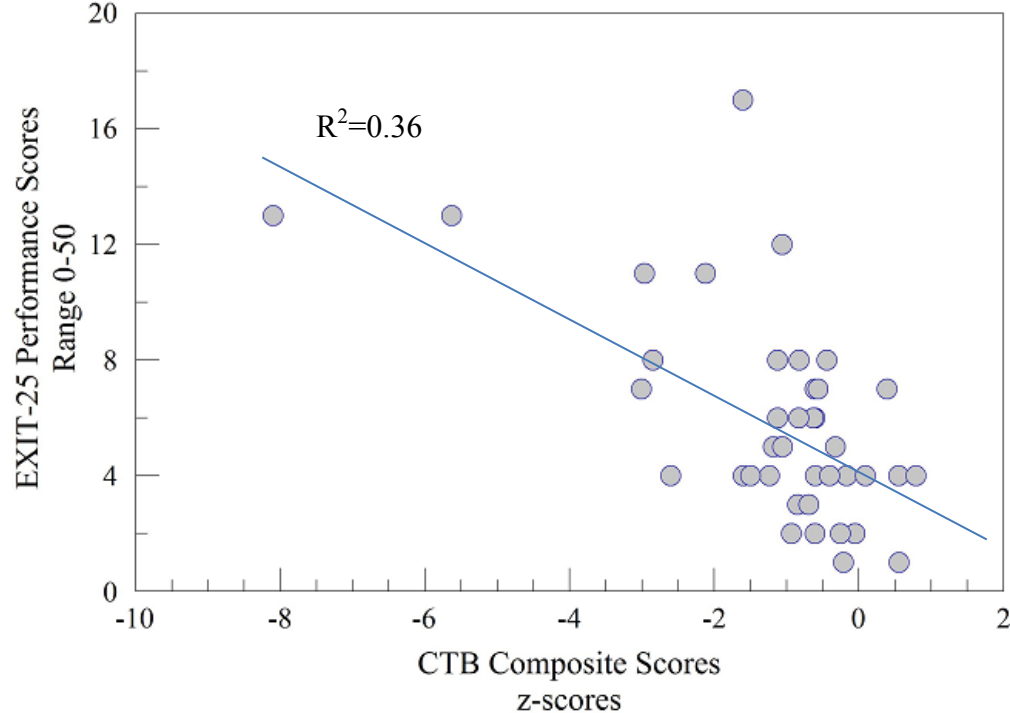
Comparison between CTB Composite and EXIT-25.

To explore the EXIT-25 as a global measure for detecting impairments of ECF in adults with PBT, EXIT-25 performance scores were examined and compared to CTB Composite scores. The EXIT-25 and CTB Composite scores were significantly associated, $r=.60$, $p<.001$. The EXIT-25 was also significantly associated with all of the standardized neuropsychological

tests for memory, attention, and verbal fluency, $p < .005$. Figure 5.6 demonstrates the relationship between the EXIT-25 and CTB Composite scores, $R^2 = .36$. Eliminating the two outliers with CTB Composite scores > -5.0 did not improve the correlation ($R^2 = .22$).

Figure 5.6.

EXIT-25 performance scores by CTB Composite scores (n=40).



Specific Aim 1 summary.

Mild to severe impairment in the domain of memory impairment was found in more subjects (32.5%) than was found in the domain of attention (27.5%). Impaired performance was found on the HVLT-DR for memory in 42.5% of subjects, and on the Trails B for attention in 37.5%. Verbal fluency was the least affected modality in these subjects, with only 22.5% demonstrating impairment. ECF integrates functions from multiple cognitive domains, and

22.5% of subjects demonstrated mild-to-severe impairment as determined by the CTB Composite score. The percentage of subjects rated as cognitively impaired varied greatly on the EXIT-25 depending on the cutoff score used (55% were rated as having mild-to-severe impairment using a cutoff score of 5, but only 15% using a cutoff score of 10). Because there is no established score indicating mild-to-moderate impairment on the EXIT-25, further research is indicated to establish its value as a cognitive screen in survivors of PBT.

Specific Aim 2

To describe self-reported ECF and its components in adults following treatment for PBT. This aim will be addressed by examining the following self-report instruments containing cognitive function items:

- a. Self-reported cognitive function on the Everyday Cognitions Scale (ECog) by total scale scores and its six subscales
- b. Self-reported PBT-specific symptom assessment by total scale scores and cognitive item scores
 - i. Functional Assessment of Cancer Therapy-Brain Tumor (FACT-BT)
 - ii. MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT)

Aim 2 was explored using three self-reported instruments for cognitive function or presence of brain tumor specific symptoms:

- a) Everyday Cognitions Scale (ECog) uses a four-point scale to measure subject's perception of change in their ability to perform everyday cognitive functions; lower scores indicate less change in cognitive function since diagnosis.
- b) Functional Assessment of Cancer Therapy – Brain Tumor Module (FACT-BT) uses a four-point scale to measure subject perception of symptoms and their impact on quality of life during the preceding week; higher scores indicate greater symptom presence and quality of life impact.
- c) MD Anderson Symptom Inventory – Brain Tumor Module (MDASI-BT) uses an 11-point scale to measure subject perception of symptom severity and interference with

daily activities for their current health state at the time of subject report; lower scores indicate less symptom severity and interference in daily activities.

Self-reported Executive Control Function: Everyday Cognitions Scale.

Total scale scores for the Everyday Cognitions Scale (ECog) ranged from 1.00 to 3.29, as displayed on Table 5.16. The average score of 1.87 (SD 0.64) represents a perceived change in everyday cognitive function since diagnosis graded as “occasionally worse.” To aid in the interpretation of data, ECog subscale scores of 2 or higher were used to describe subject perception of change in cognitive function from “occasional problems” to “consistently much worse.” Subject characteristics, including demographic variables and cancer-related factors, were explored to explain any differences observed in perceptions of cognitive function. The ECog has not been used before in PBT survivors, but it offers a more comprehensive assessment of self-reported cognitive function, so ECog scores were compared to PBT-specific symptom assessments, focusing on the cognitive items that each scale contains.

Table 5.16 shows that subject scores varied across the subscales, with the greatest variability observed in tasks requiring attention, memory, and organizing. The mean scores on the subscales ranged from 1.44 (SD 0.58) for the visuo-spatial subscale to 2.32 (SD 1.05) for the attention subscale. Thus, most cognitive functions were perceived as being affected since their diagnosis. Memory (M 2.28, SD 0.86) and attention (M 2.32, SD 1.05) functions were the most affected cognitive functions., and those requiring visuo-spatial (M 1.44, SD 0.58) and planning (M 1.49, SD 0.61) abilities were least affected. The mean scores for ECog total and subscales are consistent with reference mean scores of elderly subjects with mild cognitive impairment (Farias et al., 2006, 2008).

Table 5.16.

Self-reported cognitive function on the Everyday Cognitions scale and 6 subscales (n=40).

<u>Domain</u>	<u>Min – Max^a</u>	<u>Mean</u>	<u>SD</u>	<u>Median</u>	<u>Skewness</u>	<u>Kurtosis</u>
Total	1-3.29	1.87	0.64	1.85	0.53	-0.28
Memory	1-4.00	2.28	0.86	2.19	0.23	-1.05
Language	1-3.50	1.93	0.71	1.81	0.57	-0.55
Visuo-spatial	1-3.29	1.44	0.58	1.21	1.72	2.73
Planning	1-3.20	1.49	0.61	1.30	1.52	1.77
Organizing	1-4.00	1.75	0.86	1.33	0.97	-0.29
Attention	1-4.00	2.32	1.05	2.13	0.24	-1.35

^aPotential range of scores = 1-4; higher scores indicate more change in cognitive function since diagnosis.

Seventeen subjects (42.5%) had ECog total scale scores of ≥ 2 , indicating a change in their cognitive function” since diagnosis from “occasionally worse” to “much worse. Scores >2 were most frequently reported for tasks requiring attention (n=24, 60%), memory (n=21, 52.5%), and language (n=18, 45%). Less commonly reported were impairments of function related to organizing (n=13; 32.5%), planning (n=7, 17.5%), and visuo-spatial (n=6, 15%) domains.

Correlations between self-reported ECF and subject characteristics.

There were no significant associations between ECog total score or its subscales and subject characteristics for age, education, medications, tumor grade, or tumor location. Time since diagnosis was significantly associated with ECog planning subscale, $r=.36$, $p=.02$, and approached significance with ECog organizing subscale, $r=.26$, $p=.10$. Thus, subjects with longer survival times were more likely to report worsening cognitive functions involving planning and organizing. Tumor hemisphere was significantly associated with the total ECog score ($r=-.45$, $p<.05$.) and subscales for memory ($r=-.44$), attention ($r=-.31$), visuospatial ($r=-.37$), planning ($r=-.39$), and organizing ($r=-.51$). Thus, patients with right hemispheric lesions (n=20) were more likely to report more cognitive dysfunction since diagnosis than those with left hemispheric lesions.

Several everyday cognitive functions were significantly associated with self-reported ability to perform activities of daily living. Scores on the OARS total scale were significantly associated with cognitive functions reported on ECog total ($r=-.41, p<.05$), memory ($r=-.34$), language ($r=-.32$), visuo-perceptual ($r=-.38$), planning ($r=-.33$), and organizing ($r=-.37$) scales. In addition, scores on the OARS Instrumental subscale were significantly associated with cognitive functions reported on ECog total ($r=-.45, p<.05$), memory ($r=-.38$), attention ($r=-.32$), language ($r=-.35$), visuospatial ($r=-.042$), planning ($r=-.39$), and organizing ($r=-.40$) scales. Subjects who reported needing more assistance with instrumental activities of daily living, such as driving or preparing meals, also reported worsening of everyday cognitive activities.

The presence of depressive symptoms was significantly associated with the ECog total scale ($r=.49, p<.05$), memory ($r=.43$), attention ($r=.47$), language ($r=.47$), planning ($r=.47$), and organizing ($r=.37$) subscales. Thus, subjects who reported the presence of depressive symptoms were more likely to report worsening of everyday cognitive function.

Self-reported PBT-specific symptom assessment.

The Functional Assessment of Cancer Therapy-Brain Tumor Scale (FACT-BT) and MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) were used for self-report of subject perception of symptom presence, severity, and interference in their current everyday health state. Table 5.17 shows subject data for self-reported quality of life and symptom interference.

Table 5.17.

Self-reported quality of life and symptom interference for survivors of PBT (n=40).

<u>Scale</u>	<u>Potential Range</u>	<u>Min – Max</u>	<u>Mean (SD)</u>	<u>Median</u>
FACT-BT^a				
Total Scale	0-184	85-183	139.62 (22.99)	143.5
Cognitive Items	0-36	10-36	21.05 (6.04)	23.0
MDASI-BT^b				
Severity Subscale	0-10	0-5.73	1.25 (1.19)	0.8
Interference Subscale	0-10	0-8.67	1.35 (1.93)	0.6
Cognitive Items	0-10	0-8.75	1.83 (2.02)	1.3

^aFACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor scale; lower scores indicate greater symptom impact on quality of life.

^bMDASI-BT=MD Anderson Symptom Inventory-Brain Tumor scale; higher scores indicate greater symptom severity/interference.

Functional Assessment of Cancer Therapy-Brain Tumor Scale (FACT-BT).

The range of scores on the FACT-BT was 85 to 183, with lower scores indicating greater impact of symptoms on quality of life. The FACT-BT total score averaged 139.62 (SD 22.99), indicating subject perception that brain tumor related symptoms have a moderate impact on their quality of life (Table 5.17). These scores are similar to the mean score of 136.0 (SD 26.0) found for the FACT-BT in 101 PBT survivors (Weitzner et al., 1995). This reference sample was similar to the present study population in age (M 41.2 years), mixed tumor grade, education (14.7 years), and time since diagnosis of 0 to 247 months (M 32.1 months), and all had received surgery, chemotherapy, or radiation treatment.

The FACT-BT contains 9 items that pertain to cognitive functions of concentration, memory, verbal fluency, organization, and planning. Subject responses for these 9 cognitive items ranged from 10-32 and averaged 21.05 (SD 6.04). Thus, subject responses reflect a perception that cognitive symptoms create a moderate impact on quality of life.

MD Anderson Symptom Inventory-Brain Tumor Scale (MDASI-BT).

Scores on the MDASI-BT symptom severity subscale ranged from 0 to 5.73, and on the MDASI-BT symptom interference subscale, from 0 to 8.73; higher scores indicate greater symptom severity or interference. Subjects reported average scores of 1.25 (SD 1.20) for symptom severity and 1.35 (SD 1.95) for symptom interference. These scores indicate minimal symptom burden at time of study, and are slightly lower than mean reference scores of 1.52 for symptom severity and 2.1 for symptom interference in 151 PBT survivors (Armstrong et al., 2006). The reference sample was similar to the present study cohort in age (M 45.8 years), education (M 14.5 years), mixed tumor grade, and all had received surgery, chemotherapy, or radiation therapy.

The MDASI-BT contains four items assessing cognitive symptom severity for memory, comprehension, verbal fluency, and concentration. Subjects reported cognitive symptom scores ranging of 0 to 8.75, with an average of 1.8 (SD 2.0). This reflects mild cognitive symptom severity, but the average is slightly higher than the total symptom severity mean of 1.25, indicating slightly more symptom severity.

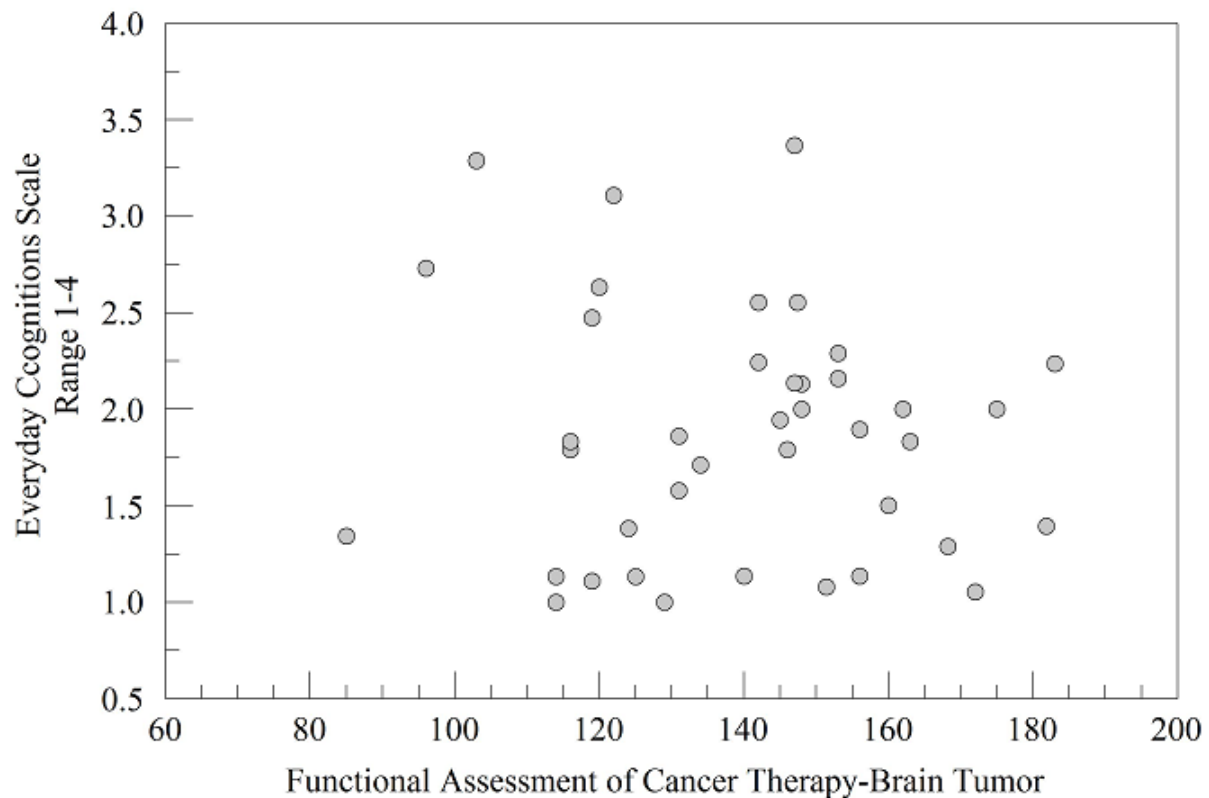
Correlations between everyday cognitive function and cancer-related symptoms.

The FACT-BT scores were significantly associated with scores for the ECoG total ($r=-.59, p<.05$), memory ($r=-.65$), attention ($r=-.47$), language ($r=-.51$), visuospatial ($r=-.38$), planning ($r=-.51$), and organizing ($r=-.36$) subscales. Figure 5.7 plots subject scores on the ECoG total against scores on the FACT-BT. Similar significant associations were observed with the FACT-BT cognitive items and the ECoG scores: ECoG total ($r=-.69, p<.05$), memory ($r=-.68$), attention ($r=-.59$), language ($r=-.68$), visuospatial ($r=-.48$), planning ($r=-.62$), and organizing

($r=-.41$). Thus, those who perceive greater symptom impact on their quality of life tend to report greater change in cognitive function since diagnosis.

Figure 5.7.

Self-reported symptom impact on quality of life versus cognitive function (n=40).

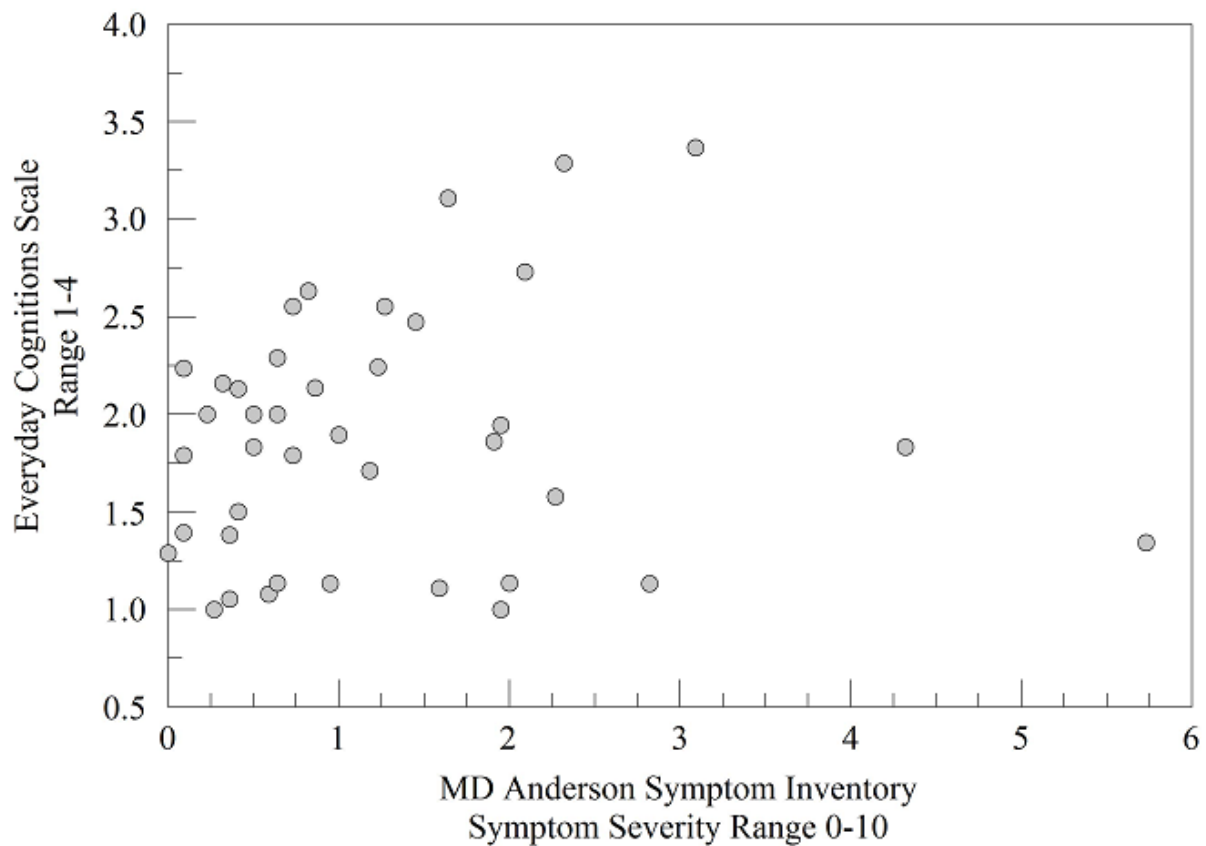


Footnote: Lower scores on the ECog reflect no change since diagnosis; lower scores on the FACT-BT reflect greater symptom impact on quality of life.

The MDASI-BT symptom severity scores were significantly associated with the ECog total ($r=.39, p<0.05$), memory ($r=.41$), visuospatial ($r=.37$), planning ($r=.33$), and organizing ($r=.33$) scores. Symptom interference scores on the MDASI-BT were also significantly associated with the ECog total ($r=.38, p<.05$), memory ($r=.41$), planning ($r=.39$), and attention ($r=.34$) scores. Similar associations were observed for the MDASI-BT cognitive items and ECog

total ($r=.44$), memory ($r=.45$), attention ($r=.40$), language ($r=.35$), and visuospatial ($r=.40$) scales. Thus, subjects who report greater symptom severity or symptom interference tend to report more change in cognitive function since diagnosis. This is seen in Figure 5.8 with subject scores plotted for symptom severity versus cognitive function.

Figure 5.8.
Self-reported symptom severity versus cognitive function (n=40).



Footnote: Lower scores on ECog indicate no change since diagnosis; lower scores on MDASI-BT indicate less symptom severity.

Specific Aim 2 summary.

Subjects tended to report “occasionally worse” cognitive function since their diagnosis. Tasks that required memory and attention were more frequently and more severely affected (“consistently worse” or “much worse”) since diagnosis. Subjects who needed assistance with instrumental activities of daily living or who endorsed depressive symptoms were more likely to perceive changes in cognitive function as worse. Subjects reported a moderate impact of symptom presence on their quality of life, yet these symptoms were not severe and did not interfere greatly with their daily activities. This may reflect subjects’ adjustment to the impact of symptoms in their lives.

Cognitive symptoms were similar across subjects, thus subjects who reported less change in cognitive function (ECog) also tended to report less cognitive symptom severity and less daily interference (MDASI-BT) or impact on their quality of life (FACT-BT). This suggests that the ECog may be useful in this population because it provides a comprehensive assessment of perceived changes in cognitive function since diagnosis rather than the assessment of symptom presence during the preceding week (FACT-BT) or the severity of interference in their lives during the previous 24 hours (MDASI-BT).

Specific Aim 3

To describe the relationship of ECF (executive control function) performance scores and subject self-report scores. This aim will be addressed by exploring the congruence or incongruence of the following relationships:

- a. Clinical Trials Battery (CTB) Composite score and Everyday Cognitions Scale (ECog) total score
- b. Trails Making Tests Parts B-A Difference (TMT Difference) score and Everyday Cognitions Scale (ECog) total score
- c. Executive Interview-25 (EXIT-25) score and Everyday Cognitions Scale (ECog) total score

To describe how executive control function (ECF) performance relates to subject self-report, scores on the Clinical Trials Battery Composite (CTB Composite), Trails Making Tests Difference Composite (TMT Difference), and Executive Interview-25 (EXIT-25) were compared to self-reported cognitive function scores on the Everyday Cognitions Test (ECog). Scatterplots of subject scores were used to examine the relationship of cognitive performance (x-axis) and self-reported cognitive function (y-axis). To describe subject patterns observed on the scatterplots, four quadrants were established using measurement cutpoints of -1.3 for CTB Composite score and -1.3 for TMT Difference score, 5 for EXIT-25 score, and 2 for ECog total score. Each quadrant contains a group of subjects defined under Methods, Chapter 4, as:

- 1) **Group A** comprises subjects who report no change in cognitive function since diagnosis and whose ECF performance scores were within normal limits.

- 2) **Group B** comprises subjects who report a change in cognitive function since diagnosis, but whose ECF performance was within normal limits.
- 3) **Group C** comprises subjects who report no change in cognitive function since diagnosis, but who had poor ECF performance scores .
- 4) **Group D** comprises subjects who report a change in cognitive function since diagnosis, and who had poor ECF performance scores

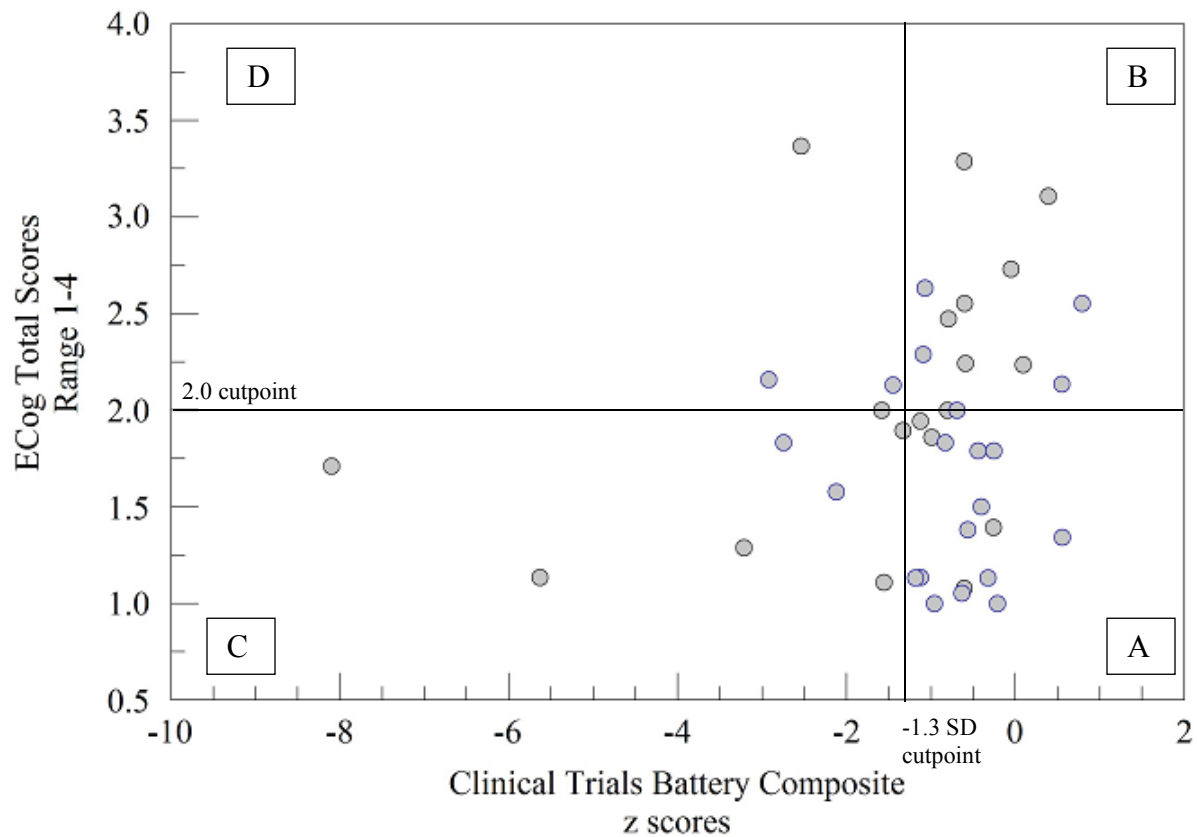
The relationship of CTB Composite and ECog.

Inspection of the scatterplot of CTB Composite performance scores versus ECog Total scale scores (Figure 5.9) shows that the majority of subject scores ($n=30$, 75%) fell above the -1.3 SD cutpoint line on the CTB Composite, indicating normal or acceptable cognitive function. Subject perception of change in cognitive function since diagnosis varied from “no change (ECog score of 1)” to “much worse (ECog score of 4)”; a score of 2 was set as the cutpoint for ECog. The resulting assignment of subjects to quadrants A and D, represent congruence of cognitive performance with cognitive function perception, while quadrants B and C represent incongruence of measured to perceived function. There was a low level of agreement between the CTB Composite and ECog Total scale scores (Overall Percent Agreement=.53; Kappa=.03), indicating that self-reported change in cognitive function is not reflected in measurement of impaired cognitive function.

There were 21 subjects (52.5%) with congruence of self-report and performance scores (Groups A and D), and 19 subjects (47.5%) with incongruence of self-report and performance scores (Groups B and C). Group A comprised 17 subjects (42.5%) who reported little or no change in cognitive function since diagnosis and had normal cognitive performance scores.

Group D comprised 4 subjects (10%) who reported a perception of cognitive function change since diagnosis and had poor cognitive performance. Group B comprised 13 subjects (32.5%) who reported a change in cognitive function since diagnosis but had normal cognitive performance scores. Group C comprised 6 subjects (15%) who reported little or no change in cognitive function yet performed poorly.

Figure 5.9. Scatterplot of CTB Composite scores and ECog total scores (n=40).



Group A=normal performance & self-report. Group B=normal performance but report change in cognitive function. Group C=poor performance but report no or little change in cognitive function. Group D=poor performance & report change in cognitive function.

Table 5.18 looks at subject and tumor characteristics to explore differences across the four group categories. Chi-square and Kruskal-Wallis tests were used to examine mean difference across groups. Gender was significantly different across groups, $\chi^2(3)=8.7, p=.03$; women formed a majority of Groups A and B while men were the majority in Groups C and D. Tumor location was significantly different between groups, $\chi^2(3)=12.6, p=.05$, with tumors of the parieto-occipital or midbrain areas being more common than frontal or temporal lobe tumors in subjects in Group D. Time since diagnosis was greater in Groups C and D with poorer performance, the differences between groups were not significant. No significant differences in age, education, tumor grade, medications, or treatment modalities were detected across groups.

Table 5.18.

CTB Composite and ECog Scores: Subject and tumor-related characteristics by group categories (n=40).

	Group A^a (n=17)	Group B^b (n=13)	Group C^c (n=6)	Group D^d (n=4)
Gender (F, %)				
Male	7 (41%)	3 (23%)	4 (66%)	4 (100%)
Female	10 (59%)	10 (77%)	2 (34%)	0
Age, in years (M, SD)	50.3 (9.7)	46.1 (9.7)	53.5 (8.7)	57.5 (6.5)
Education, in years (M, SD)	15.3 (2.0)	14.6 (1.8)	14.7 (2.1)	16.5 (1.0)
Time since diagnosis in months (M, SD)	82.7 (75.3)	98.6 (70.5)	119.8 (96.3)	160.3 (104.0)
Tumor hemisphere (F, %)				
Left	10 (59%)	3 (23%)	5 (83%)	2 (50%)
Right	7 (41%)	10 (77%)	1 (17%)	2 (50%)
Tumor location (F, %)				
Frontal	9 (53%)	7 (54%)	3 (50%)	0
Temporal	5 (29%)	4 (31%)	1 (17%)	0
Other	3 (18%)	2 (15%)	2 (33%)	4 (100%)
Tumor Grade (F, %)				
Low grade, grade 2	4 (24%)	1 (8%)	0	1 (25%)
Transformed low grade	1 (5%)	2 (15%)	1 (17%)	1 (25%)
High grade, grade 3	8 (47%)	6 (46%)	4 (66%)	1 (25%)
High grade, grade 4	4 (24%)	4 (31%)	1 (17%)	1 (25%)

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

Compared to other groups, subjects in Group A tended to report that cancer-related symptoms had less impact on their quality of life (FACT-BT), $H(3)=9.8$, $p=.02$ Table 5.19. Group A also reported less impact of cognitive symptoms on quality of life FACT-BT cognitive items), $H(3)=14.6$, $p=.002$, and less severe cognitive symptoms (MDASI-BT cognitive items), $H(3)=6.6$, $p=.09$. There was a significant difference in reported depressive symptoms (CESD-R), $H(3)=8.1$, $p=.04$, across groups. Group A reported fewer depressive symptoms and Group B, more. Subjects in Group D reported needing more assistance with activities of daily living (OARS Physical subscale), $H(3)=7.9$, $p=.05$. While the difference was not significant,

Group D reported a greater impact of symptoms on their quality of life (FACT-BT, MDASI Interference).

Table 5.19.

CTB Composite and ECog Scores: Self-reported symptom assessments by group categories (n=40).

	Group A^a (n=17) <u>M (SD)</u>	Group B^b (n=13) <u>M (SD)</u>	Group C^c (n=6) <u>M (SD)</u>	Group D^d (n=4) <u>M (SD)</u>
FACT-BT				
Total	152.4 (18.6)	128.2 (20.5)	136.8 (29.1)	126.8 (14.5)
Cognitive Items	27.6 (5.1)	19.3 (5.7)	22.3 (7.7)	16.5 (4.4)
MDASI-BT				
Severity	0.8 (0.6)	1.5 (1.0)	1.8 (2.0)	1.7 (1.8)
Interference	0.6 (0.6)	1.5 (1.5)	1.3 (1.5)	4.1 (4.5)
Cognitive Items	0.9 (0.8)	2.3 (1.9)	2.5 (3.3)	3.4 (2.8)
CESD-R	6.4 (5.7)	15.5 (10.7)	10.5 (6.3)	10.3 (4.4)
OARS				
Total	27.4 (1.4)	26.8 (1.5)	27.3 (1.0)	26.0 (2.3)
Physical	13.9 (0.5)	13.9 (0.3)	14.0 (0.0)	13.3 (1.0)
Instrumental	13.5 (1.0)	12.9 (1.3)	13.3 (1.0)	12.8 (1.5)

FACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor; MDASI-BT=MD Anderson Symptom Assessment-Brain Tumor; CESD-R=Center for Epidemiologic Studies Depression Scale-Revised; OARS=Older Americans Resources and Services Activities of Daily Living Scale.

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

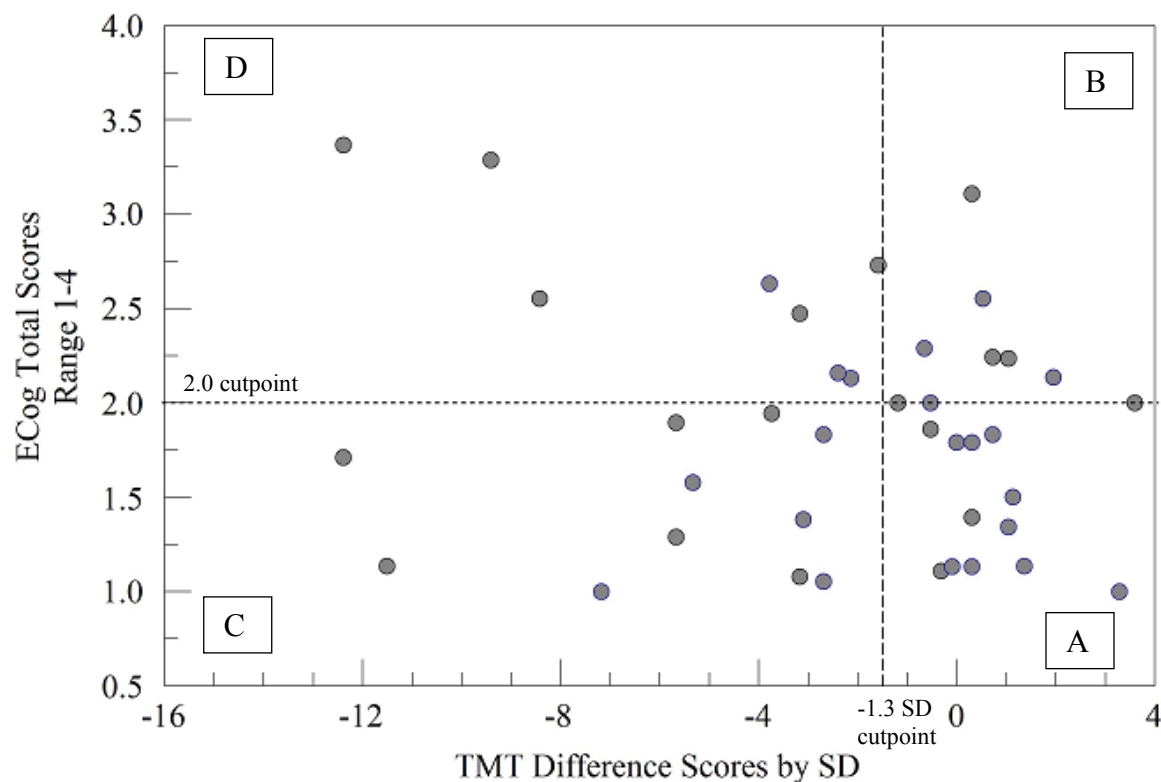
The relationship of TMT Difference and ECog.

Figure 5.10 shows the TMT Difference scores for cognitive performance and the ECog scores for self-reported cognitive function. There was more spread of subject scores on this scatterplot compared to Figure 5.10. The majority of subjects (n=25, 62.5%) remained within their groupings of A through D derived from Figure 5.9, but 15 subjects moved across groups: 7 subjects moved from Group A to C, 2 subjects moved from Group C to A, 5 subjects moved from Group B to D, and 1 subject moved from Group D to B. Thus, twelve subjects with

acceptable CTB Composite scores had TMT Difference scores consistent with mild to severe impairment. Likewise, three subjects moved from impaired CTB Composite scores to an acceptable range on TMT Difference score.

Figure 5.10.

Scatterplot of TMT Difference scores and ECog total scores (n=40).



Group A=normal performance & self-report. Group B=normal performance but report change in cognitive function. Group C=poor performance but report no or little change in cognitive function. Group D=poor performance & report change in cognitive function.

The cutpoint scores of 2 on the ECog for self-reported cognitive function and -1.3 SD on the TMT Difference composite (z-score) for cognitive performance were used to define groups of subjects with congruent and incongruent scoring patterns. There was a low level of agreement

between the TMT Difference and ECog Total scale scores (Overall Percent Agreement=.50; Kappa=.01).

Twenty subjects (50%) had congruent TMT Difference performance scores and self-reported cognitive function scores, and 20 subjects (50%) had incongruent scores. The congruent groups comprised 12 subjects (30%) in Group A who indicated relatively no change in cognitive function since diagnosis and had acceptable cognitive performance, and 8 subjects (20%) in Group D who reported a change in cognitive function since diagnosis and had poor cognitive performance. For incongruent scores, 9 subjects (22.5%) in Group B reported worsening of cognitive function since diagnosis but had acceptable cognitive performance, and 11 subjects in Group C (27.5%) who reported relatively no change in cognitive function but had poor cognitive performance by TMT Difference score.

Table 5.20 shows the gender, age, education, and tumor-specific characteristics across groups. No significant differences between groups were detected by Chi-square or Kruskal-Wallis analyses. There was a trend toward longer time since diagnosis in Group D, however this was not statistically significant. This trend was similar to that observed with the CTB Composite groups.

Table 5.20.

TMT Difference and ECog Scores: Subject and tumor-related characteristics by group categories (n=40).

	Group A^a (n=12)	Group B^b (n=9)	Group C^c (n=11)	Group D^d (n=8)
Gender (F, %)				
Male	5 (42%)	3 (33%)	6 (55%)	4 (50%)
Female	7 (58%)	6 (67%)	5 (45%)	4 (50%)
Age in years (M, SD)	50.9 (8.1)	47.9 (11.6)	51.4 (11.0)	49.8 (9.1)
Education in years (M, SD)	15.3 (2.3)	15.3 (1.4)	14.9 (1.6)	14.8 (2.1)
Time since diagnosis in months (M, SD)	84.5 (83.6)	78.9 (64.7)	101.0 (80.5)	151.6 (82.6)
Tumor hemisphere (F, %)				
Left	9 (75%)	2 (22%)	6 (55%)	3 (38%)
Right	3 (25%)	7 (78%)	5 (45%)	5 (62%)
Tumor location (F, %)				
Frontal	5 (42%)	4 (45%)	7 (64%)	3 (38%)
Temporal	3 (25%)	2 (22%)	3 (27%)	2 (24%)
Other	4 (33%)	3 (33%)	1 (9%)	3 (38%)
Tumor Grade (F, %)				
Low grade, grade 2	2 (17%)	0	2 (18%)	2 (24%)
Transformed low grade	1 (8%)	2 (22%)	1 (9%)	1 (14%)
High grade, grade 3	5 (42%)	4 (45%)	7 (64%)	3 (38%)
High grade, grade 4	4 (33%)	3 (33%)	1 (9%)	2 (24%)

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

Self-reported symptoms (Table 5.21) were similar to those observed with the CTB Composite groups. Group A tended to report less impact of symptoms on their quality of life (FACT-BT), $H(3)=10.6$, $p=.01$, and less severity of symptoms (MDASI-BT), $H(3)=7.3$, $p=.06$. Group A also reported less impact of cognitive symptoms (FACT-BT cognitive items), $H(3)=14.6$, $p=.002$. Group D tended to report the greatest impact of cognitive symptoms on quality of life. There was a significant difference in depressive symptoms (CESD-R), $H(3)=6.7$, $p=.08$, with Group A reporting fewer symptoms, and Group B reporting more.

Table 5.21.

TMT Difference and ECog Scores: Self-reported symptom assessments by group categories (n=40).

	Group A^a (n=12) <u>M (SD)</u>	Group B^b (n=9) <u>M (SD)</u>	Group C^c (n=11) <u>M (SD)</u>	Group D^d (n=8) <u>M (SD)</u>
FACT-BT				
Total	154.5 (16.9)	129.6 (19.9)	140.3 (26.4)	125.3 (18.4)
Cognitive Items	27.5 (4.2)	20.2 (5.8)	24.5 (8.0)	16.4 (4.3)
MDASI-BT				
Severity	0.6 (0.5)	1.6 (1.0)	1.7 (1.6)	1.4 (1.5)
Interference	0.6 (0.6)	2.0 (2.7)	1.0 (1.2)	2.3 (2.7)
Cognitive Items	0.9 (0.9)	2.2 (1.7)	1.8 (2.6)	3.1 (2.6)
CESD-R	6.5 (5.4)	14.7 (10.8)	8.8 (6.8)	13.7 (8.8)
OARS				
Total	27.5 (1.0)	27.0 (1.4)	27.3 (1.6)	26.3 (1.9)
Physical	14.0 (0.0)	13.9 (0.3)	13.8 (0.6)	13.6 (0.7)
Instrumental	13.5 (1.0)	13.1 (1.2)	13.5 (1.0)	12.6 (1.5)

FACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor; MDASI-BT=MD Anderson Symptom Assessment-Brain Tumor; CESD-R=Center for Epidemiologic Studies Depression Scale-Revised; OARS=Older Americans Resources and Services Activities of Daily Living Scale.

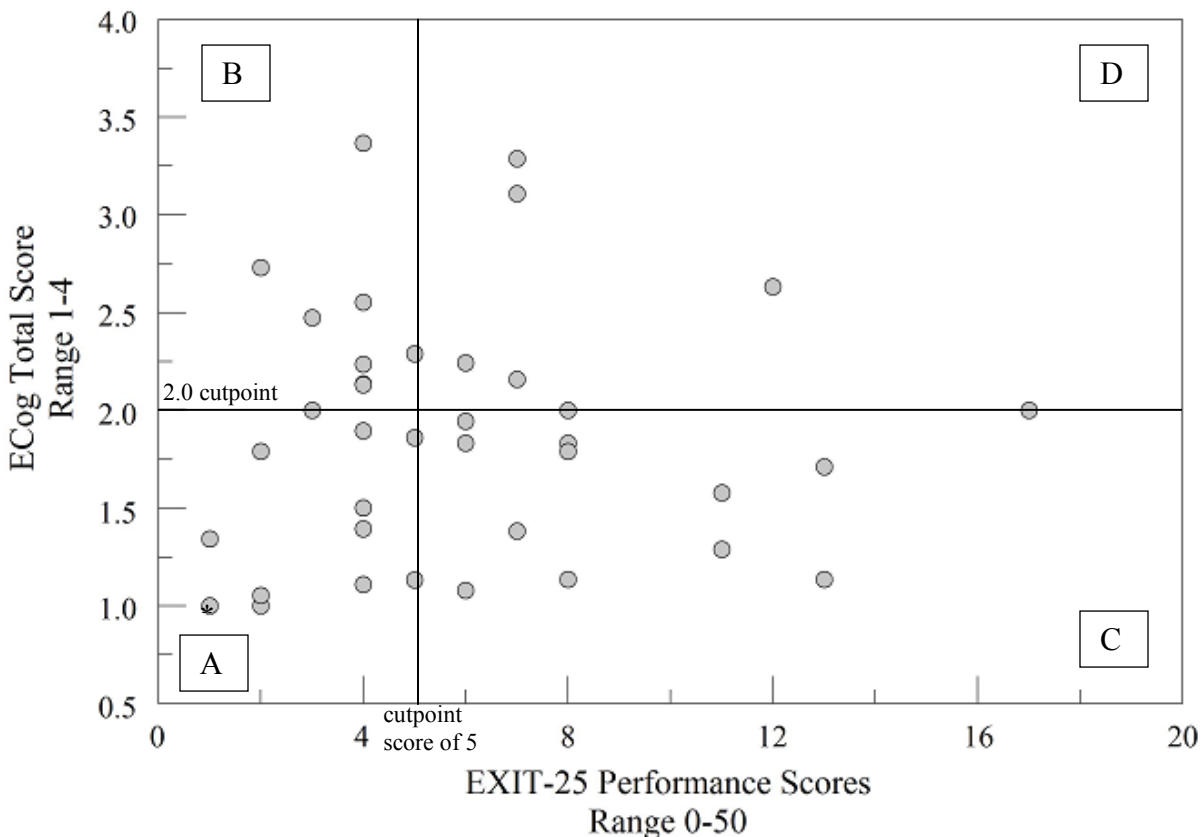
^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

The relationship of EXIT-25 and ECog.

Figure 5.11 shows an even greater dispersion of subject scores than the previous two scatterplots. When comparing subject assignment to groups in Figure 5.10, there was substantial movement (n=18, 45%) across the groups. Five subjects moved from Group B to D, 2 subjects moved from Group D to B, 9 subjects moved from Group A to C, and 2 subjects moved from Group C to A. As a result, 14 subjects with acceptable CTB Composite scores had impaired EXIT-25 scores, and 4 subjects with impaired CTB Composite scores had normal EXIT-25 scores.

Figure 5.11.

Scatterplot of EXIT-25 performance scores and ECog total scores (n=40).



Group A=normal performance & self-report. Group B=normal performance but report change in cognitive function. Group C=poor performance but report no or little change in cognitive function. Group D=poor performance & report change in cognitive function.

The cutpoint scores of 2 on the ECog and 5 on the EXIT-25 were used to define groups of subjects with congruent and incongruent scoring patterns. There was a low level of agreement between the EXIT-25 and ECog Total scale scores (Overall Percent Agreement=.48; Kappa=.06).

Nineteen subjects had congruent patterns in scores, and 21, incongruent patterns. Group A contained 12 subjects (30%) with congruence between ECog Total scale scores and the EXIT-25. Group D, also congruent, had 7 subjects (17.5%). The incongruent Group B had 10 subjects who performed well on the EXIT-25 but reported a change in cognitive function since diagnosis,

and Group C had 11 subjects (27.5%) who reported relatively little or no change in cognitive function since diagnosis yet performed poorly on the EXIT-25.

Table 5.22 shows group similarities for subject and tumor-related characteristics; Chi-square and Kruskal-Wallis analyses were used to determine significant differences across groups. Groups C and D, who performed poorly on the EXIT-25, tended to be older, $H(3)=11.4$, $p=.01$. Time since diagnosis was longer for those in Groups B and C, but not significantly different from Groups A and D. Tumor location by hemisphere was the only tumor –related characteristic that was significant between groups, $H(3)=8.5$, $p=.03$, with more right hemispheric tumor locations in Group B.

Table 5.22.

EXIT-25 and ECog Scores: Subject and tumor-related characteristics by group categories (n=40).

	Group A^a (n=12)	Group B^b (n=10)	Group C^c (n=11)	Group D^d (n=7)
Gender (F, %)				
Male	5 (42%)	3 (30%)	6 (55%)	4 (57%)
Female	7 (58%)	7 (70%)	5 (45%)	3 (43%)
Age in years (M, SD)	47.2 (8.0)	43.9 (9.5)	55.5 (9.1)	55.7 (6.8)
Education in years (M, SD)	15.0 (2.2)	15.2 (1.7)	15.3 (1.8)	14.9 (2.0)
Time since diagnosis in months (M, SD)	63.0 (50.9)	125.7 (79.8)	124.5 (96.5)	95.1 (84.1)
Tumor hemisphere (F, %)				
Left	8 (64%)	1 (10%)	7 (64%)	4 (57%)
Right	4 (33%)	9 (90%)	4 (36%)	3 (43%)
Tumor location (F, %)				
Frontal	5 (42%)	6 (60%)	7 (64%)	1 (14%)
Temporal	3 (25%)	1 (10%)	3 (27%)	3 (43%)
Other	4 (33%)	3 (30%)	1 (9%)	3 (43%)
Tumor Grade (F, %)				
Low grade, grade 2	3 (25%)	2 (20%)	1 (9%)	0
Transformed low grade	1 (9%)	2 (20%)	1 (9%)	1 (14%)
High grade, grade 3	4 (33%)	5 (50%)	8 (73%)	2 (29%)
High grade, grade 4	4 (33%)	1 (10%)	1 (9%)	4 (57%)

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

Self-reported symptoms (Table 5.23) were similar to those observed with the CTB Composite and TMT Difference groups. Group A reported less impact of symptoms on their quality of life (FACT-BT), $H(3)= 10.2, p=.02$, and less symptom severity (MDASI-BT), $H(3)= 7.8, p=.05$. Subjects in Group A also reported less impact of cognitive symptoms on their quality of life (FACT-BT cognitive items), $H(3)= 16.0, p=.001$, and less cognitive symptom severity (MDASI-BT), $H(3)= 11.4, p=.01$, while Group D subjects reported the greatest cognitive symptom severity (MDASI-BT). Depressive symptoms (CESD-R) were significantly different, $H(3)= 6.3, p=.09$, with Group A reporting fewer and Group B reporting more depressive symptoms. Group B also reported requiring more physical assistance with activities of daily living (OARS Physical subscale), $H(3)= 7.9, p=.05$.

Table 5.23.

EXIT-25 and ECog Scores: Self-reported symptom assessments by group categories (n=40).

	Group A^a (n=12) <u>M (SD)</u>	Group B^b (n=10) <u>M (SD)</u>	Group C^c (n=11) <u>M (SD)</u>	Group D^d (n=7) <u>M (SD)</u>
FACT-BT				
Total	155.1 (20.9)	127.3 (16.7)	141.0 (22.1)	128.6 (22.9)
Cognitive Items	28.9 (4.8)	18.5 (4.3)	23.3 (6.2)	18.9 (7.1)
MDASI-BT				
Severity	0.6 (0.5)	1.5 (1.3)	1.6 (1.5)	1.6 (0.9)
Interference	0.5 (0.6)	2.4 (2.3)	1.0 (1.1)	1.7 (3.1)
Cognitive Items	0.6 (0.7)	2.0 (2.2)	2.1 (2.4)	3.4 (1.8)
CESD-R	7.0 (6.2)	16.0 (12.1)	8.0 (6.1)	11.9 (4.6)
OARS				
Total	27.7 (0.9)	26.8 (1.9)	27.1 (1.6)	26.4 (1.3)
Physical	14.0 (0.0)	13.6 (0.7)	13.8 (0.6)	14.0 (0.0)
Instrumental	13.7 (0.9)	13.2 (1.3)	13.3 (1.1)	12.4 (1.2)

FACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor; MDASI-BT=MD Anderson Symptom Assessment-Brain Tumor; CESD-R=Center for Epidemiologic Studies Depression Scale-Revised; OARS=Older Americans Resources and Services Activities of Daily Living Scale.

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function; ^cGroup C=poor performance but report normal cognitive function; ^dGroup D=poor performance & report change in cognitive function.

Correlations: ECF performance and self-report.

Performance scores for the CTB composite and self-reported ECog scores were not correlated, $r=.13$, $p=.41$. Performance scores for the TMT Difference z-scores and self-reported ECog scores were not correlated, $r=-.20$, $p=.22$. Performance scores for the EXIT-25 and self-reported ECog total scores were not correlated, $r=.02$, $p=.91$.

The relationship between cognitive performance and self-reported cognitive function was explored by looking at the correlation of specific instruments measuring cognitive performance with self-reported cognitive function. Five significant correlations were found between measurements of ECF performance and self-reported cognitive function (ECog subscales). The HVLT-IR subscale for working memory was associated with the ECog organizing subscale, $r=.32$ ($p<.05$). The HVLT-RDI subscale for memory recognition was associated with the ECog total scale ($r=.31$, $p<.05$), planning subscale ($r=.33$, $p<.05$), organizing subscale ($r=.38$, $p<.05$), and attention subscale ($r=.38$, $p<.05$). These associations reflect subjects' perception of an increased demand on executive control functions for the performance of memory tasks.

Specific Aim 3 summary.

The three cognitive performance composites (CTB Composite, TMT Difference, and EXIT-25) were not significantly associated with self-reported cognitive function (ECog) scores, validating the discrepancy between self-report and actual performance. Examination of the relationship of the three measures of ECF performance (CTB Composite, TMT Difference Composite, and EXIT-25 scores) with self-reported ECF (as measured by the ECog Total score) led to the construction of the 4 subject groups, A through D. The majority of subjects fell into Groups A and B because they had better cognitive performance scores.

Group A included more female subjects between 40 to 60 years of age with college education. They tended to participate in the study 6 years after diagnosis and most had high grade tumors with predominately a left frontal location. This group of subjects tended to report fewer brain tumor-specific and depressive symptoms, less symptom severity, less impact of symptoms on their quality of life, and being able to perform most activities of daily living without needing assistance. This group demonstrates adaptation to their diagnosis with the ability to maintain everyday function.

Group B also had more female subjects with ages between 35 to 55 years of age and some college or technical training. These subjects had a longer time since diagnosis (8 years), and more right frontal, high grade tumors. Although they reported that their brain tumor specific symptoms were not severe, and that they did not need assistance with activities of daily living, they tended to report more depressive symptoms.

Group C contained more men whose ages ranged from 45 to 62 years and who had completed some college or technical training. Their time since diagnosis was longer (M 10 years), and they predominately had left hemisphere, high grade tumors. In addition to denying changes in cognitive function since diagnosis, they also reported few brain tumor specific or depressive symptoms that impacted their quality of life.

Group D subjects were older men (ages 51 to 64 years) who had a college education. Time since diagnosis was generally the longest in this group, averaging 13 years. They reported the most brain tumor specific symptoms, and required assistance with activities of daily living.

While the scores for the CTB Composite and TMT Difference were similar across subjects, there was variability in the distribution self-reported cognitive function scores (ECog) and cognitive performance on the EXIT-25. The EXIT-25 lacks accuracy in determining

presence of cognitive impairment when used with a cutpoint score of 5. In addition, 10% of impaired performances as determined by the CTB Composite were not detected on the EXIT-25. Further exploration of item discrimination for executive control dysfunction and the appropriate cutpoint score for cognitive impairment in this population before the EXIT-25 can be recommended for use as a screen for cognitive function.

Specific Aim 4

To explore whether cognitive reserve or compensatory behaviors explain the congruence or incongruence between cognitive performance scores and subject self-reported change in cognitive function scores. This aim will be addressed by two items:

- a. Cognitive reserve as measured by the Hollingshead Index
- b. Compensatory behaviors as measured by the Florida Cognitive Activities Scale

This specific aim explored whether cognitive reserve (CR) or lack of CR might explain the observed congruence or incongruence between subject self-reported cognitive function and actual performance. Analyses for Specific Aim 4 involved the examining the relationship of: 1) cognitive performance to CR, 2) self-reported change in cognitive function to CR, and 3) congruence-incongruence between performance and self-reported change in cognitive function by CR. Scatterplots, correlations, t-tests, and non-parametric statistics were used to explore differences between congruent scores, (Group A and D), and incongruent scores, Group B and C, (as described in Specific Aim 3) by CR. Changes in cognitive activities since diagnosis that might illustrate compensatory behaviors were derived from structured interviews using the Florida Cognitive Activities Scale in a subset of the sample.

Cognitive reserve is the process of optimizing cognitive performance through recruitment of neural networks to cope with or compensate for the cognitive demands of maintaining function (Stern, 2009). Cognitive reserve has been used to explain variations in cognitive function between individuals with similar neuropathology. Those with higher cognitive reserve have demonstrated greater efficiency and neural flexibility for coping or compensating with the cognitive effects from cancer and its treatment (Ahles et al., 2010). The most commonly used

measures of cognitive reserve include premorbid intelligence, educational achievement, and occupational attainment (Jones, et al., 2011).

Two instruments were used in the present study to examine the CR proxies: the North American Adult Reading Test (NAART); (Blair & Spreen, 1987, 1989) for estimating premorbid intelligence, and the Hollingshead 2-Factor Index of Social Classification (Hollingshead Index) (Hollingshead, 1957) for measuring educational and occupational attainment. Spreen and Strauss (2006) recommend excluding NAART performance scores when they meet 2 criteria in subjects with neuropathology: correct scores ≤ 28 , and correct scores ≥ 15 points below expected age and education normative data. Twenty percent ($n=9$) of this study's sample met these exclusion criteria (Appendix J). Given these limitations, the Hollingshead Index was used as the primary measure for CR. The Hollingshead Index is a measure of socioeconomic status based on educational and occupational attainment. The Hollingshead Index scores ranges from 11 to 77, with higher scores indicating less educational and occupational attainment. This sample had a mean Hollingshead Index of 31.75 (SD 11.6), which served as the cutpoint between high and low CR.

Cognitive performance by high and low CR.

Performance scores for each instrument in the neuropsychological battery and the CTB Composite were assessed by t-test for differences between high and low CR groups (Table 5.24). Those with high CR had better performance scores across all seven instruments for memory, attention, verbal fluency, and CTB Composite scores. The COWA performance scores were significantly higher in those with high CR, $t(38)=-2.01$, $p=.05$. No other significant differences were observed between high and low CR groups.

Table 5.24.

Cognitive performance scores by cognitive reserve group (n=40).

<u>Instrument</u>	Potential	<u>Low CR</u>			<u>High CR</u>		
	<u>Range</u>	<u>Min-Max</u>	<u>Mean</u>	<u>SD</u>	<u>Min-Max</u>	<u>Mean</u>	<u>SD</u>
CTB Comp	Unlimited	-8.10-0.40	-1.56	2.09	-3.0-0.80	-0.82	0.97
HVLT-IR	0-36	6-34	22.89	7.79	14-33	24.57	4.69
HVLT-DR	0-12	0-12	7.11	3.53	2-12	8.29	2.72
HVLT-RDI	0-12	4-12	9.37	2.36	4-10	9.76	2.30
Trails A	0-300	20-185	44.21	36.36	20-80	38.24	14.46
Trails B	0-300	35-300	112.63	73.18	40-180	85.05	35.46
SDMT	0-110	12-65	41.16	14.59	11-73	44.95	14.30
COWA*	Unlimited	9-55	33.68	12.83	22-72	42.05	13.43

* $p < .05$.

CR=Cognitive Reserve; CTB Comp=Clinical Trials Battery Composite; HVLT-IR=Hopkins Verbal Learning Test-Immediate Recall; HVLT-DR=Hopkins Verbal Learning Test-Delayed Recall; HVLT-RDI=Hopkins Verbal Learning Test-Recognition Discrimination Index; Trails A=Trails Making Test Part A; Trails B=Trails Making Test Part B; SDMT=Symbol Digit Modalities Test; COWA=Controlled Oral Word Association test.

Table 5.25 displays the number of subjects with impaired cognitive performance scores on the CTB Composite and each instrument according to low or high CR. The number of subjects with performance z-scores of 1.3 or more below normative comparison scores was similar in both CR groups. Three subjects with high CR and 3 subjects with low CR had no observed impairment on any of the cognitive tests. The smallest number of subjects with impairment was noted for verbal fluency test (COWA scores) in both high and low CR groups. Compared to those with high CR, subjects with low CR had more severe impairment (scores 3 SD or more below normed comparison groups).

Table 5.25.

Number of subjects with mild to severe cognitive impairment by instrument for high and low cognitive reserve groups (n=40).

Instrument	Low CR (n=19)			Frequency (%)		
	High CR (n=21)		Total	Below -1.3		Total
	Below -1.3	Below -3		Below -1.3	Below -3 SD	
	SD	SD		SD		
CTB Comp	3 (16)	3 (16)	6 (32)	3 (14)	1 (5)	4 (19)
HVLT-IR	2 (11)	5 (26)	7 (37)	7 (34)	1 (5)	8 (39)
HVLT-DR	6 (32)	3 (16)	9 (48)	6 (29)	2 (10)	8 (39)
HVLT-RDI	5 (26)	1 (5)	6 (32)	4 (19)	2 (10)	6 (29)
Trails A	3 (16)	2 (11)	5 (26)	5 (24)	2 (10)	7 (34)
Trails B	3 (16)	8 (42)	11 (58)	4 (19)	4 (20)	8 (39)
SDMT	2 (11)	4 (22)	6 (33)	4 (19)	1 (5)	5 (24)
COWA	4 (21)	1 (5)	5 (26)	4 (19)	0	4 (19)

CR=Cognitive Reserve; CTB Comp=Clinical Trials Battery Composite; HVLT-IR=Hopkins Verbal Learning Test-Immediate Recall; HVLT-DR=Hopkins Verbal Learning Test-Delayed Recall; HVLT-RDI=Hopkins Verbal Learning Test-Recognition Discrimination Index; Trails A=Trails Making Test Part A; Trails B=Trails Making Test Part B; SDMT=Symbol Digit Modalities Test; COWA=Controlled Oral Word Association test

Self-reported cognitive function (ECog) by high and low CR.

Table 5.26 displays subject self-reported change in cognitive function since diagnosis (ECog), classified by high or low CR. Differences in performance were assessed by t-tests. Subjects with high CR reported less change in everyday function since diagnosis compared to those with low CR. Subjects reported more change since diagnosis (higher scores) in memory and attention than in other subscales of the ECog. Mean scores for attention, $t(38)=2.46, p=.02$, memory, $t(38)=1.32, p=.008$, and total score, $t(38)=1.99, p=.05$, were significantly lower for those with high CR, indicating they perceived less change in function since diagnosis.

Table 5.26.

Self-reported cognitive function on the ECog by high and low CR (n=40).

Domain	Low CR			High CR		
	Min-Max^a	Mean	SD	Min-Max^a	Mean	SD
Total*	1.08-3.37	2.08	.72	1.00-2.63	1.69	.52
Memory*	1.13-4.00	2.65	.87	1.00-2.63	1.95	.70
Language	1.00-3.50	2.09	.82	1.00-3.13	1.79	.58
Visuo-spatial	1.00-3.20	1.53	.69	1.00-2.43	1.35	.47
Planning	1.00-3.29	1.64	.77	1.00-2.00	1.34	.39
Organizing	1.00-3.40	1.83	.91	1.00-4.00	1.67	.84
Attention*	1.00-4.00	2.72	1.14	1.00-3.75	1.92	.84

* $p < .05$ ^aPotential range of scores is 1- 4.

CR=cognitive reserve; ECog=Everyday Cognition Scale.

Table 5.27 shows the number (frequency) of subjects reporting changes in cognitive function, ECog score ≥ 2 by high and low CR. Memory, attention, language, and global cognitive functions were changed since diagnosis for more subjects with low CR as compared to those with high CR.

Table 5.27.

Number of subjects reporting perceived change in function since diagnosis^a on the ECog by high and low CR (n=40).

Domain	Low CR (N=19)		High CR (N=21)	
	Freq	%	Freq	%
Total	10	53	7	33
Memory	14	74	9	43
Language	10	53	8	38
Visuo-Perceptual	3	16	3	14
Planning	4	21	3	14
Organizing	7	37	5	24
Attention	13	68	12	57

^aScale mean score of 2 or greater to indicate impairment.

ECog=Everyday Cognition Scale; CR=cognitive reserve.

High and Low CR summary.

In summary, the Hollingshead Index was used to categorize subjects into high and low cognitive reserve groups. Across all subjects, cognitive performance scores and reported change in cognitive function predominantly affected the domains of memory and attention. While an equal number of subjects with high and low CR had impaired performance scores, more of those with low CR had severe cognitive impairment (-3 SD or more). Subjects with low CR also reported experiencing more change in cognitive function since diagnosis as compared to those with high CR.

Congruence between cognitive performance and self-reported cognitive function by high and low CR.

These analyses used CTB Composite scores for cognitive performance and ECog total scale scores for self-reported cognitive function to categorize congruence or incongruence in those with high or low CR. Similar to the analyses in Specific Aim 3, scatterplots of subject scores were used to examine the relationship of cognitive performance (x-axis) and self-reported cognitive function (y-axis). The cutpoint for CTB Composite scores was set at -1.3 and for ECog scores, at 2.0 . This created four quadrants, labeled as Groups A through D, to establish congruence or lack of congruence.

Figure 5.12 displays the scores of high CR subjects by cognitive performance and self-reported change in cognitive function. Group A ($n=12$, 57%) shows the congruence and Group B ($n=5$), the incongruence of subjects with high cognitive performance ($n=17$, 81%). Only 4 subjects with high CR were found in Groups C and D (low cognitive performance).

Figure 5.13 plots the scores of subjects with low CR by cognitive performance and self-reported change in cognitive function. Subject scores are spread out more evenly across the

scatterplot; Groups A and B show the congruence and incongruence of low CR subjects with high cognitive performance (n=13; 68%). The majority of subjects with low CR were in Group B (n=8, 42%) with incongruent scores. There were only 6 subjects with low CR in Groups C and D.

Figure 5.12.

Self-reported cognitive function and performance by subjects with high CR (n=21).

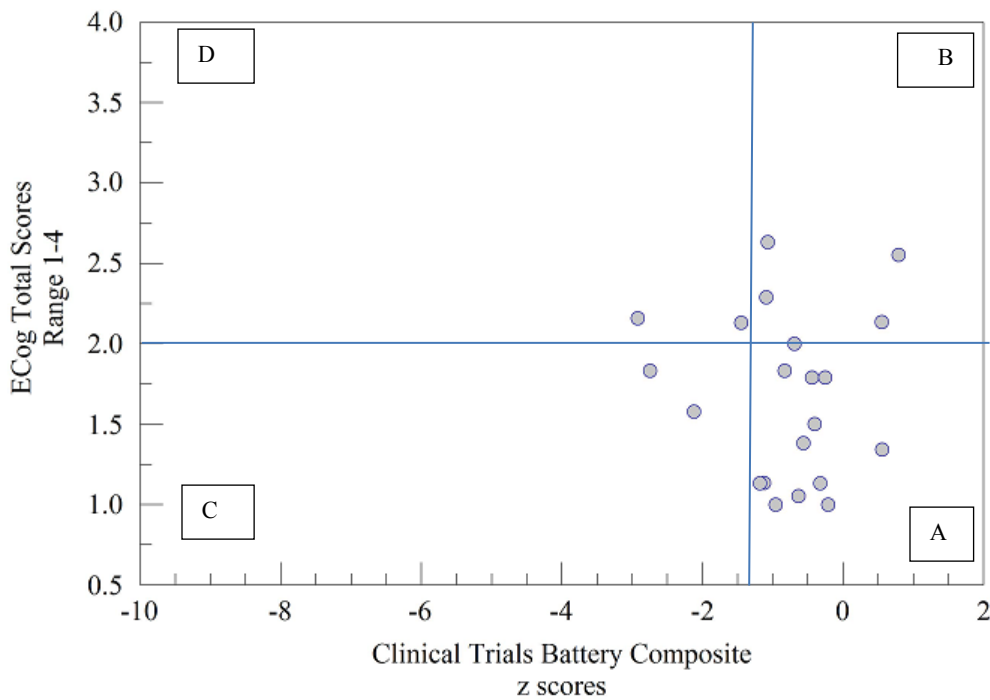
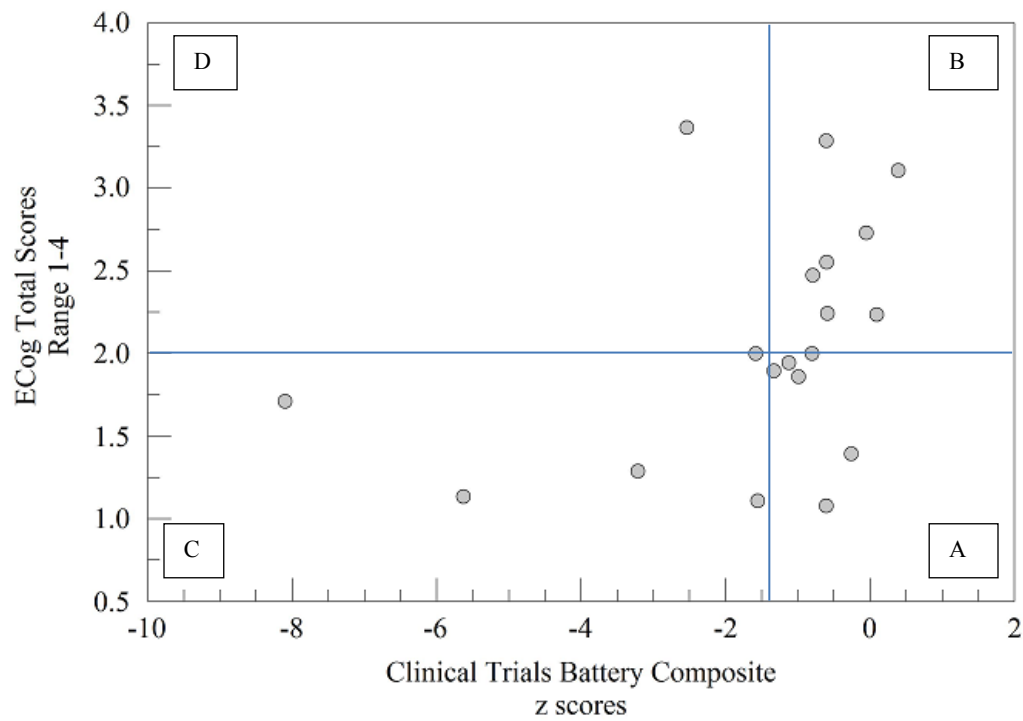


Figure 5.13.

Self-reported cognitive function and performance by subjects with low CR (n=19).



High Cognitive Reserve.

Table 5.28 lists subject and tumor characteristics of subjects with high CR for Groups A through D. The t-test and Chi-square analyses found no significant differences between groups for subject or tumor-related characteristics. Group A (congruent) tended to have recorded the shortest time since diagnosis. Subjects in Groups C and D, with poor cognitive performance, were men and had longer times since diagnosis. Those in Group B (incongruent scores) tended to be younger and reported more brain tumor specific symptoms, including depressive symptoms.

Table 5.28.

High Cognitive Reserve: Subject and tumor-related characteristics by group categories (n=21).

	Group A^a (n=12) <u>F</u>	Group B^b (n=5) <u>F</u>	Group C^c (n=2) <u>F</u>	Group D^d (n=2) <u>F</u>
Gender				
Male	6	2	2	2
Female	6	3	0	0
Age, in years (M, SD)	51.6 (9.2)	46.0 (11.8)	59.5 (0.7)	60.5 (2.1)
Education, in years (M, SD)	16.2 (1.6)	16.4 (0.9)	17.0 (1.4)	17.0 (1.4)
Time since diagnosis, in months (M, SD)	70.0 (79.3)	89.8 (74.8)	138.0 (164.1)	187.0 (77.8)
Tumor hemisphere				
Left	7	1	2	1
Right	5	4	0	1
Tumor location				
Frontal	8	3	1	0
Temporal	1	2	0	0
Other	3	0	1	2
Tumor Grade				
Low grade, grade 2	3	0	0	1
Transformed low grade	0	1	1	0
High grade, grade 3	6	2	0	1
High grade, grade 4	3	2	1	0

^aGroup A=normal performance & self-report; ^bGroup B=normal performance & reported change in function;

^cGroup C=poor performance but reported normal function; ^dGroup D=poor performance & reported change in function.

Low Cognitive Reserve.

Table 5.29 lists subject and tumor characteristics of subjects with low CR for Groups A through D. There were no significant differences in subject or tumor-related characteristics between groups by t-test or Chi-square analyses. Group B tended to have recorded the least time since diagnosis, while Group D had the longest time since diagnosis. Subjects in Groups C and D, with poor cognitive performance, were men; subjects in Groups A and B were primarily women. Subjects in Group B (incongruent) tended to be younger and reported more depressive symptoms than the other groups. However, Group D reported the greatest impact of symptoms on their quality of life (FACT-BT), severity and interference with daily lives (MDASI-BT).

Table 5.29.

Low Cognitive Reserve: Subject and tumor-related characteristics by group categories (n=19).

	Group A^a (n=5) <u>F</u>	Group B^b (n=8) <u>F</u>	Group C^c (n=4) <u>F</u>	Group D^d (n=2) <u>F</u>
Gender				
Male	1	1	4	2
Female	4	7	0	0
Age, in years (M, SD)	47.2 (11.2)	46.1 (9.1)	50.5 (9.5)	54.5 (9.2)
Education, in years (M, SD)	13.2 (1.1)	13.5 (0.9)	13.5 (0.9)	16.0
Time since diagnosis, in months (M, SD)	113.2 (61.1)	104.1 (72.3)	110.8 (78.6)	133.5 (153.4)
Tumor hemisphere				
Left	3	2	3	1
Right	2	6	1	1
Tumor location				
Frontal	1	4	2	0
Temporal	4	2	1	0
Other	0	2	1	2
Tumor Grade				
Low grade, grade 2	1	1	0	0
Transformed low grade	1	1	0	1
High grade, grade 3	2	4	4	0
High grade, grade 4	1	2	0	1

^aGroup A=normal performance & self-report; ^bGroup B=normal performance & reported change in function;

^cGroup C=poor performance but reported normal function; ^dGroup D=poor performance & reported change in function.

Congruence/Incongruence: Groups A and B.

These analyses focus on Groups A (congruence) and B (incongruence) since these two groups contained a majority of subjects (n=30, 75%). Table 5.30 shows subject characteristics by high and low CR for Groups A and B.

Table 5.30.

Subject and tumor-related characteristics by high and low CR (n=30).

	Congruent Scores		Incongruent Scores	
	Group A^a		Group B^b	
	High CR	Low CR	High CR	Low CR
	(n=12)	(n=5)	(n=5)	(n=8)
	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>
Gender, Frequency				
Male	6	1	2	1
Female	6	4	3	7
Age in years	51.6 (9.2)	47.2 (11.2)	46.0 (11.8)	46.1 (9.1)
Employed, Frequency	6	2	1	1
Time since diagnosis in months	70.0 (79.3)	113.2 (61.1)	89.8 (74.8)	104.1 (72.3)
CTB Composite	-0.5 (0.5)	-0.8 (0.4)	-0.3 (0.9)	-0.4 (0.5)
ECog Total	1.3 (0.3)	1.6 (0.4)	2.3 (0.3)	2.6 (0.5)
NAART	116.7 (6.8)	105.3 (8.8)	114.4 (7.2)	109.4 (8.4)
FACT-BT				
Total	156.5 (16.1)	142.5 (22.2)	141.6 (19.9)	119.8 (16.8)
Cognitive Items	28.5 (5.1)	25.4 (5.0)	21.4 (4.0)	18.0 (6.5)
MDASI-BT				
Severity	0.6 (0.5)	1.1 (0.9)	0.7 (0.5)	2.0 (0.9)
Interference	0.5 (0.5)	0.7 (0.9)	1.0 (1.4)	1.9 (1.6)
Cognitive Items	0.8 (0.7)	1.2 (1.0)	0.9 (0.9)	3.2 (1.7)
CESD-R	5.9 (4.4)	7.6 (8.7)	9.8 (9.5)	19.1 (10.3)
OARS				
Total	27.5 (1.5)	27.2 (1.3)	26.6 (2.0)	27.0 (1.2)
Physical	13.8 (0.6)	14.0	13.8 (0.5)	14.0
Instrumental	13.7 (0.9)	13.2 (1.3)	12.8 (1.6)	13.0 (1.2)

^aGroup A=normal performance & self-report; ^bGroup B=normal performance but report change in cognitive function. CR=Cognitive reserve; FACT-BT=Functional Assessment of Cancer Therapy-Brain Tumor; MDASI-BT=MD Anderson Symptom Assessment-Brain Tumor; CESD-R=Center for Epidemiologic Studies Depression Scale-Revised; OARS=Older Americans Resources and Services Activities of Daily Living Scale.

Subjects in Group A (congruent) tended to be women. Subjects in Group A reported fewer symptoms and less impact on their quality of life (FACT-BT, MDASI-BT interference, CESD-R scores) than subjects in Group B (Table 5.29). Group A subjects with high CR were more likely to have higher premorbid intelligence, to be employed at time of study participation, and to report fewer symptoms than those with low CR.

Subjects in Group B (incongruent) tended to be women. Low CR subjects in Group B had longer time since diagnosis and reported greater symptom impact on quality of life, symptom severity, and symptom interference (FACT-BT, MDASI-BT, CESD-R scores) compared to those with high CR.

Using Kruskal-Wallis tests to compare mean differences in symptoms between subjects within groups, it was determined that subjects with low CR in Group B tended to report greater symptom severity, $H(1)=4.82, p=.03$, cognitive symptom severity, $H(1)=5.88, p=.02$, and impact on their quality of life, $H(1)=3.62, p=.06$, as compared to those with high CR in Group B. There were no significant differences in subject or tumor characteristics for Group A between high and low CR.

Summary on congruence and cognitive reserve in Groups A and B.

Cognitive reserve was used to categorize assess cognitive performance and self-reported change in cognitive function. Thirty subjects (75%) were classified into Groups A (n=17) and B (n=13). The majority of subjects in Group A had high CR (n=12, 71%). Those with high CR in Group A reported the fewer symptoms and less symptom severity.

The majority (n=8, 62%) of subjects in Group B had low CR. Subjects who reported a perceived change in cognitive function tended to report greater symptom severity, greater impact on quality of life, and more depressive symptoms, particularly those with low CR. Thus, CR

may help moderate the cognitive effects of cancer and cancer treatment as observed in Groups A and B.

Exemplars.

Observations considered for further exploration by a researcher are referred to as exemplars. Four exemplars, 2 from Group A and 2 from Group B, were used to explore compensatory behaviors used to maintain cognitive function. The exemplars were a subset of 7 subjects (from the total sample of 40) who agreed to participate in structured interviews to explore their perception in changes in behavior since diagnosis and to identify their use of compensatory strategies to maintain everyday function. Using a list of 25 items on the Florida Cognitive Activities Scale, the subjects were asked to reflect on their everyday cognitive activities and preferences; to note whether a change had occurred, why the change might have occurred, what the nature of the change was, and whether the change was voluntary or forced due to limitations. It was expected that these questions would engage the subject in discussing the strategies employed to perform activities, the degree to which the strategies worked, and any changes in strategy they may have used over time.

Group A (congruence.

High Cognitive Reserve.

A 51 year old woman with high CR in Group A reported very few changes in activities since her diagnosis 7.5 years earlier. She stated that most of her activities were unchanged, “just less often” and she now allows more time for “get things done.” She leaves memos around the house to keep her organized and writes all appointments down on her calendar. She continues to play several musical instruments in a group, at church, and at home. During her performance on

the cognitive test battery, she used the following techniques: she asked to have instructions repeated a couple of times, she counted numbers out loud, and closed her eyes “to memorize the words.” She reported difficulty with her memory and difficulty participating in conversations, and less change in her ability to maintain attention or concentration.

Low Cognitive Reserve.

A 64 year old woman with low CR in Group A was a 12 year survivor. She reported 3 activities that she had changed since diagnosis: she did less sewing because she found it difficult to figure out where the pieces should go, less dancing, and less shopping because she required more rest on her days off. She continued to work because her employer had adjusted her work duties after a seizure that led to her initial diagnosis (none subsequently). She writes everything down in a composition notebook, from work activities to phone conversations and appointments. She integrates the notebook with her calendar or “it won’t get done.” She says she uses “tricks to remember things,” including remembering people or events by telling stories to make things “personal,” writes parking space numbers on the parking ticket to prevent getting lost, and hooks her keys to her purse to prevent losing them. During study participation, she read questionnaire items and the Symbol Digit Modalities Test numbers out loud. She looked around the room to get ideas for words to say on the Controlled Oral Word Association test.

Group B (incongruence).

High Cognitive Reserve.

A 62 year old man is an 11 year survivor with high CR in Group B. He reported that he had made changes in 6 activities, including reading, playing games and doing puzzles, social engagements, doing all the financial records, and making home repairs. He had recently retired and moved with his wife to live near his children so they may help provide support in his care.

He felt that he was less attentive at work, that his concentration was lagging, and that it was “getting too hard to think and took too long.” He was frustrated by his slow processing speed, which impacted his ability to make decisions and follow conversations. These changes in his cognitive functioning led to his decision to retire and change his living situations because he was “withdrawing from the usual social activities” and was frustrated with his inability to follow along in conversations. He and his wife organized the furniture and kitchen in their new home to resemble as closely as possible their previous home so he could remember where to find items. He found that using memos or lists helped him improve memory, organization (prioritization), and attention. He said that playing new games with his grandchildren helped his memory and communication skills, and that a new interest in photography was keeping him active. He used a paper on top of paper questionnaires to keep himself on the correct reading line, which he also does when he reads technical journals. He also repeated instructions and spoke out loud each next step for the Trails Making tests and the Symbol Digit Modalities Test.

Low Cognitive Reserve.

This exemplar is a 47 year old, 12 year survivor with low CR in Group B. She reported changes in 18 activities that ranged from playing games or doing puzzles to reading, social engagements, and trying new activities. There were 7 activities that she engaged in more often since her diagnosis (puzzles, crafts, walking), while the other 11 she participated in less often (going to social activities, driving to unfamiliar places, reading, and gardening). Her changes occurred due to a variety of reasons: she found it “hard to concentrate” while reading or following conversations in a room full of people; she felt “overwhelmed” when driving on highways to new locations, even with GPS; being in big stores; loud noises and conversations “get on my nerves.” She realized that she increased activities that have led to more social

isolation, such as gardening, doing puzzles, and calling her friends because she could “control the timing and ability to handle” the activity. During her performance on the cognitive test battery, she used the following techniques: she asked to have instructions repeated for several tests, she repeated words or instructions back to the examiner, she called out loud the next step in the test to keep on task, she used fingers to count numbers or words, and she closed her eyes “to concentrate.” At the end of the interview, she reflected that she “protects herself” to keep from getting too frustrated or overwhelmed and tells herself that she is “still doing well overall.”

Exemplars summary.

These 4 subjects used some of the same techniques for their everyday cognitive function and performance as they did on the cognitive battery. All four subjects had similar CTB Composite scores, ranging from -1.1 to -0.6. However, the subject with low CR in Group B reported more cognitive difficulties and more changes in her activities since diagnosis. These preliminary observations of changes in cognitive activities and incorporation of compensatory strategies to maintain function warrant further exploration. These individuals describe behaviors that were successfully implemented and those that were abandoned; it is hoped that such exemplars may help direct future study.

CHAPTER 6: DISCUSSION

This chapter first discusses objective cognitive performance, subjective (self-reported) change in cognitive function, and the discrepancy between objective and subjective findings in adult survivors of PBT. Thereafter, the discussion focuses on whether cognitive reserve and compensatory strategies may explain some of the discrepancy between objective and subjective findings in survivors of PBT. Finally, the chapter looks at limitations of the study and implications for future research.

Objective Cognitive Performance

Most (77.5%) of the subjects in this study did not have cognitive impairment based on the Clinical Trials Battery Composite score. Only 9 of 40 subjects were scored as impaired, a lower prevalence than that reported in the literature (>50%) for similar PBT survivors (Johnson et al., 2012; Zuchella et al., 2013). This discrepancy most likely reflects differences in time since diagnosis, tumor grade, tumor location, treatment type, and treatment duration, although variability in cognitive impairment may be due to differences in types of neuropsychological tests used to determine cognitive performance, the cutpoint z-score or sample median-split score used to define impairment (Caine, Mehta, Laack, & Gondi, 2012; Jones et al., 2011; Mandelblatt et al., 2013).

Subjects in this study had more domain-specific impairment for memory (32.5%) than attention (27.5%). While memory was more commonly impaired than attention in this sample,

impairment was more severe in the domain of attention. These domain-specific impairments of attention and memory resemble those previously reported in survivors of PBT (Johnson et al., 2012; Zucchella et al., 2013). Because the domains of attention and memory are essential components of the Executive Control Function, a decline in one or both domains before an observable decline in ECF performance may help identify those at risk for eventual decline (Wefel, Witgert, & Meyers, 2008).

No subject-, tumor-, or treatment-related factors were associated with cognitive impairment in this sample. In contrast, subject and cancer-related characteristics have been associated with cognitive impairment in other studies of survivors (Hodgson et al., 2013; Lindner, Phillips, McCabe, Mayes, Wearden, et al., 2014). Isolated studies have found that older age (Johnson et al., 2012), longer time since diagnosis (Correa, 2008; Klein et al., 2002; Moretti et al., 2004; Scheibel, Meyers, & Levin, 1996), frontal tumor location (Satoer et al., 2012), left hemispheric tumor location (Hahn et al., 2009; Zucchella et al., 2013), high-grade PBT (Johnson et al., 2012), or PBT-specific treatment (Moretti et al., 2004; Zucchella et al., 2013) are associated with impaired cognitive function in PBT survivors. Many of these studies are done soon after treatment cessation, which may increase the association of those factors with cognitive impairment. However, the purpose of the present study was to describe cognitive impairment at least one year after completion of treatment, so subjects were further removed from treatment effects and may have had more time to recoup cognitive function or learn compensatory ways to maintain function.

Self-Reported Cognitive Function

In contrast to objective neuropsychological testing, more than half of our subjects reported changes in performance of everyday activities requiring attention and memory. In addition, subjects who reported greater change in cognitive function since diagnosis tended to report greater cognitive symptom severity and interference (MDASI-BT), and impact on their quality of life (FACT-BT).

In support of the findings in the current study, Armstrong and colleagues (2006) had 201 subjects report on 4 cognitive symptoms (remembering, understanding, speaking, thinking) while validating the MDASI-BT. Symptom severity for the cognitive function items ranged from 0 to 8, similar to the findings from the current study, and less than 10% of the sample reported the severe cognitive dysfunction.

Cognitive symptoms are distressing. Changes in thinking, memory, multi-tasking, planning, slower processing, and attention impact the everyday lives of long-term PBT survivors (Godbout et al., 2005). Fox and colleagues (2007) describe how a symptom cluster involving cognitive impairment, depression, fatigue, sleep disturbances, and pain impairs the functional status (Karnofsky Performance Status) of long-term PBT survivors.

Given the above reports, most survivors of PBT report changes in cognitive function. Cognitive symptoms may vary in severity and impact on their quality of life, but it may be that these symptoms are precursors of a decline in objective cognitive performance (Ganz et al., 2013) or that they reflect an aspect of cognitive function (or construct) that is not measured by objective cognitive performance tests in present use (Caine et al., 2012).

Self-reported associated depressive symptoms.

Subjects in the present study who reported greater symptom severity (MDASI-BT severity subscale) and/or greater impact of symptoms on quality of life (FACT-BT) also tended to report more depressive symptoms (CESD-R). Twenty-two percent of our sample reported the presence of depressive symptoms although none of the subjects carried a diagnosis of depression. Nevertheless, depressive symptoms have been associated with shorter survival times (Litofsky et al., 2003), greater cognitive impairment (Cook et al., 2013; Fuller et al., 2007), and functional decline (Tomey et al., 2010; Millán-Calenti et al., 2011). Fuller and colleagues (2007) observed that patients with PBT had more ECF impairment than did patients with other cancers, and they were more likely to have depressive symptoms. The prevalence of depression is less than 25% in newly diagnosed survivors of PBT (Litofsky et al., 2003), but the presence of depressive symptoms is not unusual through the illness trajectory of PBT survivors. Albeit the prevalence is low and somewhat expected, our results exemplify the need to perform depression screening with cognitive function studies.

Discrepancy between Objective Cognitive Performance and Self-Reported Cognitive Function

This study was able to identify a discrepancy between objective cognitive performance and self-reported cognitive function. Dividing a scatterplot of objective and subjective cognitive function scores into quadrants provided the opportunity to describe four subject groupings. Because the majority of subjects (75%) were contained within two of these four groups that had normal cognitive performance scores, detailed analyses focused on those two groups – one with congruent scores and one with incongruent scores.

Seventeen subjects (42.5% of the total) had congruent scores (normal cognitive performance and no change in self-reported cognitive function since diagnosis). This group was predominately female, aged between 40 to 60 years old, and well educated, with the majority completing college. They had been diagnosed approximately 6 years earlier had predominately left frontal, high-grade tumors. These subjects tended to report fewer brain-tumor-specific and depressive symptoms, less symptom severity, less impact of symptoms on their quality of life, and were able to perform most activities of daily living without assistance.

There were 13 subjects (32.5% of the total) in the incongruent group (normal cognitive performance but self-reported a change in cognitive function); this group also had more female subjects, slightly younger (between 35 to 55 years of age), but fairly well educated, with some college or technical training. These subjects had been diagnosed approximately 8 years earlier and had predominately right frontal, high-grade tumors. Although they reported that their brain-tumor-specific symptoms were not severe, and that they did not need assistance with activities of daily living, they tended to report more depressive symptoms.

There are several similarities between these two groups: subjects had normal cognitive performance, were mostly female, middle-aged, well educated, and 6-8 years displaced from diagnosis of a high-grade, frontal tumor. The major distinctions were that subjects with incongruent cognitive function scores were aware of or sensitive to changes in cognitive function that had occurred since diagnosis, and that they reported more depressive symptoms.

The discrepancy between objective and subjective measures of cognitive impairment may be related to instrumentation issues: use of varying cutpoints, different definitions of impairment, lack of a comprehensive measure, instrument construct, and instrument sensitivity and specificity (Gondi et al., 2013; Hurria, Somio, & Ahles, 2007; Hutchinson et al., 2012). Therefore, some of

the cognitive symptoms that subjects report may be too subtle to detect on objective cognitive performance tests that are presently available; objective tests may underestimate the impact of mild cognitive impairments on everyday function, or subject reporting of cognitive symptoms may precede objective cognitive decline or impairment (Ganz et al., 2013; Meyers, 2013). While all of these issues may have some influence on the observed discrepancy, there have been suggestions that a subject's ability to cope or adapt (a product of their lifetime of experiences, or cognitive reserve) may influence their everyday cognitive function (Wilson, Barnes, & Bennett, 2003).

Cognitive Reserve and the Discrepancy between Subjective and Objective Cognitive Impairment

Cognitive impairment has been reported to compromise one's ability to cope with the impact of illness (Higgins et al., 2012; Lovely et al., 2013; Paulson, Bowen, & Lichtenberg, 2014). The theory of cognitive reserve (CR) posits that those with higher CR are better prepared to cope with or compensate for illness by adapting their environment or invoking compensatory strategies (Suchy, Kraybill, & Franchow, 2011).

In the present study, the majority of subjects with high cognitive reserve had congruent subjective and objective cognitive function scores. Thus, they had good cognitive performance and self-reported fewer changes in cognitive function since diagnosis. These subjects also reported fewer symptoms and less symptom severity. In contrast, the majority of subjects with low CR tended to have incongruent cognitive function measures. That is, they had good cognitive performance but reported a change in cognitive function since diagnosis. These subjects also tended to report more symptom severity, greater impact on quality of life, and the

presence of depressive symptoms. Tumor-specific factors, time since diagnosis, subject age, and treatment-related factors were not associated with these reported discrepancies.

The exploration of CR is still relatively new, so only a few studies have explored the effect of CR on cognitive performance and self-reported function or well-being. Ownsworth and colleagues (2013) observed that PBT survivors with higher CR reported less depression (Depression Anxiety Stress Scale), better emotional well-being (FACT-BT emotional subscale), and had fewer cognitive complaints while maintaining good cognitive function. Thus, these survivors have congruent objective and subjective cognitive function like the subjects in the current study. The congruence of self-report with objective performance may indicate that these subjects have indeed maintained function without the use of compensatory strategies or that their use of such strategies is subtle.

To demonstrate the effects of CR during task performance, Steffener and colleagues (2011) used the functional MRI scanner to look at neural reserve and neural compensation in young and older healthy subjects. Compared to those with low CR, older adults with high CR utilized neural networks with greater efficiency for task performance. High and low CR was dichotomized by a composite of premorbid IQ and education. Their high and low CR subjects had premorbid IQ and educational attainment similar to the high and low CR subjects in the current study. The report by Steffener and colleagues implies that those with congruent good cognitive function may maintain their performance by efficient utilization of neural and cognitive compensation.

Ahles et al. (2010) studied a group of younger breast cancer survivors with high CR who reported experiencing changes in cognitive function (Multiple Ability Self-Report Questionnaire) despite objectively good cognitive performances. Incongruent cognitive function

scores were observed in a smaller number of high CR subjects in the current study. The self-report from this group could reflect a change in their cognitive awareness, an increase in effort to maintain cognitive function, or movement within their illness trajectory.

As the theory of CR suggests, those with high CR are better prepared to compensate to maintain function when the need arises, and have an awareness of what they need to do to prevent functional decline (Stern, 2002). Until cognitive demand is great, compensatory strategies can be used subconsciously to maintain function (Hampstead, Gillis, & Stringer, 2014; Weiss, Hoenig, & Fried, 2007). When cognitive function is maintained, even with use of compensatory strategies, subjects are more likely to have congruent objective and subjective cognitive function measures (Sumowski, Wylie, DeLuca, & Chiaravalloti, 2009). Once cognitive demand increases, subjects employ adaptive strategies to maintain function or they will have functional decline. Those with high CR may be unaware of changes in their function for a longer period of time because they adapt using their accumulation of lifetime experiences (Foubert-Samier et al., 2012). Because of their lifetime experiences, they tend to choose compensatory strategies that require the least amount of effort or change (Barulli et al., 2013). However, those with low CR may more readily recognize their need to compensate with external aids or environmental changes, and will tend to report greater severity in the changes that they experience. Barulli and colleagues (2013) suggest that awareness of the compensations used to maintain cognitive function underlies the discrepancy between subjective, self-reported change in cognitive function and objective cognitive performance.

Compensatory Strategies

Strategies used to compensate for cognitive dysfunction include changes in the physical or social environment, the use of memory or cognitive devices (external aids), or internal mnemonics (Hampstead, Gillis, & Stringer, 2014; Huckans et al., 2013; Tomey & Sowers, 2009; Wilson, 2000). Hampstead et al. (2014) suggest that compensation may occur through several methods: rehearsal based approaches (cognitive retraining through repetition), compensatory approaches using external aids (calendars, notes, social and physical environment changes), or internal aids (mnemonic strategies). Curtailing social or leisure activities and social isolation are also examples of compensatory strategies individuals use to cope or adapt with cognitive decline (Fried et al., 1996; Schinka et al., 2005; Weiss et al., 2007; Wilson, 2000).

The exemplars presented in this study illustrate some of the compensatory strategies they used since their diagnosis. The low CR subjects tended to report a decreased frequency of activities, those with high CR continued to be cognitively engaged with some of the same activities they had been doing prior to diagnosis. Those with low CR stopped more activities since diagnosis, and were more socially isolated, than those with high CR. Regardless of CR, subjects used similar compensatory behaviors during study participation, and described incorporation of similar compensatory strategies to maintain cognitive function. Despite CR, those with congruence between performance and self-report tended to be less aware of their compensatory strategies than those with incongruence.

The strategies noted by the exemplars in the current study are similar to those described by other cancer survivors (Lovely et al., 2013; Myers, 2013; Von Ah, Habermann, Carpenter, & Schneider, 2013). Dyads of long-term PBT survivors and their caregivers describe the impact of cognitive changes in terms of loss of employment, friends and social activities, and diminution of

self-worth. Von Ah and colleagues (2013) reported similar perceptions of cognitive loss, but they also noted that breast cancer survivors who were employed reported that they had to work harder and use compensatory strategies to maintain their work performance. Myers (2013) summarized 17 qualitative studies that reported survivor use of strategies to compensate for cognitive dysfunction that included consistency in performance to prevent cognitive failures (memo writing, doing things the same way, putting the keys in the same place), mitigating cognitive failures by changing the task (reading simpler books, doing more puzzles, getting enough rest, socializing when they felt best or not fatigued), avoidance of cognitive activities that created more demands than they could give, and self-permission to make mistakes or take more time.

In the present study, these compensatory strategies were used by subjects with both high and low CR, but others have found that those with high CR use a better strategy selection than those with low CR (Barulli et al., 2013). Simply, those with high CR may use inherent strategies, earlier in their illness trajectory, to reduce effort required by cognitively demanding situations, and tend to choose the best strategies requiring the least effort. Thus, those with low CR may need direction as to which strategies to use or which require the least effort. Therefore, observing the compensatory strategies or behaviors used by PBT survivors may help identify which strategies are useful and which require too much effort; such observations can guide the design of future research into cognitive interventions.

Study Strengths and Limitations

A cross-sectional design was chosen for this study because the specific aims were descriptive and exploratory for directing future research. All of the data were collected at time

of study participation, thus facilitating data completion and reducing missing data points. All of the subjects participated at the time of their choosing when they came for an oncology clinic visit, thus reducing subject expense for travel and caregiver burden for time away from work or other obligations. A solitary time point for study participation facilitated subject enrollment and subject burden.

However, a cross-sectional design measuring cognitive performance and self-reported function limits the interpretation because there is no information about the subjects' cognitive trajectory: what was their premorbid cognitive functioning, how has that changed over time, how will it continue to change over time? This is particularly limiting regarding how those with high and low CR are affected over time. The theory of CR postulates that those with high CR maintain function longer in the presence of neuropathology than those with low CR, so knowing where these survivors are in their cognitive trajectory would help identify when intervention would be useful. In future research, a longitudinal design would permit tracking a subject's change in cognitive function over time, thereby identifying those at risk of cognitive decline, and when to implement cognitive interventions (Shadish, Cook, & Campbell, 2002).

Instrumentation.

This study explored the use of several instruments that have not been previously studied in survivors of PBT: the EXIT-25 as a measure of cognitive function, specifically executive control function; the ECog as a measure of change in cognitive function since diagnosis; and the FCAS as a measure of compensation. Lastly, the Hollingshead Index was used as a proxy for CR which has not been previously for use in survivors of PBT.

Two composites of specific performance scores were explored for use as measures of ECF: the CTB Composite score and TMT Difference scores (Johnson et al., 2012). While

composite scores compress the interpretation of many instruments into a solitary score, bias can result if one instrument score is greatly skewed, giving the composite score a value that does not accurately reflect cognitive function. For instance, positive cognitive performances in one domain or on several tests may obscure significant impairment in other areas (Jones et al., 2011).

The use of the EXIT-25 was exploratory in this sample. The EXIT-25 was developed as a screen for dementia in elderly populations (Royall et al., 1992). Since its development, there has been increasing emphasis in screening instruments to identify mild cognitive impairment in populations at risk for dementia (Malloy et al., 1997; Wefel et al., 2010). This instrument has been used in a variety of medical populations including hospitalized medical patients (Royall, Chiodo, & Polk, 2000; Schillerstrom et al., 2005), subjects with schizophrenia and other psychiatric disorders (Scully et al., 1997; Schillerstrom et al., 2003), the neurologically injured (Larson, Leahy, Duff, & Wilde, 2008), and those who have undergone radiation therapy (Fuller et al., 2007). There have been suggestions to change the standardized cutpoint of 15 for clinically significant cognitive impairment and use lower cutpoints to screen for mild cognitive impairment (Fuller et al., 2008; Larson et al., 2008; Larson & Heinemann, 2010). This may be relevant to the present study because only one subject had a score above the cutpoint of 15. Cutpoints of 5 and 10 were explored in this study, but the EXIT-25 had a low level of agreement with the standardized neuropsychological battery, therefore limiting its usefulness as a screening instrument for ECF in this clinical population.

The ECog was used to explore change in cognitive function since diagnosis. The ECog is easily administered and offers a comprehensive assessment of everyday functions that reflects cognitive activities in specified domains (Farias et al., 2006; 2008). This instrument had not been previously studied in survivors of PBT, and was validated in elderly populations (Farias et

al., 2006; 2008), so the items were compared to cognitive symptom items on 2 instruments validated for symptoms relevant to PBT, the FACT-BT and MDASI-BT. The high level of agreement between tests suggests that the instruments tap into similar cognitive functions. A strength of the ECog is that the subject must reflect whether and how much a comprehensive list of cognitive activities has changed over time rather than rate cognitive symptoms for severity, interference, or impact on their lives within the previous day (MDASI-BT) or week (FACT-BT) (Jones et al., 2011; Mandelblatt et al., 2013).

One scale designed to examine the engagement in cognitive activities of community-dwelling elders is the FCAS (Dotson, Schinka, Brown, Mortemer, & Borenstein, 2008; Schinka et al., 2005). In the present study, the FCAS was used to explore the change in cognitive activities that subjects reported during a structured interview. This instrument was helpful in facilitating conversations regarding the activity and how subjects had changed their engagement with the activity over time. Their responses indicate that this instrument may be useful in determining how changes in cognitively-engaging activities may provide insight into compensatory strategies that survivors of PBT use to maintain function (Hampstead et al., 2014; Jones et al., 2011).

This study used the Hollingshead Index as the measure of CR because it is an index for educational and occupational attainment. Research proxies of CR have included premorbid intelligence and cognitively-engaging activities as lifetime measures (Foubert-Samier et al., 2012; Reed, et al., 2011; Wilson, Barnes, & Bennett, 2003). This study did not measure cognitively-engaging activities in all subjects, but premorbid intelligence was measured by performance scores on the NAART. However, in 20% of the sample, neuropathology may have led to NAART scores that do not accurately reflect their premorbid intelligence, thereby limiting

the use of premorbid intelligence as a proxy for CR (Strauss, Sherman, & Spreen, 2006). Others have suggested the use of literacy instead of IQ (Ownsworth, Dwan, Chambers, Walker, & Shum, 2013; Puccioni & Vallesi, 2012). Additionally, education has been cited to reflect the cognitively-engaging activities that one performs at early age, and offer that occupation may better reflect cognitive stimulation in adulthood by work-related activities and demands (Reed et al., 2011; Wilson, 2000; Wilson, Barnes, & Bennett, 2003). What is needed is an index that takes into account educational, occupational, and cognitively-engaging activities as a lifetime measure for CR (Jones et al., 2011; Nucci, Mapelli, & Mondini, 2012).

Subject heterogeneity.

The present study sought to describe the discrepancy between cognitive performance and self-reported function in survivors of PBT who had undergone cancer treatment with chemotherapy or radiation therapy. Several exclusion criteria were applied to control factors that might influence cognitive function, and to assure a healthy survivor for study participation. However, this sample is heterogeneous in regards to tumor grade, location, and treatment, and it is too small to control for or explore the effect of tumor location, grade, recurrence, and treatments on cognitive function and cognitive reserve (Davidson, Gao, Mason, Winocur, & Anderson, 2008; Hodgson et al., 2013; Mandelblatt et al., 2013; Nokia, Anderson, & Shors, 2012; Robertson, 2013).

Subjects in the sample ranged in age from 31 to 64 years old. While not considered elderly, the age of the subject may affect cognitive abilities. We cannot ascertain the risk that an individual might have for developing an age-related dementia, but aging has been associated with worsening cognitive performance (Gehring et al., 2011; Zucchella et al., 2013).

Consistent with tumor registry data (CBTRUS, 2012), our sample was comprised primarily of Caucasians (92.5%) and slightly more women (55%) than men. The differences that culture, race, and gender may impose on cognitive functioning have become of interest (Dotson et al., 2008; Jones et al., 2011; Siedlecki et al., 2009; Tomey et al., 2010), but we have too few studies to fully understand the impact these characteristics on CR and survivors of PBT.

Potential sources of bias.

This study may have several sources for bias. Study recruitment occurred at 2 academic tertiary medical centers with specialized neuro-oncology departments: one focused on care regionally and one with patients from across the nation. Ninety-eight percent of this sample came from one site and represents a diverse geographical sample. These participants may have higher socioeconomic status and higher education than survivors of PBT in regional care facilities. This could be reflected in the Hollingshead Index scores for this sample, which ranged from 11 to 55, where the normal range extends to 77. Thus, considering subjects to have a low CR as determined by the cutpoint of 31.75 (sample mean) on the Hollingshead Index may not accurately define a low CR group but rather a group intermediate between high and low CR. This could have led to the finding that subjects with low CR in Group B had insight that about a change in cognitive function while the literature suggests that those with lower CR tend not to have insight into changes in cognitive function (Jones et al., 2011).

An additional potential source of bias regards those that choose to participate in research studies, particularly functional studies. Study responders tend to maintain some ability to perform everyday functional activities and participate in informed consent procedures. All of the subjects in this study also had to pass 2 cognitive screens before consenting and participating.

Thus, the participants in this study may not reflect some survivors with lower cognitive abilities and limit generalizability.

Implications for Future Research

Decline in cognitive function is one of the most distressing symptoms for adult survivors of PBT. However, many of the survivors in this study had maintained cognitive function despite neural damage from surgery, radiation, and chemotherapy. The findings from this study suggest that cognitive reserve may play a role in maintaining cognitive function in survivors of PBT. This knowledge may help to identify those at more risk of developing cognitive decline so that early intervention may occur.

Longitudinal measurement of cognitive function beginning at time of diagnosis is essential if we are to track changes in cognitive function over time. This will provide a framework for understanding the PBT survivor illness trajectory, when survivors are at risk, and when targeted interventions may be successfully implemented and sustained. Self-reported everyday function must accompany objective cognitive performance measures to identify early changes in survivor perceptions because patient reports of change may precede objective changes in cognitive performance. Learning to ask survivors about the effort needed to perform everyday activities may tell us whether compensation is occurring or changing, and may help with identifying their trajectory. Furthermore, self-reported change in cognitive function may indicate a need for referral for more comprehensive, objective cognitive function evaluation.

The theory of cognitive reserve provided a lens through which to view the discrepancy between subjective and objective cognitive function, as well as to explore compensation. The findings of the present study illustrate several of the compensatory strategies used by PBT

survivors, with or without their awareness, and provide the foundation for further exploration of compensatory strategies that maintain cognitive function. Additionally, teaching PBT survivors and their families about cues to dysfunction, and how to look for help when concerned about cognitive failure may alleviate fear and provide opportunity for early intervention to prevent cognitive decline.

APPENDIX A: IRB APPROVALS



THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: Hutch Allen
School of Nursing
UNC School of Nursing, CB 7460, Chapel Hill, NC 27514-7460

From: Public Health-Nursing IRB

Approval Date: 12/05/2011

Expiration Date of Approval: 11/26/2012

RE: Notice of IRB Approval by Full Board Review

Submission Type: Initial

Study #: 11-1635

Study Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors

Sponsors: American Cancer Society

This submission has been approved by the above IRB for the period indicated.

Study Description:

Purpose: To describe executive control function (ECF) and its components, working memory and attention (Research Question [RQ] 1); to examine the relationship of ECF and its components to self-reported ECF in adult survivors with primary brain tumor (PBT)(RQ 2); and to identify compensatory behaviors in 10 PBT survivors who report ECF problems (RQ 3).

Participants: 40 PBT survivors will comprise the sample for RQ 1 & 2; 10 adult PBT survivors and 10 healthy adult matched controls for RQ 3.

Procedures (methods): A cross-sectional descriptive-exploratory design will be used. RQ 1 & 2 will utilize a structured neuropsychological battery and the Everyday Cognition Scale (ECog); RQ 3 will utilize video-recorded behavioral observation and interviews.

Regulatory and other findings:

This approval includes a limited waiver of HIPAA authorization to identify potential subjects for recruitment into this research study, as allowed under 45 CFR 164.512. This temporary waiver provides access to protected health information (PHI) to confirm eligibility and facilitate initial contact, after which consent and HIPAA authorization will be sought. Access and use is limited to the minimum amount of PHI necessary to review eligibility criteria and to contact potential subjects.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at
http://apps.research.unc.edu/irb/eform_routing.cfm?masterid=100972&Section=attachments

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented (use the modification form at ohre.unc.edu/forms). Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at <https://irbis.unc.edu/irb>.

Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., principals, facility directors, healthcare system).

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Barbara Carlson, School of Nursing



THE UNIVERSITY
of NORTH CAROLINA
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Federalwide Assurance (FWA) #4801

To: Hutch Allen
School of Nursing

From: Non-Biomedical IRB

Approval Date: 10/14/2012

Expiration Date of Approval: 10/13/2013

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)

Submission Type: Renewal

Expedited Category: 8(c) Continuing Review - Data Analysis Only

Study #: 11-1635

Study Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors

Sponsors: American Cancer Society

This submission has been approved by the IRB for the period indicated.

Study Description:

Purpose: To describe executive control function (ECF) and its components, working memory and attention (Research Question [RQ] 1); to examine the relationship of ECF and its components to self-reported ECF in adult survivors with primary brain tumor (PBT)(RQ 2); and to identify compensatory behaviors in 10 PBT survivors who report ECF problems (RQ 3).

Participants: 40 PBT survivors will comprise the sample for RQ 1 & 2; 10 adult PBT survivors and 10 healthy adult matched controls for RQ 3.

Procedures (methods): A cross-sectional descriptive-exploratory design will be used. RQ 1 & 2 will utilize a structured neuropsychological battery and the Everyday Cognition Scale (ECog); RQ 3 will utilize video-recorded behavioral observation and interviews.

Regulatory and other findings:

This research, which was originally approved by the Full Board, is being renewed by the IRB under Expedited Review, Category 8c. The research has been closed to the accrual of new subjects and all subjects have completed intervention/interaction. Renewal is granted for data analysis only.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval.

Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/irb_event.cfm?actn=info&irbid=11-1635.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at <http://irbis.unc.edu>.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40CFR 26 (EPA), where applicable.

CC:
Barbara Carlson, School of Nursing



THE UNIVERSITY
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Federalwide Assurance (FWA) #4801

To: Hutch Allen
School of Nursing

From: Non-Biomedical IRB

Approval Date: 8/26/2013

Expiration Date of Approval: 8/25/2014

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)

Submission Type: Renewal

Expedited Category: 8(c) Continuing Review - Data Analysis Only

Study #: 11-1635

Study Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors

This submission has been approved by the IRB for the period indicated.

Study Description:

Purpose: This exploratory describes the relationship of executive control function (ECF) : and its components, working memory and attention (Research Question [RQ] 1); and self-reported ECF in adult survivors with primary brain tumor (PBT)(RQ 2). In addition, this study explored compensatory behaviors in 7 PBT survivors who report ECF problems (RQ 3). Participants: 40 PBT survivors will comprise the sample for RQ 1 & 2; 7 adult PBT survivors and 7 healthy adult matched controls for RQ 3. Procedures (methods): A cross-sectional descriptive-exploratory design was used. RQ 1 & 2 used a structured neuropsychological battery and the Everyday Cognition Scale (ECog) measurements for description of their relationship. RQ 3 used video-recorded behavioral observation and interviews.

Submission Description:

There is a change in faculty advisors from Dr. Barbara Carlson to Dr. Merle Mishel.

Regulatory and other findings:

This research, which was originally approved by the Full Board, is being renewed by the IRB under Expedited Review, Category 8c. The research has been closed to the accrual of new subjects and all subjects have completed intervention/interaction. Renewal is granted for data analysis only.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval.

Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/irb_event.cfm?actn=info&irbid=11-1635.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at <http://irbis.unc.edu>.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40CFR 26 (EPA), where applicable.

CC:
Merle Mishel, School of Nursing

IRB NOTIFICATION OF STUDY APPROVAL

Protocol ID: Pro00032121
Principal Investigator: Deborah Allen
Protocol Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors
Sponsor/Funding Source(s): None
Federal Funding Agency ID:
Date of Declared Concordance with federally funded grant, if applicable: N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

Activity:	Initial Review	Review Type: Expedited
Review Date:	10/24/2011	
Issue Date:	11/10/2011	
Expiration Date:	10/24/2012	

DUHS IRB approval encompasses the following specific components of the study:

Protocol, version/date:	--11/7/2011
Summary, version/date:	--11/8/2011
Consent form reference date:	--11/10/2011
Investigator Brochure, version/date:	--
Pediatric Risk Category:	--
Other:	--

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval for the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five (5) working days of the event.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.



DUHS Institutional Review Board
 2424 Erwin Rd | Suite 405 | Durham, NC | 919.668.5111
 Federalwide Assurance No: FWA 00009025

IRB NOTIFICATION OF CONTINUING REVIEW APPROVAL

Continuing Review ID: CR1_Pro00032121
Principal Investigator: Deborah Allen
Protocol Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors
Sponsor/Funding Source(s): None
Federal Funding Agency ID:
Date of Declared Concordance with federally funded grant, if applicable: N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

Activity:	Continuing Review	Review Type:	Expedited
Review Date:	9/27/2012		
Issue Date:	9/28/2012		
Anniversary Date:	10/24/2012		
Expiration Date:	10/24/2013		

DUHS IRB approval encompasses the following specific components of the study:

Protocol, version/date:	--11/2011
Summary, version/date:	--11/8/2011
Consent form reference date:	--9/28/2012
Investigator Brochure, version/date:	--
Pediatric Risk Category:	--
Other:	--

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval for the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five (5) working days of the event.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.



DUHS Institutional Review Board
 2424 Erwin Rd | Suite 405 | Durham, NC | 919.668.5111
 Federalwide Assurance No: FWA 00009025



IRB NOTIFICATION OF CONTINUING REVIEW APPROVAL

Continuing Review ID: CR003_Pro00032121
Principal Investigator: Deborah Allen
Protocol Title: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors
Sponsor/Funding Source(s): None
Federal Funding Agency ID:
Date of Declared Concordance with federally funded grant, if applicable: N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

Activity: Continuing Review **Review Type:** Expedited
Review Date: 9/27/2013
Issue Date: 10/1/2013
Anniversary Date: 10/24/2013
Expiration Date: 10/24/2014

DUHS IRB approval encompasses the following specific components of the study:

Protocol, version/date: --11/7/2011
Summary, version/date: --11/8/2011

Consent form reference date: --closed
Investigator Brochure, version/date: --
Pediatric Risk Category: --
Other: --

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval for the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five (5) working days of the event.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.



DUHS Institutional Review Board
2424 Erwin Rd | Suite 405 | Durham, NC | 919.668.5111
Federalwide Assurance No: FWA 00009025

APPENDIX B: IRB CONSENT FORMS

University of North Carolina-Chapel Hill Consent to Participate in a Research Study Adult Participants

Consent Form Version Date: October 10, 2011
IRB Study # 11-1635

Title of Study: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors

Additional Study Information: Adult Participants with Primary Brain Tumors, Audio Recording

Principal Investigator: Deborah Allen, RN, MSN
Principal Investigator Department: School of Nursing
Principal Investigator Phone number: 919-883-7002
Principal Investigator Email Address: allendd@email.unc.edu

Co-Investigators: Barbara Waag Carlson RN, Ph.D. (Faculty Advisor)
Virginia J. Neelon RN, Ph.D.
Merle Mishel, RN, Ph.D.
John Carlson, MA
Renee Raynor, PhD
Jing Wu, MD

Funding Source: American Cancer Society Doctoral Scholarship in Nursing

Study Contact telephone number: 919-883-7002
Study Contact email: allendd@email.unc.edu

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The major purpose of this research study is to learn what problems persons who have undergone treatment for primary brain tumors report in their memory and thinking as compared to how they perform on tests typically used to assess memory and thinking. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn what everyday activities persons continue to use or

may have difficulties with after treatment completion. With this information, we may improve how we detect changes in memory and thinking during treatment.

Are there any reasons you should not be in this study?

You should not be in this study if you cannot read or write English, younger than 30 years of age or greater than 65 years of age, have any known neurodegenerative disorders or take medications for Parkinson's disease, Alzheimer's Disease or other dementias, psychiatric disorders such as schizophrenia, mania, depression, or bipolar disorder, seizure disorders that have required medication changes in the past six months, general anesthesia in the past six months, problems with numbness or tingling or moving your arms or legs, problems sleeping such as sleep apnea, pain keeping you awake, or sleep walking, history of stroke or alcohol or drug abuse, or neuroimmune disorders such as HIV, herpes, tuberculosis, syphilis, or hepatitis. You should not participate today and this study may be rescheduled if you took an over-the-counter cold medication last night, drank alcoholic beverages or taken recreational drugs in the past 24 hours, took sleeping medicines last night which you do not routinely take every night, or if you have had recent procedures requiring anesthetics in the past two weeks.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 40 adults with primary brain tumors.

This study will take place at the University of North Carolina and Duke University.

How long will your part in this study last?

The study will take no more than 3 hours to complete.

What will happen if you take part in the study?

After you review this consent form and have opportunity to ask questions about the testing procedures, you will have your vital signs measured (heart rate, blood pressure, blood oxygen levels in your finger). Next you will be asked to complete a questionnaire about depression, your ability to take care of yourself, and if you have noticed any problems with your ability to think or remember. This can take between 15 to 30 minutes to do.

Afterwards, you will be asked to take a brief neurological test and be asked to complete some tests that measure your ability to think and remember. This part of the study should take no more than one hour to do. Between tests, we will give you time to rest, get something to drink or eat or go to the bathroom. All together, this part of the study, should take no more than 90 minutes to complete.

Audiorecording

The tests will be given in a specific order and at a specific time. We ask that you try to answer all questions or perform tasks to the best of your ability. Therefore, we will be using a tape recorder in order to make sure the person giving the test starts the test in the correct order, at the right time, and writes down your answers correctly. Only members of the research team will have access to these recordings. The recordings will be kept in a locked cabinet and will be destroyed after the study has ended.

___ OK to audiotape me.

___ Not OK to audiotape me.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You may not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

There are no major risks to you as a subject in this study. It is possible that you may feel uncomfortable with some of the tasks that we ask you to do. For example, the memory test may make you feel anxious because some of the answers will be very easy and some will be very hard. We do not expect you to know all the answers. Please do not hesitate to ask any member of the research team any question, and we want you to tell us about any problems you may be having.

Because we are taking many measurements, we may find people who may have a condition that requires medical attention. Examples of conditions that require medical attention include having a high pulse rate, high or low blood pressure, or below normal measures on a memory or thinking test. If this is detected, we will talk with you and give you a form that tells you (1) what we found, (2) what it may mean in terms of your health, and (3) where you can go to get some help. Lastly, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

How will your privacy be protected?

Every effort will be taken to protect your identity. Only Ms. Allen and the other study investigators, and their research assistants will have access to your data. As part of this study, your answers to the questions that Ms. Allen and her research team ask you will not be included in your medical record. Study records that identify you will be kept confidential as required by law. You will be assigned a unique code number in which the key to this code will be kept in a locked file in Ms. Allen's office. All data (paper forms, compact discs, audio and video recordings) will be kept under lock and key at the School of Nursing. After data analyses are completed, all data will be destroyed.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions or unable to complete several of the tests.

Will you receive anything for being in this study?

You will be receiving \$25.00 for taking part and completing the procedures in this study. You will also receive a parking voucher. There will be no costs to you for being in this study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or concerns, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant’s Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____	_____
Signature of Research Participant	Date

Printed Name of Research Participant

[LAR]

_____	_____
Signature of Research Team Member Obtaining Consent	Date

Printed Name of Research Team Member Obtaining Consent

**University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Participants**

Consent Form Version Date: October 10, 2011
IRB Study # 11-1635

Title of Study: Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors

Additional Study Information: Adult Participants with Primary Brain Tumors, Video Recording

Principal Investigator: Deborah Allen, RN, MSN
Principal Investigator Department: School of Nursing
Principal Investigator Phone number: 919-883-7002
Principal Investigator Email Address: allendd@email.unc.edu

Co-Investigators: Barbara Waag Carlson RN, Ph.D. (Faculty Advisor)
Virginia J. Neelon RN, Ph.D.
Merle Mishel, RN, Ph.D.
John Carlson, MA
Renee Raynor, PhD
Jing Wu, MD

Funding Source: American Cancer Society Doctoral Scholarship in Nursing

Study Contact telephone number: 919-883-7002
Study Contact email: allendd@email.unc.edu

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The major purpose of this supplemental research study is to learn about strategies that persons who have undergone treatment for primary brain tumors use for memory and thinking as compared to persons who do not have primary brain tumors. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn about the strategies persons use. This additional information will assist

This form has been approved by the IRB for use until 11/26/2012

us in identifying ways to promote maintaining thinking and memory abilities.

Are there any reasons you should not be in this study?

You should not be in this study if you cannot read or write English, younger than 30 years of age or greater than 65 years of age, have any known neurodegenerative disorders or take medications for Parkinson's disease, Alzheimer's Disease or other dementias, psychiatric disorders such as schizophrenia, mania, depression, or bipolar disorder, seizure disorders that have required medication changes in the past six months, general anesthesia in the past six months, problems with numbness or tingling or moving your arms or legs, problems sleeping such as sleep apnea, pain keeping you awake, or sleep walking, history of stroke or alcohol or drug abuse, or neuroimmune disorders such as HIV, herpes, tuberculosis, syphilis, or hepatitis. You should not participate today and this study may be rescheduled if you took an over-the-counter cold medication last night, drank alcoholic beverages or taken recreational drugs in the past 24 hours, took sleeping medicines last night which you do not routinely take every night, or if you have had recent procedures requiring anesthetics in the past two weeks

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 10 adults with primary brain tumors and 10 healthy adults in this research study.

This study will take place at the University of North Carolina and Duke University.

How long will your part in this study last?

This supplemental study will take 30 additional minutes to complete after the testing battery. Both studies will take no longer than 3 hours to complete.

What will happen if you take part in the study?

In this supplemental study, you will be video-recorded while you complete the tests for your memory and thinking. This will be done so that the researcher learn more about what you may do that helps you to successfully complete the tests. Often times, people move or do thing that while they are not aware of it, helps them to do a task faster or more accurately. The tapes will help us to see these things. The video camera will include your face as well as your upper portion of your body. The video recordings will be kept in a locked cabinet. These tapes will be destroyed after the researcher reviews the tapes.

☐ OK to audio/videotape me.

☐ Not OK to audio/videotape me.

At the end of the tests for your memory and thinking, you will be asked a few questions asking you about what tests were more or less difficult and what strategies you may have used to complete the tests. This should take no more than 30 minutes to complete.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You may not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

There are no major risks to you as a subject in this study. It is possible that you may feel uncomfortable with some of the tasks that we ask you to do. For example, the memory test may make you feel anxious because some of the answers will be very easy and some will be very hard. We do not expect you to know all the answers. Please do not hesitate to ask any member of the

research team any question, and we want you to tell us about any problems you may be having.

Because we are taking many measurements, we may find people who may have a condition that requires medical attention. Examples of conditions that require medical attention include having a high pulse rate, high or low blood pressure, or below normal measures on a memory or thinking test. If this is detected, we will talk with you and give you a form that tells you (1) what we found, (2) what it may mean in terms of your health, and (3) where you can go to get some help. Lastly, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

How will your privacy be protected?

Every effort will be taken to protect your identity. Only Ms. Allen and the other study investigators, and their research assistants will have access to your data. As part of this study, your answers to the questions that Ms. Allen and her research team ask you will not be included in your medical record. Study records that identify you will be kept confidential as required by law. You will be assigned a unique code number in which the key to this code will be kept in a locked file in Ms. Allen's office. All data (paper forms, compact discs, audio and video recordings) will be kept under lock and key at the School of Nursing. After data analyses are completed, all data will be destroyed.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions or unable to complete several of the tests.

Will you receive anything for being in this study?

You will receive a total of \$25.00 for taking part and completing the study procedures while being video-recorded and interviewing. You will also receive a parking voucher. There will be no costs to you for being in this study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or concerns, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant’s Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____	_____
Signature of Research Participant	Date

Printed Name of Research Participant

[LAR]

_____	_____
Signature of Research Team Member Obtaining Consent	Date

Printed Name of Research Team Member Obtaining Consent



DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Primary Study

You are being asked to take part in this research study because you have received treatment for your primary brain tumor. Research studies include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Ms. Deborah Allen and Dr. Annick Desjardins will conduct the study.

WHY IS THIS STUDY BEING DONE?

The major purpose of this research study is to learn what problems persons who have undergone treatment for primary brain tumors report in their memory and thinking as compared to how they perform on tests typically used to assess memory and thinking. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn what everyday activities persons continue to perform or may have difficulties with after treatment completion. With this information, we may improve how we detect changes in memory and thinking during treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

If you decide to be in this study, you will be one of approximately 40 adults with primary brain tumors in this research study at Duke University.

WHAT IS INVOLVED IN THE STUDY?

After you review this consent form and have an opportunity to ask questions about the testing procedures, you will have your vital signs measured (heart rate, blood pressure, blood oxygen levels in your finger). Next you will be asked to complete questionnaires about depression, your ability to take care of yourself, and if you have noticed any problems with your ability to think or remember. This can take between 15 to 30 minutes to do.

Afterwards, you will be asked to take a brief neurological test and be asked to complete some tests that measure your ability to think and remember. This part of the study should take no more than one hour to do. Between tests, we will give you time to rest, get something to drink or eat or go to the bathroom. All together, this part of the study, should take no more than 90 minutes to complete.

Audio-recording

The tests we will be using must be given in a specific order, at a specific time, and many require that you tell us the correct answer. Therefore, we will use a tape recorder to make sure the person giving the test starts the test in the correct order, at the right time, and writes down your answers correctly. Only members of the research team will have access to these recordings. The recordings will be kept in a locked cabinet and will be destroyed after the study has ended.

Protocol ID: **Pro00032121**
Continuing Review Before: **10/24/2012**
Reference Date: **11/10/2011**

Page 1 of 4

Subject Initials: _____



DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Primary Study

ARE THERE ANY REASONS NOT TO BE IN THIS STUDY?

You should not be in this study if you have had any seizures in the past six months requiring medication changes, any known neurodegenerative disorders or taking medications for a similar disorder such as Parkinson's disease, multiple sclerosis, Alzheimer's Disease or other dementias, psychiatric disorders such as schizophrenia, mania, or bipolar disorder, known problems holding a pen in your hand or moving your arms or legs, problems speaking clearly, problems with sleep such as sleep apnea, or history of stroke, HIV, herpes, tuberculosis, syphilis, or hepatitis. You should not participate today if you have been treating a cold with over-the-counter medications in the past two weeks, drank alcoholic beverages or taken recreational drugs in the past 24 hours, or took sleeping medicines last night which you do not routinely take every night, or smoked tobacco products within four hours prior to testing procedures.

HOW LONG WILL I BE IN THIS STUDY?

The study will take no more than 2 hours to complete.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to participate by telling the study staff and declining to sign the consent form. If you begin the study, you can choose to stop participating at any time without penalty at any time. You may opt not to complete a survey or refuse to participate in a structured interview.

WHAT ARE THE RISKS OF THE STUDY?

There are no major risks to you as a subject in this study. It is possible that you may feel uncomfortable with some of the tasks that we ask you to do. For example, the memory test may make you feel anxious because some of the answers will be very easy and some will be very hard. We do not expect you to know all the answers. Please do not hesitate to ask any member of the research team any question, and we want you to tell us about any problems you may be having.

Because we are taking many measurements, we may find people who may have a condition that requires medical attention. Examples of conditions that require medical attention include having a high pulse rate, high or low blood pressure, or below normal measures on a memory or thinking test. If this is detected, we will talk with you and give you a form that tells you (1) what we found, (2) what it may mean in terms of your health, and (3) where you can go to get some help. Lastly, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Research is designed to benefit society by gaining new knowledge. We hope that the information learned from this study will help identify successful strategies used for remembering and thinking that will benefit survivors of primary brain tumors. You may not benefit personally from being in this

Protocol ID: **Pro00032121**

Continuing Review Before: **10/24/2012**

Reference Date: **11/10/2011**

Page 2 of 4

Subject Initials: _____



DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Primary Study

research study.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, you will be assigned a unique code number. The key to the code will be kept in a locked file in Ms. Allen's office.

As part of this study, Ms. Allen and her study team will ask you to answer questions and complete memory tests. Results of these tests and questionnaires will not be included in your medical record. The data collected at Duke University and University of North Carolina at Chapel Hill will be merged into one dataset for study analyses procedures after unique code numbers are assigned.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Duke University Health System Institutional Review Board. If this group reviews your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

WHAT ABOUT COMPENSATION?

You will receive \$25.00 for taking part and completing the procedures in this study. You will also receive a parking voucher. There will be no costs to you for being in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have problems, concerns, questions or suggestions about the research, contact Ms. Deborah Allen at 919-883-7002 at any time including after hours and on weekends and holidays.

Protocol ID: **Pro00032121**
Continuing Review Before: **10/24/2012**
Reference Date: **11/10/2011**

Page 3 of 4

Subject Initials: _____



DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Primary Study

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

Signature of Subject

Date

Signature of Person Obtaining Consent

Date

Protocol ID: **Pro00032121**
Continuing Review Before: **10/24/2012**
Reference Date: **11/10/2011**

Page 4 of 4

Subject Initials: _____



DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Supplemental Study

You are being asked to take part in this research study because you have received treatment for your primary brain tumor. Research studies include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Ms. Deborah Allen and Dr. Annick Desjardins will conduct the study..

WHY IS THIS STUDY BEING DONE?

The major purpose of this research study is to learn about strategies that persons who have undergone treatment for primary brain tumors use for memory and thinking as compared to persons who do not have primary brain tumors. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn about the strategies persons use. This additional information will assist us in identifying ways to promote maintaining thinking and memory abilities.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

If you decide to be in this part of the study, you will be one of approximately 10 adults with primary brain tumors and 10 healthy adults who will participate at Duke University.

WHAT IS INVOLVED IN THE STUDY?

In this supplemental study, you will be video-recorded while you complete the tests for your memory and thinking. This will be done so that the researcher can learn more about what you may do that helps you to successfully complete the tests. Often times, people move or do things that, while they are not aware of it, may help them to do a task faster or more accurately. The tapes will help us to see these things. The video camera will include your face as well as the upper portion of your body. The video recordings will be kept in a locked cabinet. These tapes will be destroyed after the researcher reviews the tapes.

At the end of the tests for your memory and thinking, you will be asked a few questions asking you about what tests were more or less difficult and what strategies you may have used to complete the tests. This should take no more than 30 minutes to complete.

ARE THERE ANY REASONS NOT TO BE IN THIS STUDY?

You should not be in this study if you have had any seizures in the past six months requiring medication changes, any known neurodegenerative disorders or taking medications for a similar disorder such as Parkinson's disease, multiple sclerosis, Alzheimer's Disease or other dementias, psychiatric disorders such as schizophrenia, mania, or bipolar disorder, known problems holding a pen in your hand or moving your arms or legs, problems speaking clearly, problems with sleep such

Protocol ID: **Pro00032121**

Continuing Review Before: **10/24/2012**

Reference Date: **11/10/2011**

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DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Supplemental Study

as sleep apnea, or history of stroke, HIV, herpes, tuberculosis, syphilis, or hepatitis. You should not participate today if you have been treating a cold with over-the-counter medications in the past two weeks, drank alcoholic beverages or taken recreational drugs in the past 24 hours, or took sleeping medicines last night which you do not routinely take every night, or smoked tobacco products within four hours prior to testing procedures.

HOW LONG WILL I BE IN THIS STUDY?

This supplemental study will take 30 additional minutes to complete after the first testing battery.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to participate by telling the study staff and declining to sign the consent form. If you begin the study, you can choose to stop participating at any time without penalty at any time in this study. You may opt not to complete a survey or refuse to participate in a structured interview.

WHAT ARE THE RISKS OF THE STUDY?

There are no major risks to you as a subject in this study. It is possible that you may feel uncomfortable with some of the tasks that we ask you to do. For example, the memory test may make you feel anxious because some of the answers will be very easy and some will be very hard. We do not expect you to know all the answers. Please do not hesitate to ask any member of the research team any question, and we want you to tell us about any problems you may be having.

Because we are taking many measurements, we may find people who may have a condition that requires medical attention. Examples of conditions that require medical attention include having a high pulse rate, high or low blood pressure, or below normal measures on a memory or thinking test. If this is detected, we will talk with you and give you a form that tells you (1) what we found, (2) what it may mean in terms of your health, and (3) where you can go to get some help. Lastly, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Research is designed to benefit society by gaining new knowledge. We hope that the information learned from this study will help identify successful strategies used for remembering and thinking that will benefit survivors of primary brain tumors. You may not benefit personally from being in this research study.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

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DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Supplemental Study

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, you will be assigned a unique code number. The key to the code will be kept in a locked file in Ms. Allen's office.

As part of this study, Ms. Allen and her study team will ask you to answer questions and complete memory tests. Results of these tests and questionnaires will not be included in your medical record. The data collected at Duke University and University of North Carolina at Chapel Hill will be merged into one dataset for study analyses procedures after unique code numbers are assigned.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Duke University Health System Institutional Review Board. If this group reviews your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

WHAT ABOUT COMPENSATION?

You will be receiving \$25.00 for taking part and completing the procedures in this study. You will also receive a parking voucher. There will be no costs to you for being in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have problems, concerns, questions or suggestions about the research, contact Ms. Deborah Allen at 919-883-7002 at any time including after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Exploring Compensatory Behaviors Used to Maintain Executive Control Function in Adults with Primary Brain Tumors, Supplemental Study

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

Signature of Subject

Date

Signature of Person Obtaining Consent

Date

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Continuing Review Before: **10/24/2012**
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Subject Initials: _____

APPENDIX C: RECRUITMENT STRATEGIES



December 5, 2011

«Title» «First» «MidI» «Last»
«Street_1»
«City», «State» «Zip5»«Zip9»

Dear «Title» «Last»:

The University of North Carolina School of Nursing is performing a research study with adult survivors of primary brain tumors to explore how persons maintain cognitive function after receiving cancer-related treatment.

The major purpose of this research study is to learn how persons who have undergone treatment for primary brain tumors use memory and thinking for the completion of everyday activities. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn what everyday activities persons continue to use or may have difficulties with after treatment completion. With this information, we may be able to design better methods to detect these changes during treatment and design ways to promote maintaining thinking and memory abilities.

You are being asked to consider participating in this research study. Your participation in the study is voluntary. If you decide to be in this study, you will be one of 40 adults with primary brain tumors to participate. This study will take place at the University of North Carolina or Duke University in coordination with your routine oncology clinic visit so you will not have additional travel. The study will take no longer than 3 hours to complete.

After you review this consent form and have opportunity to ask questions about the testing procedures, you will be asked to complete a questionnaire about depression, your ability to take care of yourself, and if you have noticed any problems with your ability to think or remember. Afterwards, you will be asked to take a brief neurological test and be asked to complete some tests that measure your ability to think and remember. This part of the study should take no more than two hours to do. Between tests, we will give you time to rest, use the restroom, and will provide you something to drink or eat. You will be compensated for your time and travel with \$25.00 cash.

This form has been approved by the IRB for use until 11/26/2012

If participating in this study sounds like something you might be interested in please call Ms. Allen, the Principal Investigator of this research study, at the number below to discuss the study in further detail. This will take no more than 15 minutes of your time. Thank you for your consideration.

The number to call Ms. Allen is:

919-883-7002

Sincerely,

Deborah H. Allen, RN, MSN, FNP-BC, AOCNP
Predoctoral Student, School of Nursing
University of North Carolina at Chapel Hill



Date

Name

Address Street

Address City, State Zip

Dear Name,

I am a doctoral student at the University of North Carolina School of Nursing. I am writing to you regarding a research study that I am conducting at the Neuro-Oncology clinics at both UNC and Duke University. This study is exploring how persons with primary brain tumors maintain cognitive function after receiving cancer-related treatment. Based on your treatment records, you are eligible to consider participating in this research study.

The major purpose of this research study is to learn how persons who have undergone treatment for primary brain tumors use memory and thinking for everyday activities. While studies have shown that the brain's ability to think and remember may be affected in persons following treatment for primary brain tumor, studies have not been done to learn what everyday activities persons continue to use or may have difficulties with after treatment completion. With this information, we may be able to design better methods to detect these changes during treatment and design ways to promote maintaining thinking and memory abilities.

You are being asked to consider participating in this research study. Your participation in the study is voluntary. If you decide to be in this study, you will be one of 40 adults with primary brain tumors to participate. This study will take place at the University of North Carolina or Duke University in coordination with your routine oncology clinic visit so you will not have additional travel. The study will take no longer than 2 hours to complete.

The following information relates to the study procedures if you decide to participate. When you present to the agreed upon time for study participation, you will have the opportunity to review the study consent form and ask questions about the testing procedures. You will then be asked to complete a questionnaire about depression, your ability to take care of yourself, and if you have noticed any problems with your ability to think or remember. Afterwards, you will be asked to

take a brief neurological test and be asked to complete some tests that measure your ability to think and remember. This part of the study should take no more than 2 hours to do. Between tests, we will give you time to rest, use the restroom, and will provide you something to drink or eat. You will be compensated for your time and travel with \$25.00 cash and a parking garage voucher.

If participating in this study sounds like something you might be interested in please call Ms. Allen, the Principal Investigator of this study, at the number below to discuss the study in further detail. Thank you for your consideration.

The number to call Ms. Allen is:

919-883-7002

Sincerely,

Deborah H. Allen, RN, MSN, FNP-BC, AOCNP
Predoctoral Student, School of Nursing
University of North Carolina at Chapel Hill
Clinical Associate, School of Nursing
Duke University

A handwritten signature in dark ink, appearing to read "A. Desjardins", written in a cursive style.

Annick Desjardins, MD, FRCPC
Assistant Professor of Medicine
Preston Robert Tisch Brain Tumor Center at Duke
Duke Cancer Institute

**ARE YOU A SURVIVOR OF A BRAIN TUMOR
and Interested in Participating in Research?**

If you are between 30 & 65 years of age and have undergone treatment for a primary brain tumor, you may be eligible to participate in a research study that is examining cognitive function in survivors of primary brain tumors.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, connect numbers and letters, and memory skills.

We will provide you with free parking and \$25 for your time upon completion of testing procedures.

There are no needles or blood draws!!!!

For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

Supported by the Biobehavioral Laboratory at

The School of Nursing, The University of North Carolina at Chapel Hill

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 11- 1635)

Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002
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This form has been approved by the IRB for use until 11/26/2012

ARE YOU A HEALTHY ADULT
and Interested in Participating in Research?

If you are between 30 & 65 years of age and have no neurological disorders, you may be eligible to participate in a research study that is examining cognitive function, particularly your thinking and memory.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, connect numbers and letters, and memory skills.

We will provide you with free parking and \$25 for your time upon completion of testing procedures.

There are no needles or blood draws!!!!

For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

Supported by the Biobehavioral Laboratory at

The School of Nursing, The University of North Carolina at Chapel Hill

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 11- 1635)

Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002
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Are You Interested in Participating in a Research Study?

If you are 30-65 years of age and have undergone treatment for a primary brain tumor OR 30-65 years of age with no known neurological disorder and willing to serve as a healthy adult control, then you may be eligible to participate in a research study that is examining cognitive function, particularly your thinking and memory.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, to connect numbers and letters, and memory skills.

We will provide you with free parking and \$25 for your time upon completion of the testing procedures.

There are no needles or blood draws!!!!

For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 11-1635)

APPENDIX D: TELEPHONE SCREENING

Date ____/____/____

ID: _____

Appendix A.1

TELEPHONE SCREENING INSTRUMENT

I. PHONE RECRUITMENT SCRIPT

A. Introductory Remarks:

"Hello, this is Debbie Allen, from the University of North Carolina School of Nursing. I understand that you would like to learn more about participating in a research study involving how you think and remember and any strategies you may use to maintain your ability to think and remember. Is this a good time to talk?" If not, ask the potential participant "when is a good time to call you?"

If we need to call again, date/time agreed upon: _____

B. Brief Description of the Study

"I thank you for your call and your interest to discuss this study more. The purpose of this research is to compare thinking and memory in persons who have undergone treatment for a primary brain tumor as to persons who have not had a brain tumor and to learn what strategies you may use to maintain your thinking and memory."

"We will ask you questions about your health, how well you think and remember, and your daily activities, as well as measure your ability to think and remember. It is our aim to use this information to design better methods to detect early changes in cognition and design interventions to decrease the risk of further decline. We are testing this only in adults with primary brain tumors and healthy adults. The total time to complete the study will be no longer than three hours and we will compensate you for your time and travel with \$25.00 cash. Does this sound like something you might be interested in?"

Response:	Yes	No
If they say yes, go to the Mini-Consent for Telephone Screening.		
If they say no, thank them for their time and interest in speaking with you.		

Date ____/____/____

ID: _____

C. Mini-Consent for the Telephone Screen

After the respondent tells you that they are interested in participating, ask them
“Is it okay to ask you a few questions about your health and the medications you take? It
should take no more than 15 minutes.”

<p>If they say yes, go to Health Screening Questionnaire.</p> <p>If they need to reschedule, ask them for preference of contact phone numbers and a date/time to call.</p> <p>Phone number 1: (____) ____ - ____</p> <p>Phone number 2: (____) ____ - ____</p> <p>Date & Time: _____, _____ AM/PM</p>

Date ____/____/____

ID: _____

II. RESPONDENT TELEPHONE SCREENING

A. Tracking Information

Date respondent called for information: _____

Date PI returned call: _____

____/____/____
____/____/____

B. Group Assessment

1. Have you had a brain tumor?

If they say yes, they are assigned to the brain tumor subject group.
Proceed to ask questions **a** and **b** below.

If they say no, they are assigned to the control group.
Proceed to question 2.

a. Have you had surgery, chemotherapy, or radiation therapy as treatment for your brain tumor?

Yes

No

i. Date of surgery

____/____/____

or NA

ii. Date of radiation therapy

____/____/____

or NA

iii. Date of chemotherapy

____/____/____

or NA

b. Are you still on any chemotherapy?

Yes

No

If yes, what kind of chemotherapy are you taking? _____

If they do not remember the name, ask them if it is the following agents (circle the agent they indicate):

Carmustine, Lomustine (CeeNU), Carboplatin, Temozolomide (Temodar),
Etoposide (Vepesid, VP-16), Irinotecan (CPT-11, Camptosar), Procarbazine
(Matulane)

If any of the agents listed is an agent the responder is currently taking,
stop interview and go to **NOT ELIGIBLE** section on the last page.

c. Do you have any problems with holding a pen, writing, or speaking? **Yes** **No**

If YES, stop interview here and go to **NOT ELIGIBLE** section on the last page

This form has been approved by the IRB for use until 11/26/2012

Date ____/____/____

ID: _____

2. Medications

Are you taking medications (including prescription & over-the-counter)? **Yes** **No**

If they say yes, ask “What medications are you taking?”

If they do not know, ask them to read all medication bottles to you that they have.

Record below:

Medication Name	Reason for taking
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	

Compare the list of medications to the Medication Exclusion Card. Exclude the subject if she or he is taking any of the medications listed on the Medication Exclusion Card. Put a check next to the name of any drug that excludes the subject from participating.

MEDICATION EXCLUSION

Changes in seizure medications in the last six months	YES	NO
Dopaminergics	YES	NO
Major anticholinergics	YES	NO
Alzheimer’s drugs	YES	NO
Cold medications, sedative hypnotics in past 48 hours?	YES	NO

Medication Exclusion:

Taking a medication on the Medication Exclusion Card? **Yes** **No**

If YES, STOP interview here.
Go to **Not Eligible** section on last page.

Date ____/____/____

ID: _____

3. Neurological Conditions

I'm now going to read a list to you. Please wait until I have read the entire list, and then say 'yes' if you have been diagnosed with any of these conditions, or say 'no' if you have not.

- a. Alzheimer's Disease
- b. Dementia
- c. Parkinson's Diseases
- d. Schizophrenia
- e. Mania
- f. Bipolar Disorder
- g. Unstable Seizure Disorder requiring antiepileptic changes in the last six months
- h. Any problems with numbness or tingling in your arms or legs
- i. Any problems moving your arms or legs
- j. Had any surgery requiring general anesthesia in the last two weeks

Neurological Disease Exclusion:

Answer of "Yes" to any of the neurological conditions?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

4. Other Neuroimmune Disorders

For this next list, again, please wait until I have read the entire list, and then say 'yes' if you have been diagnosed with any of these conditions, or say 'no' if you have not.

- a. Tuberculosis
- b. Hepatitis
- c. HIV or AIDS
- d. Herpes
- e. Syphilis

Neuroimmune Disorder Exclusion:

Answer of "Yes" to any of the neuroimmune disorders?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

5. Cerebrovascular Events

For this next list, please wait until I have read the entire list, and then say 'yes' if you have had any of these conditions **in the past 6 months** or say 'no' if you have not.

- a. Stroke or Transient Ischemic Attack
- b. Hit your head and lost consciousness

Cerebrovascular Event Exclusion:

Answer of "Yes" to any of the cerebrovascular events?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

A.1-5

6. Sleep-Related Symptoms

After I have read the next list, please say ‘yes’ if you have had any of the following problems **in the past month**, or say ‘no’ if you have not.

- a. Pain so bad it keeps you awake
- b. Having to get up and urinate 3 or more times a night
- c. Being easily awakened by sounds
- d. Having difficulty sleeping when away from home
- e. Walking in your sleep
- f. Falling out of bed
- g. Waking from sleep violent or confused

<u>Sleep-Related Exclusions:</u>		
Answer of “Yes” to any of the sleep-related symptoms questions?	Yes	No
If YES, STOP interview here.		
Go to “Not-Eligible” section on last page.		

7. Alcohol & Drug Exclusions

These next questions are about alcohol and illegal drugs. Please wait until I have read the entire list, and then just say ‘yes’ if you do any of the following or ‘no’ if you do not:

- a. Have more than 3 cans of beer on more than 3 nights/week
- b. Have more than 3 glasses of wine on more than 3 nights/week
- c. Have more than 3 shots of distilled liquor on more than 3 nights/week
- d. Currently smoke marijuana or use illegal drugs

<u>Alcohol and Drug Exclusion:</u>		
Answer of “Yes” to any of the alcohol/drug questions?	Yes	No
If YES, STOP interview here.		
Go to “Not-Eligible” section on last page.		

Date ____/____/____ ID: _____

8. Age in Years

What is your date of birth? ____/____/____

Born In	Years Old	Born in	Years old
Before 1946	> 65	1964	47
1946	65	1965	46
1947	64	1966	45
1948	63	1967	44
1949	62	1968	43
1950	61	1969	42
1951	60	1970	41
1952	59	1971	40
1953	58	1972	39
1954	57	1973	38
1955	56	1974	37
1956	55	1975	36
1957	54	1976	35
1958	53	1977	34
1959	52	1978	33
1960	51	1979	32
1961	50	1980	31
1962	49	1981	30
1963	48	After 1981	< 30

“That would mean that you are: _____ years old.”
.

Age exclusion:

Age < 30 years

OR

Age > 65 years

Yes

No

If YES, STOP interview here.

Go to “Not-Eligible” section below.

9. Years of Education

How many years of education have you completed? _____ years

Date ____/____/____

ID: _____

10. Mental Status Exam

The Telephone Interview for Cognitive Status
(Brandt, Spencer, & Folstein, 1988)

Instructions to Patient: “Now I’d like you to answer some questions and ask you to follow some instructions. Do your best to respond to each question or instruction. Some will seem very simple and some will be more difficult.”

Code in margin any question that patient refuses to answer (9) or is physically unable to answer (8). Do not include the 8’s and 9’s in the total score, but do indicate reason code was used (where applicable).

	Points Avail.	Points Earned
1. Ask “Please tell you full name?”		
First Name	1	_____
Last Name	1	_____
2. Ask “What is today’s date?”		
Month	1	_____
Date	1	_____
Year	1	_____
Day of week	1	_____
Season	1	_____
If incomplete, ask specifics, such as ask “What is the month? “		
“What season are we in?”		
3. Ask: “Where are you right now?”		
House number	1	_____
Street	1	_____
City	1	_____
State	1	_____
Zip	1	_____
If incomplete, ask specifics, such as ask “What street are you on right now?”		
4. Ask “Count backwards from 20 to 1.”		
2 points if completely correct on the first trial	2	_____
1 point is completely correct on second trial	1	_____
0 points for anything else	0	_____
Total Score for this Page	14	_____

Date ____/____/____

ID: _____

	Points Avail.	Points Earned
5. State "I am going to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many words as you can, in any order. Ready? The words are cabin, pipe, elephant, chest, silk, theatre, watch, whip, pillow, giant . Now tell me all the words you can remember."		
Cabin	1	_____
Pipe	1	_____
Elephant	1	_____
Chest	1	_____
Silk	1	_____
Theatre	1	_____
Watch	1	_____
Whip	1	_____
Pillow	1	_____
Giant	1	_____
There is no penalty for repetitions or intrusions.		
6. State "I want you to start with the number 100, subtract 7, and tell me your answer. So 100 minus 7 equal what?" "And 7 from that?" "Keep subtracting seven until I tell you to stop."		
Stop after five answers; you may prompt after each answer. 1 point for each correct subtraction. Do not inform the subject of incorrect responses, but allow subtractions to be made from the last response (e.g. "93-85-78-71-65" would get 3 points)		
Record responses: _____ Correct Responses: 93 86 79 72 65	5	_____
7. Ask the following questions: "What do people usually use to cut paper?" 1 point for "scissor" or "shears" only "How many things are in a dozen?" 1 point for "12" "What do you call the prickly green plant that lives in the desert?" 1 point for "cactus" only " What animal dose wool come from" 1 point for "sheep" or "lamb" only	1 1 1 1	_____ _____ _____ _____
Total Score for this Page	19	_____

Date ____/____/____

ID: _____

	Points Avail.	Points Earned
8. Have the patient repeat these statements. “Say this: ‘No ifs, ands, or buts’.” Stress s’s when you say it, s’s must be repeated back for a correct response. 1 point for each complete repetition on the first trial. Repeat only poorly presented.	1	_____
“Say this: ‘Methodist episcopal’.” 1 point for each complete repetition on the first trial. Repeat only poorly presented.	1	_____
9. Ask these questions: “Who is the President of the United States right now?” 1 point for correct first and last name.	1	_____
“Who is the Vice-President?” 1 point for correct first and last name.	1	_____
10. State: “With your finger, tap 5 times on the part of the phone you speak into.” 2 points if 5 taps are heard 1 point if subject taps more or less than 5 times	2 1	_____ _____
11. State: “I’m going to give you a word and I want you to give me its opposite. For example, the opposite of hot is cold. What is the opposite of ‘west’?” 1 point for “east”	1	_____
“What is the opposite of ‘generous’?” 1 point for “selfish,” “greedy,” “stingy,” “tight,” “cheap,” “mean,” “meager,” “skimpy,” or other good antonym	1	_____
Total Score for this Page	8	_____
Total Score for Page 1	14	_____
Total Score for Page 2	19	_____
Total Score	41	_____

<u>Mental Status Exclusion</u>		
Score of 30 OR Less	Yes	No
If YES, STOP interview here. Go to “Not-Eligible” section.		

A.1-10

Date ____/____/____

ID: _____

Modified Everyday Cognition Scale
(Farias, 2007; Allen 2009)

Instructions to Responder:

Read aloud: “Now I will ask you to rate your ability to perform certain everyday tasks **NOW**, as compared to your ability to do these same tasks 10 years ago. Try to remember how you were 10 years ago and indicate any change you have seen.”

Check the box that fits their responses to the following sentence:

Compared to 10 years ago, I have noticed a change in...

	No problems	Yes I have problems
1. Planning the sequence of stops on a shopping trip.	<input type="checkbox"/>	<input type="checkbox"/>
2. The ability to anticipate weather changes and plan accordingly (i.e. bring a coat or umbrella).	<input type="checkbox"/>	<input type="checkbox"/>
3. Developing a schedule in advance of anticipated events.	<input type="checkbox"/>	<input type="checkbox"/>
4. Thinking things through before acting.	<input type="checkbox"/>	<input type="checkbox"/>
5. Thinking ahead.	<input type="checkbox"/>	<input type="checkbox"/>
6. Keeping living and work space organized.	<input type="checkbox"/>	<input type="checkbox"/>
7. Balancing the checkbook without error.	<input type="checkbox"/>	<input type="checkbox"/>
8. Keeping financial records organized.	<input type="checkbox"/>	<input type="checkbox"/>
9. Prioritizing tasks by importance.	<input type="checkbox"/>	<input type="checkbox"/>
10. Keeping mail and papers organized.	<input type="checkbox"/>	<input type="checkbox"/>
11. Using an organized strategy to manage a medication schedule involving multiple medications.	<input type="checkbox"/>	<input type="checkbox"/>
12. The ability to do two things at once.	<input type="checkbox"/>	<input type="checkbox"/>
13. Returning to a task after being interrupted.	<input type="checkbox"/>	<input type="checkbox"/>
14. The ability to concentrate on a task without being distracted by external things in the environment.	<input type="checkbox"/>	<input type="checkbox"/>
15. Cooking or working and talking at the same time.	<input type="checkbox"/>	<input type="checkbox"/>

Subsample Eligibility for Compensatory Behavior Observation (video-recording) in the UNC SON Biobehavioral Laboratory:

If the responder indicated difficulty by answering yes 5 or more items, ask the responder:

“A component of this study is looking at how you maintain your thinking and memory abilities.

A way to do this is through video-recording in a laboraoty setting at the UNC School of Nursing. Would you consider doing the study procedures in the UNC School of Nursing so that we may video-record your thinking and memory abilities.” **Yes** **No**

IF yes, schedule with UNC SON BBL, otherwise schedule with neuro-oncology clinic.

A.1-11

Date ____/____/____

ID: _____

Not-Eligible Section

If the subject is deemed ineligible for study, state:

“Thank you for you time today. We appreciate your interest. However some health conditions or medications may interfere with the results with the study tests. We are not able to enroll you in the study, but greatly appreciate your time and effort.”

Date ____/____/____ ID: _____

COMPLETION OF TELEPHONE ELIGIBILITY

Script
Thank you for answering all of these questions. You may enroll to participate in the study by completing more study questions that will be done at the UNC School of Nursing or Neuro-Oncology Clinic. What upcoming date or days of the week are you able to come to the School of Nursing or Neuro-Oncology Clinic?

Date 1: ____/____/____	Time: ____:____
Date 2: ____/____/____	Time: ____:____

Enter these dates to schedule the study procedures to check for availability with the UNC SON BBL calendar on the Scheduling Form, next page.

Instructions to the Participant
You will receive a subject information packet that provides a letter telling you the scheduled study date and time, instructions for transportation and parking with a map, an overview of the study and things you will need to do the night before the study. I want you to read over all these instructions when you received them in the mail and call me if you have any questions.

What address would you like for us to mail this information packet to?

Street or Box: _____

City: _____

State: _____ Zip: _____

It is expected that you will complete the study within three hours, depending on your needs. While you are with us, you will be provided some nourishing refreshments. Please bring any medications that you need to take during those times with you.

Would you like to have a reminder call the day before you come in for the research study?

Yes	No
------------	-----------

If yes, ask them for two phone numbers of their choice to contact them.

Contact 1: (____) _____ - _____

Contact 2: (____) _____ - _____

We thank you for your interest in this study and your willingness to participate. I look forward to working with you in this research study at the UNC School of Nursing.

SUBJECT INFORMATION PACKET

Instructions for sending the Subject Information Packet

1. After consulting with the UNC SON Biobehavioral Laboratory calendar to schedule the subject, you will send the Subject Information Packet to the subject.

This packet contains:

1. Letter to subject with their scheduled study date and time
2. Instructions labeled “Overview of the study”
3. Instructions labeled “What you should know before coming for the study”
4. Instruction sheet labeled “Directions”
5. Map of the UNC Campus

2. Be sure to address the letter to the subject.
3. Be sure to insert in the letter (Item #1) the scheduled date and time.
4. Make a copy of the letter to be retained in the subject file which will be kept in the locked cabinet.



March 22, 2014

«Title» «First» «MidI» «Last»
«Street_1»
«City», «State» «Zip5»«Zip9»

Dear «Title» «Last»:

Thank you for participating in our research study titled “Pilot Study of Sensory Information Processing and Motor Processing: Relationship to Executive Control in Adults with Primary Brain Tumors.” We’re very excited that you called us about this important study and we’re looking forward to seeing you for your scheduled appointment in the University of North Carolina, School of Nursing Biobehavioral Laboratory. We presently have you scheduled to come in as follows:

Date: «BDay1», «BDate1», at
Time: «BTime2»
Place: «BPlace3»

I have enclosed materials that provide more detailed information that I hope you will find helpful. Please pay special attention to the page entitled, “What you should do now.”

If you indicated that you prefer to receive a reminder call prior to the study, I will call you at the indicated number and date to make sure that you received this packet and to answer any questions you may have. Please bring this packet with you when you come for your study, because you will be receiving other information that you may want to keep together. In the meantime, please feel free to phone me (919-883-7002) with any questions or concerns you might have. We’ll look forward to seeing you then!

Sincerely,

Deborah H. Allen, RN, MSN, FNP-BC, AOCNP
Predoctoral Student, School of Nursing
University of North Carolina at Chapel Hill

Date: ____/____/____

ID: _____

OVERVIEW OF THE STUDY PROTOCOL

The study will be conducted at:

- _____ the Biobehavioral Laboratory at the UNC School of Nursing, located in Carrington Hall.
- _____ the Neuro-Oncology Clinic at UNC Lineberger Cancer Center
- _____ the Tisch Brain Tumor Center at Duke Cancer Institute

We will ask that you report to the lab at the scheduled time of _____ as indicated in your letter. The study will take 3 hours.

You will be given time for breaks, as well as snacks and drinks. You may opt to bring in food, drinks, or items like pillows to make sitting more comfortable. Let us know if you have any special needs that we should know; you may call us at 919-883-7002.

What You Should Do Now

1. Please let us know if you have any food allergies or other dietary requirements of which we might not already be aware. You may call us at (919) 883-7002.
2. Please let us know if you plan to park in the hospital parking deck so that we may have a parking voucher prepared for you. If you are scheduled to perform the study at the UNC School of Nursing, let us know if you plan to drive so that we can reserve a parking space for you (see directions on the following page). You may reach us by telephone at (919) 883-7002.

If you would prefer not to drive, you may ride one of the Chapel Hill Transit busses free of charge. There is a bus stop located directly in front of the School of Nursing. If you are having difficulty in arranging for transportation, please call so that we may help. If you would like for us to do this, please call us as soon as possible (919-883-7002) so we may have enough time to make plans for your transportation.

Date: ____/____/____

ID: _____

On the day of your appointment:

If you are going to be late or need to cancel your study,
please call Deborah Allen directly
at phone number 919-883-7002.

What You Should Know Before Coming In For Your Study

1. On the day before the study, you should do the things that you would regularly do. This includes going to bed and getting up at your usual times, eating what you usually eat, and taking your medications as prescribed by your doctor. (The exceptions to this are listed below under the heading “What we ask you to avoid.”)
2. If you have been taking cold medicines the week before the study, please call us to discuss rescheduling the study procedures.
3. Do not bring any valuables (large amounts of money or jewelry) that could be stolen. Although this is unlikely to occur, it is better to be safe than sorry.
4. Your family or friends may come with you to see the laboratory.

What We Ask You To Avoid

We would ask that you avoid the following so we get the best recordings possible:

- a. Any alcoholic beverages after dinner (including wine and beer) on the night before coming in for your study,
- b. Medications that help you sleep or cold medications for 24 hours before coming in for your study, and
- c. Do not smoke any tobacco products for 4 hours before coming in for your study.

Date: ____/____/____

ID: _____

Directions to the UNC School of Nursing Biobehavioral Laboratory

1. North on 15-501 Bypass (from Burlington/Carrboro): Take the Chapel Hill-Pittsboro exit. At the stoplight, make a left onto South Columbia Street. Follow the road up the hill and go through the intersection of South Columbia and Manning Drive. Start to get into the right lane and turn right at the stop light onto Medical Drive.

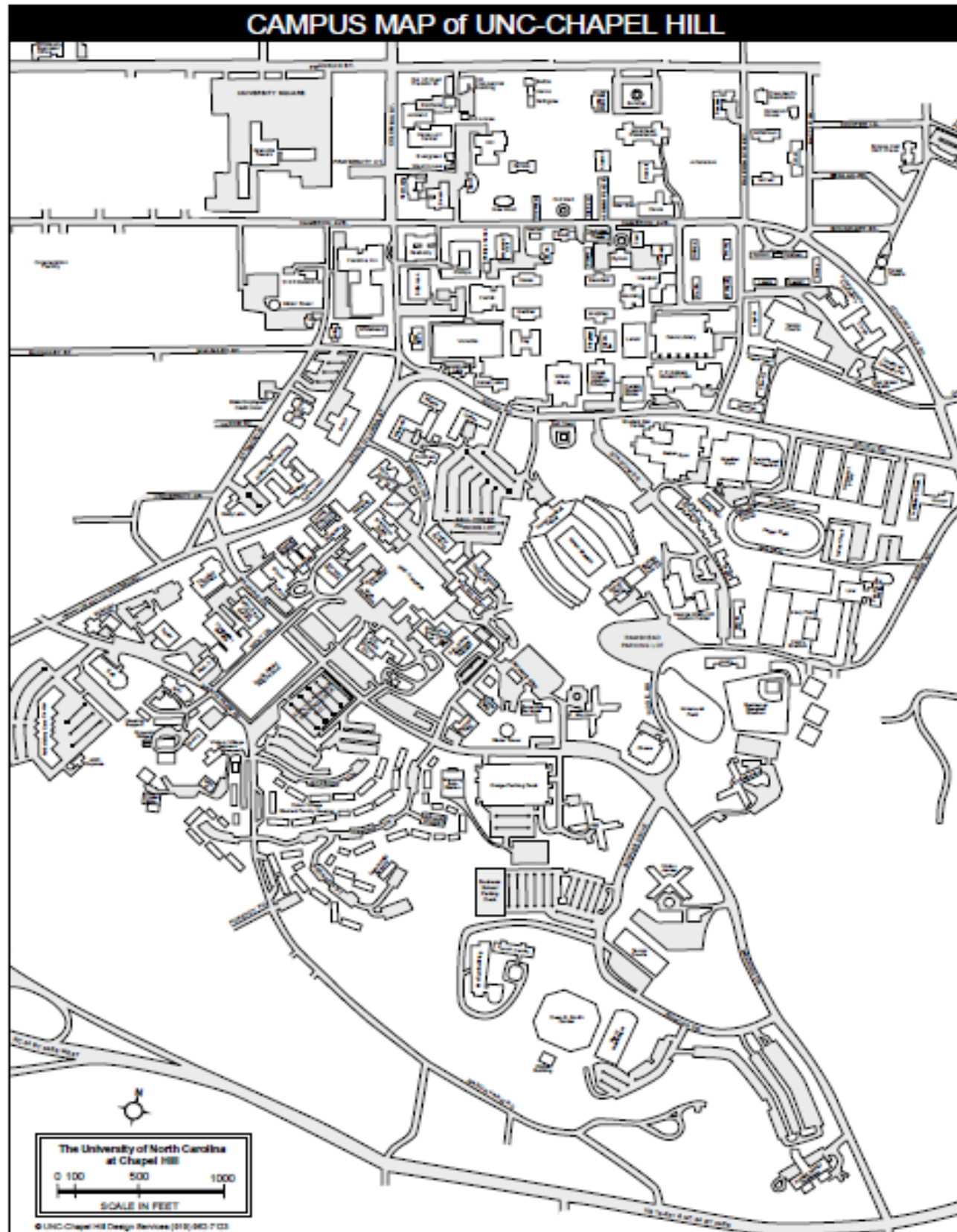
2. South on 15-501 Bypass (from University Mall/Durham): From University Mall, get ready to make a right turn at the Highway 54 exit (as you head into campus this becomes South Road). At the first stoplight at the top of the hill you will see the Institute of Law to your left. Continue going straight on South Road. At the second stoplight you will see Fetzer Gymnasium to your left and Raleigh Road to your right. You'll next see Student Stores on your right, and the Bell Tower on your left. Continue straight, through another 2 stoplights past Manning Drive. Make a left turn onto Pittsboro Road. Get in the left turn lane as this will bring you to South Columbia and Manning Drive. Take a left onto Manning Drive at the stop light. Start to get into the right lane and turn right at the stop light onto Medical Drive.

3. From Highway 54 (RTP or Raleigh): Take Highway 54 toward campus, go under the 15-501 bypass, and continue up the hill (as you head into campus, Hwy 54 becomes South Road). At the first stoplight at the top of the hill you will see the Institute of Law to your left. Continue going straight on South Road. At the second stoplight you will see Fetzer Gymnasium to your left and Raleigh Road to your right. You'll next see Student Stores on your right, and the Bell Tower on your left. Continue straight, through another 2 stoplights past Manning Drive. Make a left turn onto Pittsboro Road. Get in the left turn lane as this will bring you to South Columbia and Manning Drive. Take a left onto Manning Drive at the stop light. Start to get into the right lane and turn right at the stop light onto Medical Drive.

4. From Downtown Chapel Hill (Coming from Franklin Street): From the intersection of Franklin and South Columbia Streets (Spanky's is on this corner), take South Columbia into campus. At the second stop light, make a right onto Cameron Avenue and get into the left lane. At the next stoplight, make a left onto Pittsboro Street. Then make a left again at the next stop light, which will be at McCauley Street. Cross South Columbia Street (at this point McCauley Street becomes South Road). Make a right at the next stop light, which is Bell Tower Drive (which will take you into the Bell Tower parking area).

Date: ____/____/____

ID: _____



APPENDIX E: LABORATORY SCREENING

Date: ____/____/____

ID: _____

A.4 Laboratory Intake Screen & Mini-Consent

LABORATORY INTAKE SCREEN

Subject Preparation

For study procedures in the UNC School of Nursing: Give the subject a tour of the BBL including the test area, bathroom, and nourishment station. Offer them something to drink and have them seated in the testing interview area. Make sure the door is closed to the BBL and the interview room prior to proceeding with the Laboratory Intake Screen.

For study procedures in the Neuro-Oncology Clinic: Make sure the subject has had an opportunity to use the restroom and have some nourishment. Offer them something to drink and have them seated in the provided clinic room. Make sure the door has a sign "Do Not Disturb" to prevent interruptions.

Mini Consent

Ask the potential subject:

"Before we start, I'd like to ask you a few questions and would like to perform a brief exam on your ability to process and think. This is to make sure that you have had not changes in your health status since we spoke on the telephone. There are some health conditions or problems with thinking that may keep you from participating in the study. If you are not eligible to be involved in the study, I will shred all of the information that you have given me over the phone and what we have done today and you will not receive the \$25 for your time and travel. Is it okay to proceed with the questions and test now?"

If yes, proceed with the four questions below.

If no, stop the interview and thank the subject for coming.

Escort the subject and ask if they need directions back to their parking area.

Adjunct to Pre-Study Instrument

"Since we've last talked have you had any of the following:

1. Surgical procedures requiring general anesthesia? **Yes** **No**

2. Please tell me about any new medicine you are taking.

List the medications: _____

Are any of these drugs a sedative hypnotic or cold medication? **Yes** **No**

3. Have you had alcohol in the last 24 hours? **Yes** **No**

4. Have you smoked in the last 4 hours? **Yes** **No**

If yes to any of the question, reschedule the research study time.

Date: ____/____/____ Time: ____:____

If no, proceed to the Mini-Mental Status Examination, next page.

1

A.5 Mini-Mental Status Examination

The Mini-Mental State Examination
(Folstein et al., 1975)

Instructions to Patient: “Now I’d like you to answer some questions and follow some Instructions. Do your best to respond to each question or instruction. Some will seem very simple and some will be more difficult.”

Code in margin any question that patient refuses to answer (9) or is physically unable to answer (8).
Do not include the 8’s and 9’s in the total score, but do indicate reason code was used (where applicable).

	Points Avail.	Points Earned
Orientation		
1. Ask first: “What is the day, date and season?”		
If information is omitted, ask as needed:		
Year	1	_____
Season?	1	_____
Date?	1	_____
Day?	1	_____
Month?	1	_____
If patient can’t answer three of these correctly ask, “What part of the day is this?” (morning, afternoon, evening, night). Code response at end of MMSE total (see item #13)		
2. Ask: “What is the name of this place and where is it located?”		
If information is omitted, ask as needed:		
State?	1	_____
County?	1	_____
Town or City?	1	_____
Building?	1	_____
Floor?	1	_____
Registration		
3. Name three objects, taking one second to say each.		
“I am going to give you a list of 3 words. I want you to listen carefully then repeat them back to me. The words are book, house, candle . Please tell me the three words.”		
Book	1	_____
House	1	_____
Candle	1	_____
(Score responses on first try. Then repeat objects until all are learned.)		
Tell patient, “Try to remember those objects because I’m going to ask you to repeat them from memory later.”		

Attention and Calculation

4. Serial Sevens. Give one point for each correct answer.
 “I want you to start with the number 100, subtract 7, and tell me
 your answer. So how much is 7 from 100? ____ (93)
 Now keep subtracting seven until I tell you to stop.”
 (Stop after five answers; you may prompt after each answer.)
 Record responses: _____
 Correct Responses: 93 86 79 72 65 5 _____

 If patient missed any calculation, then ask the following:
 “Now I am going to spell a word forward and I want you to spell
 it backwards. The word is ‘world,’ W-O-R-L-D. Spell ‘world’
 backwards.”
 (Answer: D-L-R-O-W; repeat if necessary but not after spelling starts.)
 Record responses: _____

Recall

5. Ask for the names of the three objects learned in Question 3.
 (Give 1 point for each correct answer.)
 (book, house, candle) : _____ 3 _____

Language

6. Point to a pencil & a watch. Have patient name them as you point.
 “What do you call this?” “What is this?” 2 _____
7. Have the patient repeat: “No ifs, ands, or buts.” 1 _____
 (Stress s’s when you say it, s’s must be repeated back for a correct response.)
8. Have the patient follow a three-step command (using next page):
 “Take this paper in your right hand, fold the paper in half with
 both hands, and put the paper on the bed (floor, etc.).” 3 _____
9. Have the patient read and obey the following from the next page:
 “CLOSE YOUR EYES.” 1 _____
10. Have the patient write a simple sentence of his or her choice. 1 _____
 (The sentence should contain a subject and a verb and should make sense.
 Ignore spelling errors when scoring.)
11. Put the Bender Gestalt design before patient and ask patient to,
 “Copy this shape.” 1 _____
 (Give one point if all sides and angles are preserved and if the intersecting
 sides form a quadrangle.)
12. Total Score (sum 0’s & 1’s). 30 _____

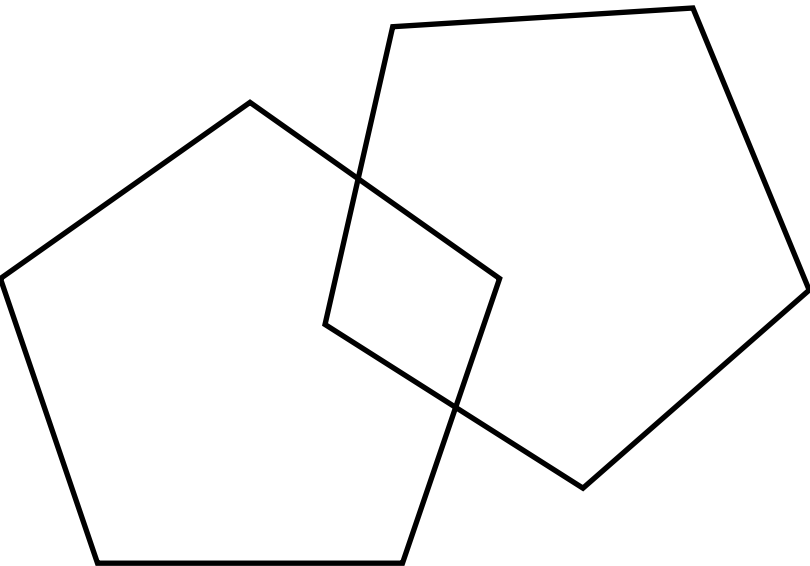
Date: ____/____/____

ID: _____

Close your eyes.

Date: ____/____/____

ID: _____



Date: ____/____/____

ID: _____

A.6 Subject Eligibility Form

SUBJECT	ELIGIBILITY FORM			
Eligibility Criteria for Adult with Primary Brain Tumor	TS / Lab Screen	Yes	No	N/A
Age 30 to 65 years old	TS			
Read and write English language	TS			
Primary Brain Tumor: 1. Treated with prior chemotherapy or radiation therapy 2. No signs of paresis or aphasia 3. Has stable tumor status determined by neuro-oncologist	TS			
Stable seizure status for last six months with no antiepileptic medication changes in the last six months	TS			
TICS > 30 points	TS			
MMSE > 24 points	Lab			
Signed informed consent	Lab			
Exclusion Criteria <i>Exclude subject is yes to any of these</i>				
General anesthesia within the last six months	TS			
Paresis or Aphasia	TS			
Known neurologic or cardiovascular disorders listed in Health History Screen (Example: Parkinson's disease, multiple sclerosis, Alzheimer's disease, CVA, immune disorders, depression, sleep disorder)	TS			
Medications: Dopaminergics (Pramipexole, Ropinirole, Carbidopa, Levodopa) Major anticholinergics (Example: Phenothiazines, Antiparkinson meds) Alzheimer's medications (Aracept, Remeril, Exelon, Namenda)	TS			
Chemotherapy: Carmustine, Lomustine (CeeNU), Carboplatin, Temozolomide (Temodar), Etoposide (Vepesid, VP-16), Irinotecan (CPT-11, Camptosar), Procarbazine (Matulane)	TS			
Sleep disorder/apnea or sedative hypnotic the night before	TS & Lab			
Had cold meds, alcohol night before; tobacco 4 hr before	Lab			

TS=telephone screen; N/A=not applicable

Eligibility Criteria for Adult Healthy Control	TS / Lab Screen	Yes	No	N/A
Age 30 to 65 years old	TS			
Read and write English language	TS			
TICS > 30 points	TS			
MMSE > 24 points	Lab			
Signed informed consent	Lab			
Exclusion Criteria <i>Exclude subject is yes to any of these</i>				
General anesthesia within the last six months	TS			
Paresis or Aphasia	TS			
Known neurologic or cardiovascular disorders listed in Health History Screen (Example: Parkinson's disease, multiple sclerosis, Alzheimer's disease, CVA, immune disorders, depression, sleep disorder)	TS			
Medications: Dopaminergics (Pramipexole, Ropinirole, Carbidopa, Levodopa) Major anticholinergics (Example: Phenothiazines, Antiparkinson meds) Alzheimer's medications (Aracept, Remeril, Exelon, Namenda)	TS			
Sleep disorder/apnea or sedative hypnotic the night before	TS & Lab			
Had cold meds, alcohol night before; tobacco 4 hr before	Lab			

APPENDIX F: STUDY BATTERY

Date: ____/____/____

ID: _____

1. Subject Packet
 - a. Demographic Information
 - b. Older Adults Resource Services Activities of Daily Living Scale
 - c. Center for Epidemiological Studies Depression Scale
 - d. Functional Assessment of Cancer Therapy – Brain Tumor
 - e. MD Anderson Symptom Inventory – Brain Tumor
2. Investigator Packet
 - a. Health Information Form
 - b. Everyday Cognitions Scale
 - c. EXIT-25
 - d. North American Adult Reading Test
 - e. Trails-Making Test Parts A and B
 - f. Controlled Word Association Test
 - g. Hopkins Verbal Learning Test
 - h. Arrow Flanker Test
 - i. Symbol Digit Modalities Test
 - j. Visual Analog Scale for Subject Rating on Instrument Difficulty

Date: ____/____/____

ID: _____

C.1 Subject Packet

Instructions for Subject Packet

The following questionnaires are to be completed by the subject:

- a. Demographic Information Sheet
- b. Older Adults Resource Services Activities of Daily Living Scale
- c. Center for Epidemiological Studies Depression Scale
- d. Functional Assessment of Cancer Therapy – Brain Tumor
- e. MD Anderson Symptom Inventory – Brain Tumor

Provide a pencil with the forms for the subject.

Be available to answer any questions.

When the subject indicates that they are done, review the form to make sure all items are answered.

The subject may indicate that they prefer to take the forms home to complete.

If this is the case, provide them a stamped return envelope.

Subject decided to completed forms here	_____ Yes	_____ No
Subject opted to take forms with them to return	_____ Yes	_____ No
Forms are returned and completed	_____ Yes	_____ No

Record scores on data collection forms for data entry.

Check the data collection forms for accuracy.

File in subject record and store in locked file cabinet.

Date: ____/____/____

ID: _____

C.1.a. Demographic Information

DEMOGRAPHIC INFORMATION
(Carlson, 1999)

1.

Race

1=Caucasian/white

2=African American

3=American Indian

4=Hispanic

5=Asian/Pacific islander

6=Other

2.

Gender (1=male, 2=female)

3.

How many grades did you complete in school?

(Record highest grade)

1-12=Grade school/High school

12=GED/High school diploma

13=Technical only

14=Baccalaurean only

15=Graduate School

16=Doctorate

4.

What activities best describe what you typically do:

1=employed, full time

2=employed, part time

3=retired

4=never had a job outside home

5=disabled

6=other

5.

Marital Status

1=married, living with spouse

2=married, separated

3=single, living alone

4=single, living with someone

5=single, recently widowed (2 years)

6.

Age (rounded to the nearest year)

7.

What types of jobs have you had?

Date: ____/____/____

ID: _____

C.1.b Older Adults Resource Services Activities of Daily Living Scale

Older Adults Resource Services Activities of Daily Living Scale

(Fillenbaum, 1978)

Instructions: The following questions are about some of the activities of daily living (ADLs), the things that we all need to do as part of our daily lives. I would like to know if, within the last month, you could do these activities without any help at all, or if you needed some help to do them, or if you couldn't do them at all. Please write the number for the best answer in the space provided.

Physical ADLS

1. Can you eat . . . _____
2 = without help (able to feed yourself completely),
1 = with some help (need help with cutting, etc.),
0 = or are you completely unable to feed yourself?
2. Can you dress and undress yourself . . . _____
2 = without help (able to pick out clothes, dress and undress yourself),
1 = with some help,
0 = or are you completely unable to dress and undress yourself?
3. Can you take care of your own appearance, for example combing your hair or shaving . . . _____
2 = without help,
1 = with some help,
0 = or are you completely unable to maintain your appearance yourself?
4. Can you walk . . . _____
2 = without help (except for a cane),
1 = with some help from a person or using a walker, crutches, etc.,
0 = or are you completely unable to walk?
5. Can you get in and out of bed . . . _____
2 = without any help (without grabbing hold of the bedstand or aids),
1 = with some help (either from a person, grabbing hold of a bedstand or with the aid of some device),
0 = or are you totally dependent on someone else to lift you?
6. Can you take a bath or shower . . . _____
2 = without help,
1 = with some help (need help getting in and out of the tub, or need special attachment on the tub),
0 = or are you completely unable to bathe yourself?
7. Do you ever have trouble getting to the bathroom on time? _____
2 = no
1 = yes

Date: ____/____/____

ID: _____

If yes, how often do you wet our soil yourself? _____

1 = once or twice a week?

0 = three times a week or more?

Independent ADLS

8. Can you use the telephone . . . _____

2 = without help, including looking up the number and dialing,

1 = with some help (could answer phone or dial operator in an emergency, but need a special phone or help),

0 = or are you completely unable to use the telephone?

9. Can you get to places out of walking distance . . . _____

2 = without help (travel alone on buses, taxis, or drive your own car),

1 = with some help (need someone to help you or be with you when traveling),

0 = or are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

10. Can you go shopping for groceries or clothes (assuming you have transportation) . . . _____

2 = without help (take care of all shopping needs yourself),

1 = with some help (need someone to go with you on all shopping trips),

0 = or are you completely unable to do any shopping?

11. Can you prepare your own meals . . . _____

2 = without help (plan and cook full meals yourself),

1 = with some help (could prepare something but unable to cook full meals yourself),

0 = or were you completely unable to prepare your meals?

12. Can you do your housework or yardwork . . . _____

2 = without help (scrub floors, cut grass, etc.),

1 = with some help (could do light work but need help with heavy work),

0 = or are you completely unable to do any of this type of work?

13. Can you take your own medicine . . . _____

2 = without help (in the right dose, at the right time),

1 = with some help (able to take medicine if someone prepares it for you or reminds you to take it),

0 = or are you completely unable to take your medicine?

14. Can you handle your own money... _____

2 = without help (write checks, pay bills, etc.),

1 = with some help (could manage day-to-day buying but need help with managing your checkbook or paying your bills),

0 = were you completely unable to handle money?

Total Score _____

Date: ____/____/____

ID: _____

C.1.c Center of Epidemiology Screen for Depression

Mood Screen

Please indicate how often in the past seven days you have agreed with the following statements

During the past week:	Rarely (<1 day)	Some of the time (1-2 days)	Occasionally (3-4 days)	Most of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I did not feel like eating; my appetite was poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt that I was just as good as other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I had trouble keeping my mind on what I was doing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I felt depressed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I felt that everything I did was an effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I felt hopeful about the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I thought my life had been a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I felt fearful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. My sleep was restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I was happy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I talked less than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I felt lonely.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. People were unfriendly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I enjoyed life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I had crying spells.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I felt sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I felt that people disliked me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I could not get "going."	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

C.1.d Functional Assessment of Cancer Therapy – Brain Tumor Module

Instructions

Below are statements that other people with your illness have said are important.
Please mark the box that indicates your response as it applies to the past 7 days.

	Not at all	A little bit	Some- what	Quite a bit	Very Much
Physical Well-being	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. I have a lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I have nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Because of my physical condition, I have trouble meeting the needs of my family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I have pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I am bothered by side effects of treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I feel ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I a forced to spend time in bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Social/Family Well-Being	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. I feel close to my friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I get emotional support from my family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I get support from my friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. My family has accepted my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I am satisfied with family communication about my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I feel close to my partner (or the person who is my support)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I am satisfied with my sex life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Emotional Well-Being	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. I feel sad	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I am satisfied with how I am coping with my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I am losing hope in the fight against my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I feel nervous	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I worry about dying	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I worry that my condition will get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Functional Well-Being	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. I am able to work (inlcude work at home)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. My work (include work at home) is fulfilling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I am able to enjoy life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I have accepted my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I am sleeping well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I am enjoying the things I usually do for fun	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I am content with the quality of my life right now	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

Additional Concerns Instructions:

Please mark the box that indicates your response as it applies to the past 7 days.

	Not at all	A little bit	Some- what	Quite a bit	Very Much
Additional Concerns	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. I am able to concentrate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I have had seizures (convulsions)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I can remember new things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I get frustrated that I cannot do things I used to	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I am afraid of having a seizure (convulsion)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I have trouble with my eyesight	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I feel independent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I have trouble hearing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I am able to find the right word(s) to say what I mean	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I have difficulty expressing my thoughts	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. I am bothered by the change in my personality	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I am able to make decisions and take responsibility	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I am bothered by the drop in my contribution to the family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I am able to put my thoughts together	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. I need help in caring for myself (bathing, dressing, eating, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I am able to put my thoughts into action	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I am able to read like I used to	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I am able to write like I used to	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I am able to drive a vehicle (my car, truck, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I have trouble feeling sensations in my arms, hands, or legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. I have weakness in my arms or legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. I have trouble with coordination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. I get headaches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

C. 1.e MD Anderson Symptom Inventory – Brain Tumor Module

MD Anderson Symptom Inventory-Brain Tumor Module

Instructions:

Part 1. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	As Bad As You Can Imagine											
	Not Present	0	1	2	3	4	5	6	7	8	9	10
1. Your pain at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Your fatigue (tiredness) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Your nausea at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Your disturbed sleep at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Your feeling of being distressed (upset) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Your shortness of breath at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Your problem with remembering things at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Your problem with lack of appetite at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Your feeling drowsy (sleepy) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Your having a dry mouth at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Your feeling sad at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Your vomiting at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Your numbness or tingling at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Your weakness on one side of the body at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Your difficulty understanding at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Your difficulty speaking (finding the words) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Your seizures at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Your difficulty concentrating at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Your vision at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Your change in appearance at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Your irritability at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

	<div> <div>Not Present</div> <div>As Bad As You Can Imagine</div> </div>										
	0	1	2	3	4	5	6	7	8	9	10
16. Your difficulty speaking (finding the words) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Your seizures at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Your difficulty concentrating at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Your vision at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Your change in appearance at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Your irritability at its WORST?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 2. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	<div> <div>Did Not Interfere</div> <div>Interfered Completely</div> </div>										
	0	1	2	3	4	5	6	7	8	9	10
23. General activity?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Mood?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Work (including work around the house)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Relations with other people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Walking?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Enjoyment of life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

C.2 Investigator Packet

Instructions for Investigator Packet

The following evaluations are to be completed by the researcher:

- a. Health Information Form
- b. Everyday Cognitions Scale
- c. EXIT-25
- d. North American Adult Reading Test
- e. Trails-Making Test Parts A and B
- f. Controlled Word Association Test
- g. Hopkins Verbal Learning Test
- h. Arrow Flanker Test
- i. Symbol Digit Modalities Test
- j. Visual Analog Scale for Subject Rating on Instrument Difficulty

Date: ____/____/____

ID: _____

C.2.a Health Information Form

Health Information

I. Vital Signs

Have the subject sitting comfortably. Inform the subject that you are going to take their vital signs, starting with their blood pressure in their right arm. Loose any restrictive clothing on the right arm (roll up sleeve of shirt if necessary).

- 1. Place the Dynamap 1846 SX cuff on the right arm and begin the machine.
- 2. Place the Nonin1500 pulse oximeter on the middle finger of the left hand.
- 3. Take oral temperature with the IVAC thermometer.
- 4. Record vital signs below.

Heart rate	_____	_____	_____
Systolic blood pressure	_____	_____	_____
Diastolic blood pressure	_____	_____	_____
Respiratory rate	_____	_____	
Oral Temperature to nearest .1 degree Fahrenheit	_____	_____	_____
Oxyhemoglobin saturation:	_____	_____	%

Date: ____/____/____ ID: _____

II. Key Medical-Related Events

Ask the subject the following:
“Over the past three months, have you had any of the following?”

KEY MEDICAL RELATED EVENTS	YES	NO
General:		
Falls		
Fainting spells /blacking out		
Dizziness		
Numbness/weakness		
Chills/fever		
Headaches or migraines		
Seizures		
Orthnopia		
Shortness of breath		
Chest pain		
Tachycardia		
Leg swelling		
#Pillows to sleep		
Numbness/weakness		
Upper respiratory infection in past week?		
Coughing		
Hemoptysis		
Wheezing		
Shortness of breath in the past week		
Weakness of any extremity		
Problems walking		
Joint problems		
Difficulty with dexterity (button clothes, etc)		
Self-Report Health Rating: How would you say that your health at this time compares with your health one month ago? Is it: 3=better than 1 month ago 2=about the same as 1 month ago 1=worse than 1 month ago	_____	

If subject is in the healthy control group, have the subject proceed with the Everyday Cognitions Scale.

If subject is in the primary brain tumor group, complete the following set of questions below. Upon completion, proceed to the Everyday Cognitions Scale.

ID: _____

1. When were you diagnosed with your tumor? _____

2. What kind of tumor was it?

_____ astrocytoma

_____ oligodendroglioma

_____ anaplastic astrocytoma

_____ glioblastoma multiforme

_____ other: _____

3. Do you know the location of the tumor?

<input type="checkbox"/> right side	<input type="checkbox"/> frontal
<input type="checkbox"/> left side	<input type="checkbox"/> parietal
	<input type="checkbox"/> temporal
	<input type="checkbox"/> occipital
	<input type="checkbox"/> cerebellum
	<input type="checkbox"/> brain stem

4. What kind of surgical procedure did you have when you were diagnosed?
 _____ biopsy
 _____ partial surgical resection
 _____ gross total resection

5. Date of surgery or surgeries: _____

6. What kind of treatments did you have for your tumor?
 ____ radiation therapy
 ____ stereotactic radiosurgery
 ____ stereotactic radiotherapy

7. Date of radiation therapies: _____

8. Did you have chemotherapy? _____ yes _____ no
If yes, duration _____

Date: ____/____/____

ID: _____

C. 2.b Everyday Cognition Scale

Everyday Cognition Scale (Farias, 2007)

Instructions

Please rate your ability to perform certain everyday tasks **NOW**, as compared to your ability to do these same tasks 10 years ago. Try to remember how you were 10 years ago and indicate any change you have seen. Check the box that fits your response to the following sentence:

Compared to 10 years ago, I have noticed a change in...

	Better or no change	Questionable or occasionally worse	Consistently a little worse	Consistentl y much Worse	Don't know
1. Remembering a few shopping items without a list.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Remembering things that happened recently (such as recent outings, events in the news).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Recalling conversations a few days later.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Remembering where she/he has placed objects.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Repeating stories and/or questions.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Remembering the current date or day of the week.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Remembering he/she has already told someone something.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Remembering appointments, meetings, or engagements.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Forgetting the names of objects or people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Verbally giving instructions to others.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Finding the right words to use in a conversation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Communicating thoughts in a conversation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Following a story in a book or on TV.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Understanding the point of what other people are trying to say.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Remembering the meaning of common words.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Describing a program he/she has watched on TV.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

	Better or no change	Questionably or occasionally worse	Consistently a little worse	Consistently much worse	Don't know
17. Following a map to find a new location.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Reading a map and helping with directions when someone else is driving.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Finding one's car in a parking lot.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Finding the way back to a meeting spot in the mall or other location.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Finding his/her way around a familiar neighborhood.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Finding his/her way around a familiar store.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Finding his/her way around a house visited many times.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Planning the sequence of stops on a shopping trip.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. The ability to anticipate weather changes and plan accordingly (ie, bring a coat or umbrella).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Developing a schedule in advance of anticipated events.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Thinking things through before acting.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Thinking ahead.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Keeping living and work space organized.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Balancing the checkbook without error.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. Keeping financial records organized.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. Prioritizing tasks by importance.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33. Keeping mail and papers organized.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Using an organized strategy to manage a medication schedule involving multiple medications.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35. The ability to do two things at once.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36. Returning to a task after being interrupted.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
37. The ability to concentrate on a task without being distracted by external things in the environment.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
38. Cooking or working and talking at the same time.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

C.2.c EXIT-25

EXIT-25 (Royall, 1995)

EXIT EXIT25 (page 1 of 11)																	
<p>INDICATE ONE RESPONSE FOR EACH QUESTION BY PLACING A MARK IN THE APPROPRIATE NUMBERED BOX.</p> <div style="border: 1px solid black; padding: 2px; margin-bottom: 10px;"> Mark appropriate box</div> <p>1. NUMBER-LETTER TASK</p> <p>"I'd like you to say some numbers and letters for me like this."</p> <p style="padding-left: 40px;">"1-A, 2-B, 3-what would come next?"</p> <p style="padding-left: 40px;">"C"</p> <p>"Now you try it starting with the number 1. Keep going until I say "stop".</p> <table style="margin-left: auto; margin-right: auto;"><tr><td style="padding: 0 10px;">1</td><td style="padding: 0 10px;">2</td><td style="padding: 0 10px;">3</td><td style="padding: 0 10px;">4</td><td style="padding: 0 10px;">5</td><td style="padding: 0 10px;">"Stop"</td></tr><tr><td style="padding: 0 10px;">A</td><td style="padding: 0 10px;">B</td><td style="padding: 0 10px;">C</td><td style="padding: 0 10px;">D</td><td style="padding: 0 10px;">E</td><td></td></tr></table> <p>SCORE: 0 <input type="checkbox"/> No errors 1 <input type="checkbox"/> Complete task with prompting (or repeat instruction) 2 <input type="checkbox"/> Doesn't complete task</p>	1	2	3	4	5	"Stop"	A	B	C	D	E		<p style="text-align: center;">Examiner's Initials</p> <div style="border: 1px solid black; padding: 5px; text-align: center; margin: 5px auto; width: 80%;"><div style="display: flex; justify-content: space-around; height: 40px;"><div style="border: 1px solid black; width: 20px; height: 20px;"></div><div style="border: 1px solid black; width: 20px; height: 20px;"></div><div style="border: 1px solid black; width: 20px; height: 20px;"></div></div><p style="font-size: small; margin: 0;">Print Initials</p></div>				
1	2	3	4	5	"Stop"												
A	B	C	D	E													
<p>2. WORD FLUENCY</p> <p>"I am going to give you a letter. You will have one minute to name as many words as you can think of which begin with that letter."</p> <p>"For example, with the letter 'P' you could say 'people, pot, plant'... and so on. Are you ready?"</p> <p>"Do you have any questions?"</p> <p>"The letter is - A -. Go!"</p> <table style="width: 100%; border-collapse: collapse;"><tr><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr></table> <p>SCORE: 0 <input type="checkbox"/> 10 or more words 1 <input type="checkbox"/> 5 - 9 words 2 <input type="checkbox"/> Less than 5 words</p>																	

Date: ____/____/____

ID: _____

EXIT	EXIT25 (page 2 of 11)
3. DESIGN FLUENCY	
"Look at these pictures. Each is made with only four (4) lines. I am going to give you one minute to draw as many DIFFERENT designs as you can. The only rules are that they must each be different and be drawn with four lines. Now go!"	
SCORE:	0 <input type="checkbox"/> 10 or more unique drawings (no copies of examples)
	1 <input type="checkbox"/> 5 - 9 unique drawings
	2 <input type="checkbox"/> Less than 5 unique drawings

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 3 of 11)

4. THEMATIC PERCEPTION

(Patient shown picture by examiner)

"Tell me what is happening in this picture."

- SCORE:**
- 0 ☐ Tells spontaneous story (story = setting, 3 characters, action)
 - 1 ☐ Tells story with prompting x 1 ("anything else?")
 - 2 ☐ Fails to tell story despite prompt




Date: ____/____/____

ID: _____

EXIT EXIT25 (page 4 of 11)	
5. ANOMALOUS SENTENCE REPETITION	
<div>Mark appropriate box</div>	
"Listen very carefully and repeat these sentences exactly..."	
(Read the sentence in the usual tone of voice.)	
<div>1. "I pledge allegiance to those flags." 2. "Mary fed a little lamb." 3. "Throw, throw, throw your boat." 4. "Tinkle tinkle little star." 5. "A B C D U F G"</div>	
SCORE:	<div>0 <input type="checkbox"/> No errors 1 <input type="checkbox"/> Fails to make one or more changes 2 <input type="checkbox"/> Continues with one or more expressions (e.g. "Mary had a little lamb whose fleece was white as snow")</div>
6. MEMORY/DISTRACTION TASK	
"Remember these three words:"	
"APPLE, TABLE, PENNY"	
(Patient repeats words until all three are registered.)	
"Remember them - I'll ask you to repeat them for me later."	
"Now - spell CAT for me..."	
"Good. Now spell it backwards..."	
"OK. Tell me those three words we learned."	
<div>_____</div>	
SCORE:	<div>0 <input type="checkbox"/> Patient names some or all of the three words correctly without naming CAT (Examiner may prompt: "Anything else?") 1 <input type="checkbox"/> Other responses, Describe: <div></div> 2 <input type="checkbox"/> Patient names CAT as one of the three words (intrusion)</div>

Date: ____/____/____

ID: _____

EXIT		EXIT25 (page 5 of 11)	
7. INTERFERENCE TASK		 Mark appropriate box	
"What color are these letters?"			
(Examiner shows patient and sweeps hand back and forth over all letters.)			
SCORE:	0	<input type="checkbox"/>	"black"
	1	<input type="checkbox"/>	"brown" (prompt "Are you sure?") > "black"
	2	<input type="checkbox"/>	"brown" (prompt) "brown" (intrusion)
<div style="text-align: center; font-size: 48pt; font-weight: bold; margin-top: 20px;">brown</div>			
8. AUTOMATIC BEHAVIOR I			
(Patient holds hands forward palms down.)			
"Relax while I check your reflexes..."			
(Rotate patient's arms one at a time at the elbow as if to check for cogwheeling. Gauge patients <u>active</u> participation/anticipation of the <u>rotation</u> .)			
SCORE:	0	<input type="checkbox"/>	Patient remains passive
	1	<input type="checkbox"/>	Equivocal
	2	<input type="checkbox"/>	Patient actively copies the circular motion

Date: ____/____/____

ID: _____

EXIT	EXIT25 (page 6 of 11)
9. AUTOMATIC BEHAVIOR II (Patient holds hands out palms <u>up</u> .) "Just relax." (Examiner pushes down on patient's hands - gently at first, becoming more forceful. Gauge patient's active participation in the response.) SCORE: 0 <input type="checkbox"/> Patient offers no resistance (remains passive) 1 <input type="checkbox"/> Equivocal response 2 <input type="checkbox"/> <u>Actively</u> resists (or complies) with examiner	
10. GRASP REFLEX (Patient holds hands out with open palms <u>down</u> .) "Just relax." (Both palms are lightly stroked simultaneous by the examiner, who looks for grasping/gripping actions in the fingers.) SCORE: 0 <input type="checkbox"/> Absent 1 <input type="checkbox"/> Equivocal 2 <input type="checkbox"/> Present If present, does the patient grasp firmly enough to be drawn up and out of chair by examiner? 1 <input type="checkbox"/> NO 2 <input type="checkbox"/> YES	
11. SOCIAL HABIT I Fix patient's eyes. Silently count to three while maintaining patient's gaze, then say "Thank you." SCORE: 0 <input type="checkbox"/> Replies with a question (e.g. "Thank you for what?") 1 <input type="checkbox"/> Other responses, Describe: <input type="text"/> 2 <input type="checkbox"/> "You're welcome."	
12. MOTOR IMPERSISTENCE "Stick out your tongue and say 'aah' till I say stop... Go!" (count to three silently) (Subject must sustain a constant tone, not "ah...ah...ah...") SCORE: 0 <input type="checkbox"/> Completes task spontaneously 1 <input type="checkbox"/> Completes task with examiner modelling task for patient 2 <input type="checkbox"/> Fails task despite modelling by examiner	

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 7 of 11)	
13. SNOUT REFLEX	
"Just relax."	
(Examiner slowly brings index finger towards patient's lips, pausing momentarily 2" away. Finger is then placed vertically across lips and then is lightly tapped with the other hand. Observe lips for puckering.)	
SCORE:	0 <input type="checkbox"/> Not present
	1 <input type="checkbox"/> Equivocal
	2 <input type="checkbox"/> Present
	If present, does the patient pucker lips while examiner is pausing 2" away? 1 <input type="checkbox"/> NO 2 <input type="checkbox"/> YES
14. FINGER-NOSE-FINGER TASK	
(Examiner holds up index finger.)	
"Touch my finger."	
(Leaving finger in place, examiner says...)	
"Now touch your nose."	
SCORE:	0 <input type="checkbox"/> Patient complies, using same hand
	1 <input type="checkbox"/> Other response, Describe: <input type="text"/>
	2 <input type="checkbox"/> Patient complies, using other hand while continuing to touch examiner's finger
15. GO/NO-GO TASK	
"Now..."	
"When I touch my nose, you raise your finger like this." (Examiner raises index finger.)	
"When I raise my finger, you touch your nose like this." (Examiner touches nose with index finger.)	
Have patient repeat instructions if possible. The examiner should put their finger in their lap between instructions to reduce the potential for confusion.	
(Examiner begins task. Leave finger in place while awaiting patient's response. Put your finger back in your lap between trials to reduce the potential for confusion)	
Examiner	Patient
F	N F
N	F N
F	N F
F	N F
N	F N
SCORE:	0 <input type="checkbox"/> Performs bold sequence correctly
	1 <input type="checkbox"/> Correct, requires prompting/repeat instructions
	2 <input type="checkbox"/> Fails sequence despite prompting/repeat instructions

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 8 of 11)

16. ECHOPRAXIA I

"Now listen carefully. I want you to do exactly what I say. Ready?"

"Touch your ear." (Examiner touches his nose and keeps finger there.)

- SCORE: 0 ☐ Patient touches his ear
- 1 ☐ Other response, Describe:
(look for "mid-position" stance)
- 2 ☐ Patient touches his nose

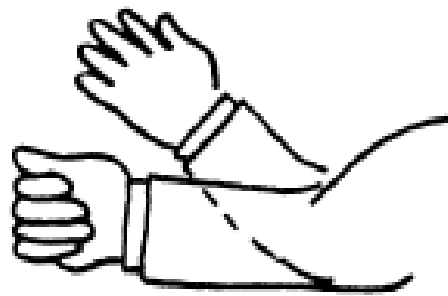
17. LURIA HAND SEQUENCE I

☒ Mark appropriate box

Palm/Fist

"Can you do this?"

(Invite patient to watch while alternating palm/fist with either hand. Once the patient appears to have mastered the task, have them demonstrate it. Ask the patient to "**keep going**" while the examiner stops. Count the number of successive palm/fist cycles.)



- SCORE: 0 ☐ 5 cycles without error after examiner stops
- 1 ☐ 5 cycles with additional verbal prompt
- 2 ☐ Unsuccessful despite prompting/modeling (watch for "mid-position" stances)

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 9 of 11)

18. LURIA HAND SEQUENCE II

3 Hands

"Can you do this?"

(Examiner models: a) slap, b) fist, c) cut - while patient imitates each step)



"Now follow me." (Examiner begins to repeat sequence.)

Once the patient appears to have mastered the task, have them demonstrate it. Ask the patient to "keep going" while the examiner stops. Count the number of successive cycles.

Prompting is allowed at thirty seconds "are you sure you got it?"

Terminate the procedure after one minute has elapsed.

- SCORE:**
- 0 ☐ 4 cycles without error after examiner stops
 - 1 ☐ 4 cycles with additional verbal prompt ("Keep going") or modeling
 - 2 ☐ Unsuccessful

19. GRIP TASK



"Squeeze my fingers."

- SCORE:**
- 0 ☐ Patient grips fingers
 - 1 ☐ Other response, Describe:
 - 2 ☐ Patient pulls examiner's hands together

20. ECHOPRAXIA II

(Suddenly and without warning, the examiner slaps his hands together.)

- SCORE:**
- 0 ☐ Patient does not imitate examiner
 - 1 ☐ Patient hesitates, uncertain
 - 2 ☐ Patient imitates slap

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 10 of 11)	
<div>21. COMPLEX COMMAND TASK<div>Mark appropriate box</div><p>"Put your left hand on top of your head and close your eyes. That was good..."</p><p>(Examiner remains aloof, Quickly go onto next task.)</p><p>SCORE: 0 <input type="checkbox"/> Patient stops when next task began</p><p>1 <input type="checkbox"/> Equivocal - holds posture during part of next task</p><p>2 <input type="checkbox"/> Patient maintains posture through completion of next task - has to be told to cease</p></div>	
<div>22. SERIAL ORDER REVERSAL TASK<p>(Have patient recite the months of the year.)</p><p>"...Now start with January and say them all backwards..."</p><p>SCORE: 0 <input type="checkbox"/> No errors, at least past September</p><p>1 <input type="checkbox"/> Gets past September but requires repeat instructions ("Just start with January and say them all backwards.")</p><p>2 <input type="checkbox"/> Can't succeed despite prompting</p></div>	
<div>23. UTILIZATION BEHAVIOR<p>(Examiner holds pen near point and dramatically "presents" it to the patient asking:)</p><p>"What is this called?"</p><p>SCORE: 0 <input type="checkbox"/> Doesn't reach</p><p>1 <input type="checkbox"/> Reaches, hesitates</p><p>2 <input type="checkbox"/> Patient takes pen from examiner (utilization behavior)</p></div>	
<div>24. IMITATION BEHAVIOR<p>(Examiner flexes wrist up and down and points to it asking:)</p><p>"What is this called?"</p><p>SCORE: 0 <input type="checkbox"/> "Wrist"</p><p>1 <input type="checkbox"/> Other response, Describe: <input type="text"/></p><p>2 <input type="checkbox"/> Patient flexes wrist up and down (echopraxia)</p></div>	

EXIT

EXIT25 (page 11 of 11)

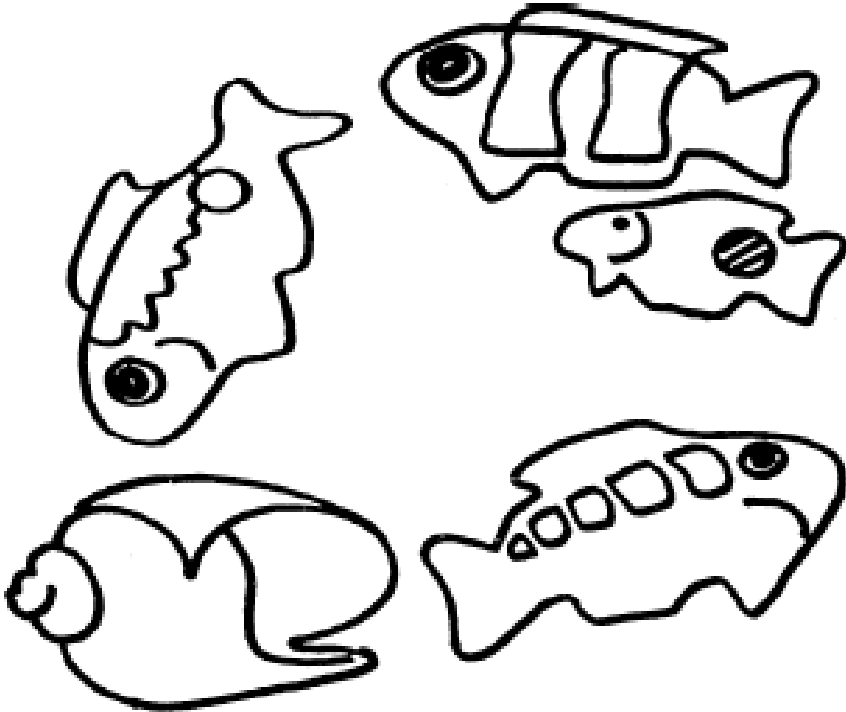
25. COUNTING TASK 1

"Please count the fish in this picture out loud."

SCORE: 0 ☐ Four

1 ☐ Other

2 ☐ More or less than four



Date: ____/____/____

ID: _____

C.2.d North American Adult Reading Test

Instructions for Administration of the NAART

Read to the Subject:

Please read out loud the following words on this list.

Scoring:

Mark the incorrect pronunciations by using the pronunciation key as the subject reads the list out loud. Have the subject read all the words to the best of their ability.

Answer Key for the NAART

	<u>Word</u>	<u>SCORE</u>	<u>Pronunciation</u>
1.	DEBT	_____	Det
2.	DEBRIS	_____	dě-brē, dā-brē´, dā-brē
3.	AISLE	_____	Īl
4.	REIGN	_____	Rān
5.	DEPOT	_____	dē-pō,dé pō
6.	SIMILE	_____	sim´ ə lē
7.	LINGERIE	_____	lan´ zhə rē´, lon´ zhə rā´
8.	RECIPE	_____	res´ ə pē
9.	GOUGE	_____	Gauj
10.	HEIR	_____	Ār
11.	SUBTLE	_____	sət´ əl
12.	CATACOMB	_____	kat´ ə kōm
13.	BOUQUET	_____	bō kā´, bū kā´
14.	GAUGE	_____	Gāj
15.	COLONEL	_____	kərn´ əl
16.	SUBPOENA	_____	sə pē´ nə
17.	PLACEBO	_____	plə sē´ bō
18.	PROCREATE	_____	prō krē āt
19.	PSALM	_____	sām, sālm
20.	BANAL	_____	bə nāl´, bā nal´, bān´ əl
21.	RAREFY	_____	rār´ ə fī
22.	GIST	_____	Jist

Date: ____/____/____

ID: _____

23.	CORPS	_____	kor, korz
24.	HORS D'OEUVRE	_____	or' dærv(r)'
25.	SIEVE	_____	Siev
26.	HIATUS	_____	hī ā təs
27.	GAUCHE	_____	Gōsh
28.	ZEALOT	_____	zel' ət
29.	PARADIGM	_____	par' ə dīm, par' ə dim
30.	FAÇADE	_____	fə sād'
31.	CELLIST	_____	chel' əst
32.	INDICT	_____	in dīt'
33.	DETENTE	_____	dā tā(n)t
34.	IMPUGN	_____	im pyün'
35.	CAPON	_____	kā' pən, kā' pon
36.	RADIX	_____	rād' iks
37.	AEON	_____	ē' ən, e' an
38.	EPITOME	_____	i pit' ə mē
39.	EQUIVOCAL	_____	i kwiv' ə kəl
40.	REIFY	_____	rā' ə fī, rē' ə fi
41.	INDICES	_____	in' də sēz
42.	ASSIGNATE	_____	as' ig nāt'
43.	TOPIARY	_____	tō pē er' ē
44.	CAVEAT	_____	kav' ē at, kāv' ē at, kā vē at'
45.	SUPERFLUOUS	_____	sû pēr' flü əs
46.	LEVIATHAN	_____	li vī' thən
47.	PRELATE	_____	prel' ət, prēl āt
48.	QUADRUPED	_____	kwād' rə ped
49.	SIDEREAL	_____	sī dir' ē al, sə dir' ē al
50.	ABSTEMIOUS	_____	ab stē' mē əs
51.	BEATIFY	_____	bē at' ə fī
52.	GAOLED	_____	Jāld
53.	DEMESNE	_____	dī măn', dī mēn'
54.	SYNCOPE	_____	sing' kə pē, sin' k'rrn pē

Date: ____/____/____

ID: _____

55.	ENNUI	_____	an wē´
56.	DRACHM	_____	Dram
57.	CIDEVANT	_____	sēd ə vā(n)´
58.	EPERGNE	_____	i pərn´, ā pərn´
59.	VIVACE	_____	vē vāch´ ā, vē vāch ē
60.	TALIPES	_____	tal´ ə pēz
61.	SYNECDOCHE	_____	sə nek´ də kē
	Total Errors:	_____	

Date: ____/____/____

ID: _____

C.2.e Trails-Making Test, Parts A & B

Instructions for Administering the Trails A & B

Part A

1. Tell the subject “For this test I want you to work as quickly as possible but try to avoid making mistakes.”
2. Place the example for Trails A in front of the participant, the bottom of the test should be about 6 inches from the edge of the table.
3. Give the participant a pencil and say: “On this page are some numbers” (Point at the numbers). Begin at number 1 (point to 1) and draw a line from 1-2 (point to 2), 2 to 3 (point to 3), 3-4 (point to 4) and so on, in order, until you reach the end (point to the circle marked ‘end’) Draw the lines as fast as you can. Ready—Begin.”
4. If the participant completes the sample and shows he/she understands the instructions then say: “Good! Why don’t you try this next one.”
5. Turn the page over and give Part A of the test and say: ”On this page are some more numbers. Begin with the number 1 (point to 1) and draw a line from 1 to 2 (point to 2) and so on, until you reach the end (point to end). Remember to work as fast as you can.”

Start timing as soon as the subject moves the pencil toward the number 2. Watch the participant closely in order to catch any errors as soon as they are made. If the subject makes any errors, call it to her/his attention immediately, return the subject’s pencil to the last correct circle and continue the test from that point. Do not stop timing while correcting the subject’s error.

6. After the subject completes Part A, take the test sheet and record the time as it is shown on the stop watch.
7. Then say “That’s fine. Now we’ll try another one.”
8. Write down the stopwatch time in the upper right hand corner 00:00:00

Part B

1. Place the sample side of Part B on the table in front of the subject in the same position as the sheet for Part A.
2. Point to the sample and say “On this page are some numbers and letters. Begin at 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end. Ready ---Begin.”
3. When the subject completes Sample B, say. On this page are both number and letters. Please do this the same way. Begin at 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end. Ready ---Begin.”

Start timing as soon as the subject moves the pencil toward the letter ‘A’. Watch the participant closely in order to catch any errors as soon as they are made. If the subject makes any errors, call it to her/his attention immediately, return the subject’s pencil to the last correct circle and continue the test from that point. Do not stop timing while correcting the subject’s error.

4. Write down the stopwatch time in the upper right hand corner 00:00:00

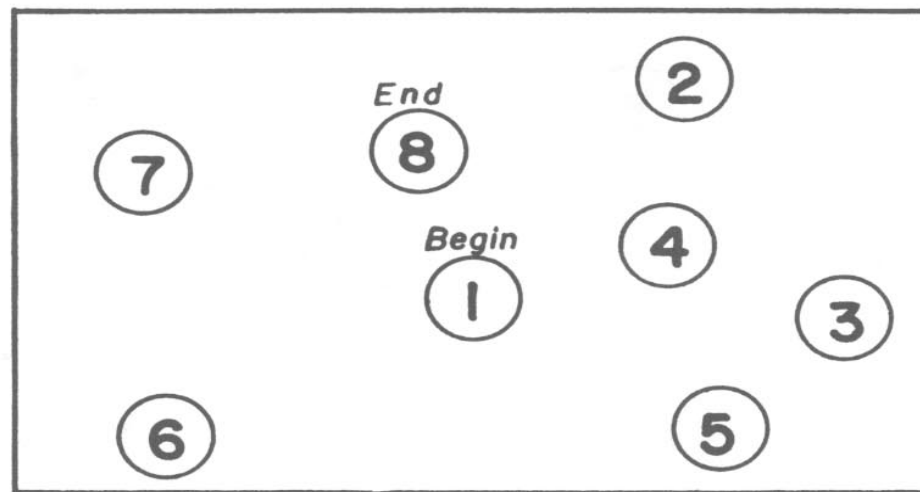
Date: ____/____/____

ID: _____

TRAIL MAKING

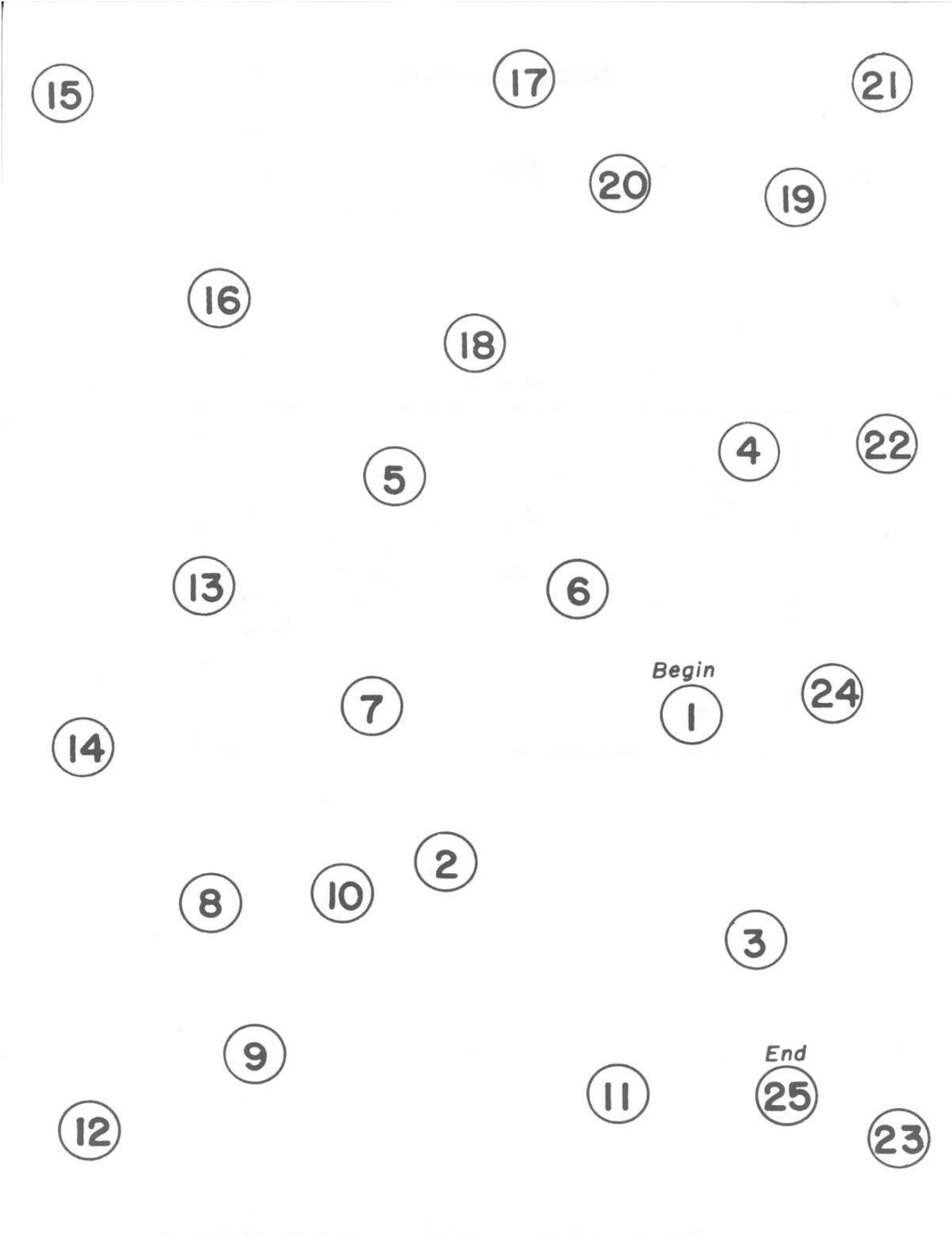
Part A

SAMPLE



Date: ____/____/____

ID: _____



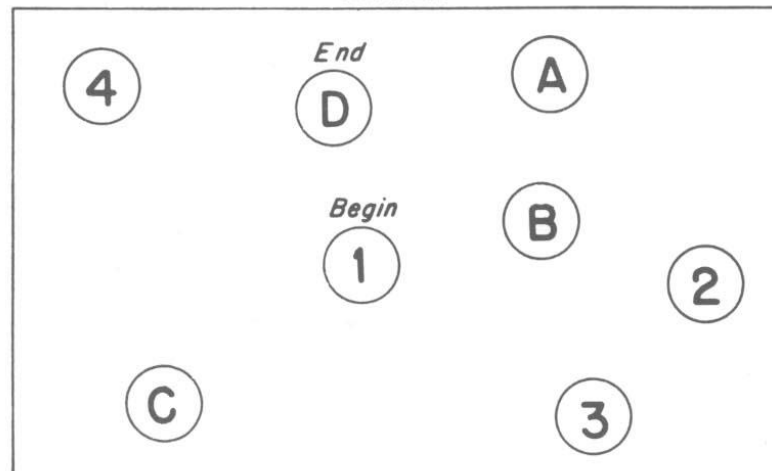
Date: ____/____/____

ID: _____

TRAIL MAKING

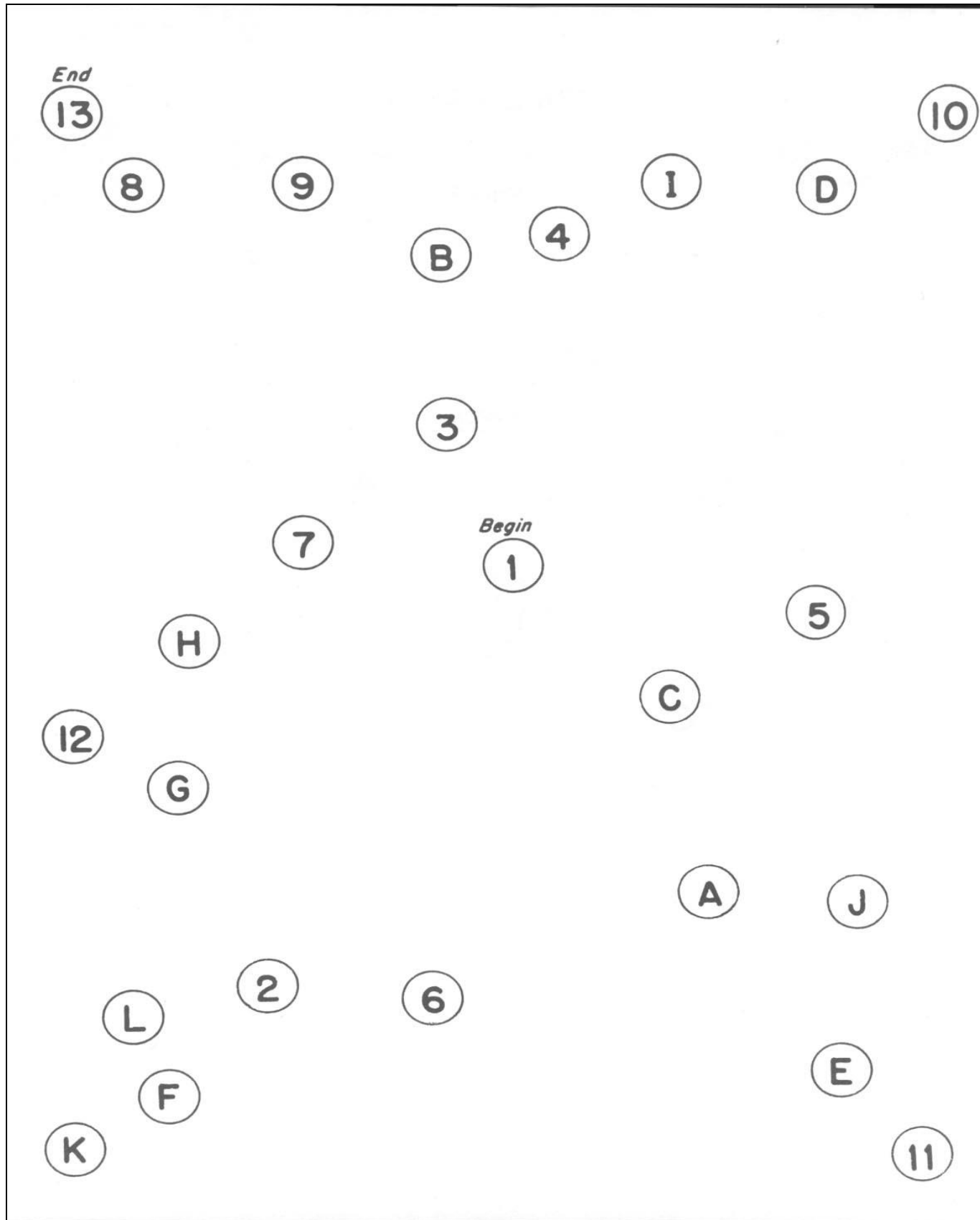
Part B

SAMPLE



Date: ____/____/____

ID: _____



Date: ____/____/____

ID: _____

C.2.f Controlled Word Association Test

Controlled Oral Word Association (Bechtoldt, Benton, & Fogel, 1962; Benton, 1967)

GET OUT STOPWATCH

Instructions to the Subject:

"I am going to say a letter of the alphabet and I want you to say as quickly as you can all the words you can think of which begin with that letter. You may say any word at all except proper names, such as names of people or places or brand names. So you would not say "Raleigh" or "Robert" or "Radioshack." Also, do not use the same words again with a different ending, such as "eat" and "eating." For example, if I say "S", you could say "sun, sit, shoe, or slow". Can you think of other words beginning with the letter "S?"

Wait for the subject to give a work, indicate if the word is correct by saying "That is correct, that word begins with "S." Can you think of another word?" Once two appropriate words beginning with the demonstration letter are given, say "That is fine. Now I'm going to give you another letter, and again say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you keep on trying until the time limit is up. You will have a minute for each one."

"The first letter is C and 1 minute is allowed."

Do not interrupt the subject during the minute. At the end of one minute, stop the subject and clarify any answers (e.g. "frank" which could represent a proper name). Then say "The same instructions apply for the second letter. The second letter is "F." You have one minute."

Follow the same rules for the second letter "F" and the third letter "L."

Instructions for Responses:

Version A and Version B use the same procedure (version B is used with the alternate letters PRW). Record subject responses on the numbered record sheet. If the subject is stating words quickly, you may record + on the line for correct responses. Be sure to record all responses verbatim for those that are incorrect or need clarification. Many words have two or more meaning therefore a repetition of the word is accepted only in those cases where the subject definitely indicates the alternate meaning. For responses that need clarification, do not interrupt the subject during the one-minute interval. At the end of the minute, ask the subject what was meant by the word (example of "frank" above). Slang terms are admissible as correct answers, as well as certain foreign words (e.g. "lasagna") as long as these words are listed as standard English. Perseverative errors are also scored, even in the case where a word has two or more meaning and the subject does not indicate the different meanings (e.g. "four" and "for").

Date: ____/____/____

ID: _____

	First Letter: C or P	Second Letter: F or R	Third Letter: L or W
1.	_____	_____	_____
2.	_____	_____	_____
3.	_____	_____	_____
4.	_____	_____	_____
5.	_____	_____	_____
6.	_____	_____	_____
7.	_____	_____	_____
8.	_____	_____	_____
9.	_____	_____	_____
10.	_____	_____	_____
11.	_____	_____	_____
12.	_____	_____	_____
13.	_____	_____	_____
14.	_____	_____	_____
15.	_____	_____	_____
16.	_____	_____	_____
17.	_____	_____	_____
18.	_____	_____	_____
19.	_____	_____	_____
20.	_____	_____	_____
21.	_____	_____	_____
22.	_____	_____	_____
23.	_____	_____	_____
24.	_____	_____	_____
25.	_____	_____	_____

Date: ____/____/____

ID: _____

C.2.g Hopkins Verbal Learning Test-Revised

Hopkins Verbal Learning Test-Revised

Copyright protected and not reproduceble; available through purchase with licensure of
Dr. Renee Raynor (neuropsychologist) only.

Will be purchased and available for subject test battery administration.

Date: ____/____/____

ID: _____

C.2.h Arrow Flanker Test (also seen in attached Computerized Tests)

Arrow Flanker Test

Instructions to the Subject

This is a reaction time task, so you should always respond as quickly as possible but it is most important to be as accurate as possible, so to avoid making errors. You will press the right or left arrow key on the computer screen according to the object's direction that is placed in the center of the screen. These are examples of something you might see. Which direction arrow would you press? The right arrow or left arrow?



The left arrow key would be correct.

As you see, the object in the center is an arrow in the middle of squares. But you might see the same object and have to find the middle direction.

Which direction arrow would you press for this example?



The right arrow key would be correct.

Now try this example. What is the correct direction?



The right arrow key is again correct. Are you ready to start the program? It will only take 5 minutes to complete.

Date: ____/____/____

ID: _____

C.2.i Symbol Digit Modalities Test

Symbol Digit Modalities Test (Smith, 1991)

Instructions for administering the Symbol Digit Modalities Test

1. GET OUT STOPWATCH.
2. Place the test page in front of the subject
3. “In this task, you will use this key (point), to complete the page of symbols.”
Point at the key at the top of the page. “You can see that each box in the upper row has a little mark in it. Now look at the boxes in the row just underneath the marks. Each of the boxes under the marks has a number. Each of the marks in the top row is different, and under each mark in the bottom row is a different number.”
4. Then say “Now look at the rest of the sheet. Notice that the boxes on the top have marks, but the boxes underneath are empty. You are to fill each empty box with the number that should go there according to the way they are paired in the key at the top of the page.”
5. Start the sample items by saying “For example if you look at the first mark, and then look up at the key, you will see that the number 1 goes in the first empty box. So write the number 1 in the first box.”
6. Make a vertical line to indicate the end of the sample and the start of the test.
7. Then say, “The boxes here are just practice, why don’t you try it”.
8. Once the participant finishes the practice set, say “Now you will have 90 seconds to fill out as many boxes as you can on the rest of the sheet. In other words, when you come to the end of the first line, go quickly to the next line without stopping and so on. If you make a mistake, do not erase, just write the correct answer over your mistake. Do not skip any boxes and work as quickly as you can. Start when you are ready”.
9. Start the stopwatch at the first number is being drawn.
10. Stop the participant after 90 seconds (1 minute, 30 seconds)

Date: ____/____/____

ID: _____

KEY

(÷	└	┐	└	>	+)	÷
1	2	3	4	5	6	7	8	9

(└	÷	(└	>	÷	┐	(>	÷	(>	(÷

┐	>	(÷	└	>	└	┐	(÷	>	÷	┐	└)

┐	└	+)	(└	+	┐)	└	÷	÷	└	┐	+

÷	┐	└	(>	┐	(└	>	+	÷)	└	>	┐

÷	└)	└	>	+	┐	└	÷	└	+	÷	÷)	(

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÷)	+	÷	└	+)	└	(÷	÷	(┐	└	>

└	÷	(>	┐	÷	(>	÷	+	└	└	┐)	÷

Date: ____/____/____ ID: _____

C.2.j Visual Analog Scale for Subject Rating of Test Difficulty

Visual Analog Scale for Subject Rating

Name of Test

____ Exit-25	____ NAART	____ Trails Part A
____ Trails Part B	____ COWA	____ HVLТ-R
____ HVLТ-R Delayed	____ Arrow Flanker	____ SDMT

Instructions

On the line below, place an X where you feel it indicates how difficult the test was for you to complete.

Very	Very
Difficult	Easy
<hr/>	

APPENDIX G: REFERRAL LETTERS

F.1 Referral Protocol and Letter for Subjects

Instructions for Referring Subjects based on the findings from this study

A referral letter must be given to all subjects who *attains*:

1. An EXIT-25 score of > 20 ,
2. Trails Making Test B time > 3 minutes,
3. An OARS score of < 20 ,
4. A CESD score of > 15 ,
5. A blood pressures over 140 systolic or 90 diastolic,
6. A heart rate > 120 bpm,
7. A low arterial oxygen desaturation of $< 90\%$,
8. Prolonged anxiety or fear during testing procedure of > 10 minutes.

All of these conditions are serious and the lab director should be notified for adverse events requiring emergency personnel.

Attached are two major types of study referral letters: one for cognitive impairments and one for vital signs.

Please make sure that a copies of each form are on file in the research office under subject referrals.



Date: March 6, 2011

To: Mr. XXX
Address

From: Deborah Allen
Principal Investigator
School of Nursing
University of North Carolina at Chapel Hill

RE: Results of test here

Dear Mr. XXX,

As one of my study participants, you underwent a battery of health, memory and functional tests at the University of North Carolina, School of Nursing Biobehavioral Laboratory. In the process of our evaluation, we found that you are having difficulties with _____ and thought that it would be good for you to tell your doctor.

Specifically, you scored below normal on the EXIT-25 Exam. The EXIT-25 Exam is a test of cognitive function. The average passing score on the Mini-Mental Status Exam is 35 and you scored a __ on this test. You may also want to tell your doctor about these problems. Please let you doctor know that I would be happy to talk with him/her about the findings of this study. I can be reached at (919) 883-7002.

Sincerely,

Deborah Allen
Principal Investigator
UNC School of Nursing

The UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

[Click to type Unit Name] • CB#7460, Carrington Hall • Chapel Hill, NC 27599-7460
PHONE: [PHONE NUMBER] • FAX: [FAX NUMBER]



Date: January 8, 2009

To: Mr. XXX
Address

From: Deborah Allen
Principal Investigator
School of Nursing
University of North Carolina at Chapel Hill

RE: Results of test here

Dear Mr. XXX,

As one of my study participants, you underwent a battery of health, memory and functional tests at the University of North Carolina, School of Nursing Biobehavioral Laboratory. In the process of our evaluation, we found that you are having difficulties with one of your vital signs and thought that it would be good for you to tell your doctor.

Specifically, you had a blood pressure that was very high. Your blood pressure was _____ systolic / _____ diastolic. The average blood pressure is below 120 systolic / 80 diastolic. You may also want to tell your doctor about these problems.

Please let your doctor know that I would be happy to talk with him/her about the findings of this study. I can be reached at (919) 883-7002.

Sincerely,

Deborah Allen
Principal Investigator
UNC School of Nursing

APPENDIX H: BBL SAFETY PLAN

SAFETY-MONITORING PLAN

Operational Definition of an Adverse Event

An adverse event will be defined as an event that occurs during the course of the study that should be documented and reported to the director of the School of Nursing Biobehavioral Laboratory (BBL) and Public Health/School of Nursing (SON) IRB. This study does not involve an intervention but does involve individuals with a neurologic impairment from a primary brain tumor. Therefore, this safety plan reflects provisions to prevent or rapidly identify adverse events that could occur while undergoing the three hour study protocol: seizures, CNS cerebrovascular event, confusion, personality/behavioral alteration, or mood disturbance. The safety monitoring protocol and basic laboratory emergency protocol (including 911 protocol and phone number of the medical director for the study) is posted in the monitoring area of the observation room where the study protocol will be performed. Human subject issues such as psychological distress associated with cognitive testing, subject confidentiality, and incidents that are not directly associated with testing (falls, theft) have been addressed in the IRB application. Although important, violations of these issues will be reported to the IRB but will not be directly addressed in this subject safety-monitoring plan.

1. Seizures: Unstable seizure disorders can produce alterations in mental status or cognitive issues. Seizure disorders may present as brief sensory or motor events without altered consciousness to prolonged generalized seizure states including status epilepticus. Therefore the telephone screen is designed to review the seizure history of the potential subject to assure that there is a seizure-free state of 6 months and that no recent changes in anticonvulsants have occurred that could place the potential subject more at risk for seizures. As there may be a few weeks between the telephone screen and the subject presenting or consent and study procedures, a laboratory screen will be performed. Questions include:
 - a. Changes in medications will be reviewed to assure that changes in anticonvulsant therapy have not occurred.
 - b. Occurrence of any seizures to assure a stable seizure status.
 - c. No recent use of cold medicines that could interfere with anticonvulsant therapy serum levels, placing the subject at risk for seizure occurrence.
 - d. Studies will be rescheduled if a subject or a member of the study staff reports to the laboratory a cold or flu.
2. Cerebrovascular event: Survivors of primary brain tumors who have undergone surgery, chemotherapy, and/or radiation therapy are at more risk for the development of stroke. While telephone screening will eliminate those with a history of prior cerebrovascular events, the laboratory screen will serve to ask if there have been any changes in their health status which could indicate transient events. In addition, vital signs will be performed to assure a stable cardiovascular state for study procedures.
3. Confusion, personality/behavioral alterations, and mood disturbances: While it is not anticipated that these adverse events may occur at a grade 3 or 4 severities constituting a medical emergency, study personnel are aware survivors of primary brain tumors may have frontal lobe damage which could result in extreme changes in mental status, personality, behaviors, or mood. The subject will be reassured that their performance is within expected parameters. In addition, subjects will be provided regularly scheduled rest periods and opportunities for nutrition.

Reporting Procedure

The principal investigator will monitor the study throughout for adverse events. Primary safety

measures as described above will be implemented in presence of an adverse event. While in the BBL, the subjects will be monitored continuously for any sign of an adverse event. In the case of an adverse event, regardless of whether the event is identified by the staff or the subject, the PI and the BBL director will be notified and the following NCI Common Toxicity Criteria Adverse Event version 3 scale will be used to grade its severity: Grade 1 -- no intervention needed/not a problem; neuro-oncologist informed of occurrence, Grade 2 -- instituted initial safety protocol and neuro-oncologist informed of occurrence, Grade 3 or 4 -- initiated safety protocol and called for local EMS. The table below provides the criteria for recording and reporting adverse events. The principal investigator will review all adverse events with study subjects or their family before they leave the BBL. The principal investigator will also review each occurrence with the co-investigators, BBL director, and subject's neuro-oncologist. Serious adverse events (Grades 3 or 4) will be reported to the IRB. All adverse events will be compiled to describe common events in this small sample size.

Table 1. Adverse Event Severity Form

	1	2	3	4
Seizure	None	One brief generalized seizure; seizure well controlled by medications; infrequent focal motor seizures not interfering with activities of daily living (ADL)	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g. status epilepticus, intractable epilepsy)
Cerebrovascular event	None	Asymptomatic	Transient event of ≤ 24 hours duration	CVA, neurologic deficit > 24 hours duration
Confusion	Transient confusion, disorientation, or alteration deficit	Confusion or delirium not interfering with activities of daily living ADL	Confusion or delirium interfering with ADL (such as testing procedures)	Harmful to others or self; hospitalization indicated
Personality/behavioral alterations	Change, but not adversely affecting subject or family	Change, adversely affecting subject or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated
Mood alteration – select one: <ul style="list-style-type: none"> ■ Agitation ■ Anxiety ■ Depression ■ Euphoria 	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function but not interfering with ADL	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others

Post in BBL Observation Room

In case of Emergency dial “911”

Tell the Operator:

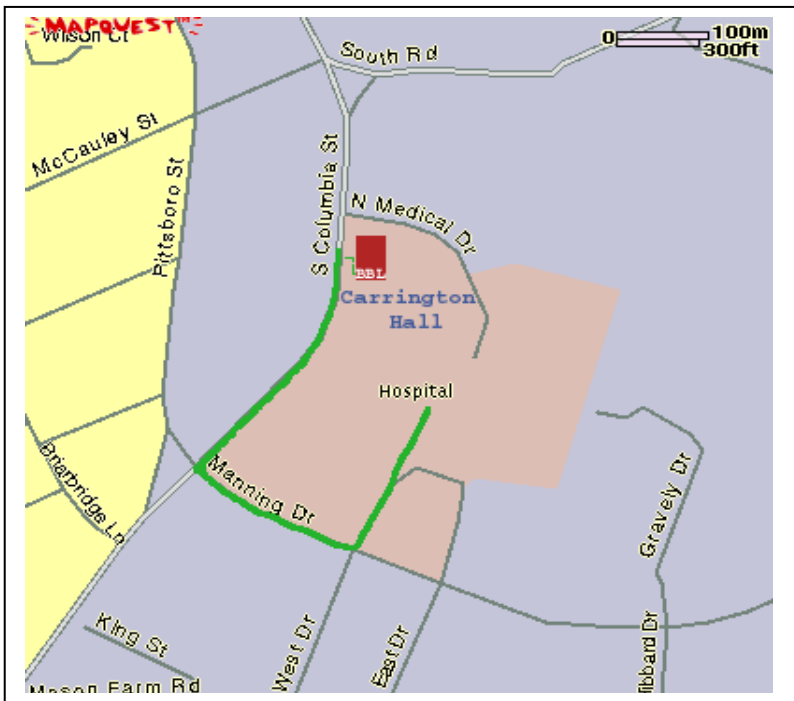
Hello, my name is _____ and I am calling you from the Biobehavioral Laboratory, Observation Room 3, Carrington Hall, School of Nursing. I am calling to report a medical emergency: one of our research subjects is _____ (symptoms) and _____ is being done to help him/her.

For a CPR victim say:

- The person is unresponsive, does not have a pulse, and is not breathing.
- CPR with AED is being administered.

Where are we? Our laboratory is located on the ground floor of Carrington Hall, the School of Nursing. The phone number is 966-7598.

STAY ON THE LINE UNTIL YOU ARE TOLD TO HANG UP THE PHONE



Directions to Carrington Hall (if asked)

- 1) Head south on Airport Road
- 2) Turn right on Cameron and go around the Carolina Inn, heading south on Pittsboro Road.
- 3) At the intersection with Manning Dr. take a *right onto Columbia Street*.
- 4) Go through one light and stop curbside just before the intersection with N. Medical Dr.
- 5) The School of Nursing (Carrington Hall) is the building on your *right*

After Contacting 911

- 1) Unlock and prop open the BBL Main Door (from the hallway)
- 2) LISTEN OUT FOR EMS
- 3) Keep your cell phone on for further contact with BBL personnel, EMS, Campus Police
- 4) Assist with CPR and AED diagnostics
- 5) Contact the lab director and PI of the study

Contact information

Dr. Virginia Neelon – Lab Director
Dr. Barbara Carlson – Faculty Chair
Deborah Allen – PI

Mobile

225-4214
883-7002

Home phone

(919) 286-3334
(919) 929-1112
(919) 542-9933

911 protocol for BBL

APPENDIX I: FEASIBILITY STUDY

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

CLINICAL ONCOLOGY RESEARCH PROGRAM

SCHOOL OF MEDICINE

UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

MEMORANDUM

Principal Investigators: Carlson, MD, Barbara

Oncology Protocol Review Committee

Third Floor Administrative Office

Lineberger Cancer Center, CB# 7295

<http://cancer.med.unc.edu/research/prc/default.asp>

November 03, 2008

NUMBER: LCCC0822

TITLE: Pilot Study Of Sensory Information Processing And Motor Processing Relationship To Executive Control In Adults With Primary Brain Tumors

New Study Application [PRC approval]

This letter is written to notify you that the protocol application listed above was approved with on **November 03, 2008** by the Lineberger Comprehensive Cancer Center Clinical Oncology Research Program's Protocol Review Committee (PRC).

This application and PRC approval letter may be forwarded to the Behavioral Institutional Review Board for review. **Please note: This letter does not constitute IRB approval for use of human subjects in clinical trials.**

For the purposes of the NCI approved Lineberger Data and Safety Monitoring Plan, this trial has been assigned a Risk Level of Minimal and a Complexity rating of 0.

If you have any questions, please contact Micah Sam, PRC Coordinator at 843-6901, email msam@med.unc.edu, or Lisa Carey, MD, PRC Chair at 966-4431.

cc: IRB Chairman PRC Chair, GCRC Chairman (if applicable), PRC file, Reg Associate, Reg file

DESIGNATED A COMPREHENSIVE CANCER CENTER BY THE NATIONAL CANCER
INSTITUTE

UNC LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

MEMORANDUM

To: Barbara Carlson, PhD., RN.
From: **Data Safety and Monitoring Committee**
Third Floor Administrative Office
Lineberger Cancer Center, CB# 7295
Date: **January 5, 2010**
Subject: IRB #: 08-1888
LCCC#: LCCC0822
Title: Pilot Study Of Sensory Information Processing And Motor Processing
Relationship To Executive Control In Adults With Primary Brain Tumors
RE: **DSMC REVIEW- RESULTS AND COMMENTS**

This letter is written to notify you that the Lineberger Comprehensive Cancer Center Clinical Oncology Research Program's Protocol Review Committee (PRC), in compliance with the NCI approved UNC Lineberger CCC's Data and Safety Monitoring Plan, and has reviewed your study on December 28, 2009. As a result of the review, the following comments were generated:

- A report was received from the PI and the DSMC thanks the PI for the materials provided.
- **There were no safety concerns at this time. As a minimal risk trial with little to no risk to patient safety this study is exempt from further DSMC review.**
- Abstentions: None
- **Next scheduled review: Exempt**

If you have any questions please contact Micah Sam, PRC/DSMC Coordinator at 843-6901, email msam@med.unc.edu.

A copy of the UNC Lineberger CCC's Data and Safety Monitoring Plan may be found at <http://cancer.med.unc.edu/research/PRC/>.

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INSTITUTE

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

CLINICAL ONCOLOGY RESEARCH PROGRAM

SCHOOL OF MEDICINE

UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

MEMORANDUM

TO: **Principal Investigator:** Barbara Carlson, PhD., RN.

FROM: Oncology Protocol Revision Committee
Third Floor Administrative Office
Lineberger Cancer Center, CB# 7295
<http://cancer.med.unc.edu/research/prc/default.asp>

DATE: **May 06, 2010**

SUBJECT: **IRB #: 08-1888**

PROTOCOL#: LCCC0822

TITLE: Pilot Study Of Sensory Information Processing And Motor
Processing Relationship To Executive Control In Adults With Primary Brain
Tumors

Renewal Application (PRC Approval)

This is to notify you that the protocol application listed above was approved on **May 05, 2010** by the Lineberger Comprehensive Cancer Center Clinical Oncology Research Program's Protocol Revision Committee (PRC).

The renewal application packet and PRC approval letter may now be forwarded to the Medical School Institutional Review Board for review. If you have any questions, please contact Micah Sam, PRC Coordinator at 843-6901, email msam@med.unc.edu, or Lisa Carey, MD, PRC Chair at 966-4431.

Please note: This letter does not constitute IRB approval for use of human subjects in clinical trials.

cc: IRB Chairman

PRC Chair

GCRC Chairman (if applicable)

reg/prc files

Reg Associate

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INSTITUTE

UNC LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

MEMORANDUM

TO: **Principal Investigator:** Barbara Carlson, MD
FROM: Oncology Protocol Revision Committee
Third Floor Administrative Office
Lineberger Cancer Center, CB# 7295
<http://cancer.med.unc.edu/research/prc/default.asp>
DATE: **June 9, 2011**
SUBJECT: **IRB #: 08-1888**
PROTOCOL#: LCCC0822
TITLE: Pilot Study Of Sensory Information Processing And Motor Processing
Relationship To Executive Control In Adults With Primary Brain Tumors
Renewal Application (PRC Approval)

This is to notify you that the protocol application listed above was approved on **June 8, 2011** by the Lineberger Comprehensive Cancer Center Clinical Oncology Research Program's Protocol Revision Committee (PRC).

The renewal application packet and PRC approval letter may now be forwarded to the Medical School Institutional Review Board for review. If you have any questions, please contact Micah Sam, PRC Coordinator at 843-6901, email msam@med.unc.edu, or Lisa Carey, MD, PRC Chair at 966-4431.

Please note: This letter does not constitute IRB approval for use of human subjects in clinical trials.

cc: IRB Chairman

PRC Chair

GCRC Chairman (if applicable)

reg/prc files

Reg Associate

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INSTITUTE

UNC LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

May 05, 2010

Barbara Carlson, PhD., RN
5105 Carrington Hall
UNC Chapel Hill
Chapel Hill, NC 27599
CB#7460

RE: **LCCC0822**– UNC

Dear Dr. Carlson,

Thank you for your participation in the **March 26, 2010** audit of the Lineberger Comprehensive Cancer Center studies.

During our audit of study number **LCCC0822** for site UNC patients **E.B.-. Sequence# 0822002** and **F.A. – Sequence# 0822005** were audited:

The audit for this site was **acceptable** and requires no response at this time.

Sincerely,

Young E. Whang, MD
Chair, LCCC Audit Committee

cc: Joy Ostroff, RN, BSN, OCN, Facility Director, Clinical Protocol Office
Micah Sam, Audit Committee Coordinator, PRC Coordinator, DSMC Coordinator
Mary O'Dwyer, Assoc. Director for Regulatory and Admin Services, CPO
Deborah Allen, RN, Protocol Coordinator

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INSTITUTE

**University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Participants
Social Behavioral Form**

IRB Study # 08-1888

Consent Form Version Date: February 9, 2009

Title of Study: Pilot Study of Sensory Information Processing and Motor Processing: Relationship to Executive Control in Adults with Primary Brain Tumors

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What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The major purpose of this research study is to compare how the ability to perceive touch as well as the ability to initiate and sustain movements differs in persons who have and have not undergone treatment for primary brain tumor. Studies have shown that the brain's ability to perceive touch and initiate and maintain movements may be affected first in persons following treatment for primary brain tumor. With this information, we may be able to design better methods to detect cognitive changes and design interventions to decrease the risk of further cognitive decline. You are being asked to be in the study because you are in good health and do not have any problems taking care of yourself.

Are there any reasons you should not be in this study?

You should not be in this study if you have had any seizures in the past six months requiring medication changes, any known neurodegenerative disorder or taking medications for a similar disorder such as Parkinson's disease, multiple sclerosis, Alzheimer's Disease or other dementias, psychiatric disorders such as schizophrenia, mania, or bipolar disorder, known problems feeling touch or vibration, problems moving your arms or legs, problems speaking clearly, problems with sleep such as sleep apnea, or history of stroke, HIV, herpes, tuberculosis, syphilis, or hepatitis. You should not participate if you have been treating a cold with over-the-counter medications in the past two weeks, drank alcoholic beverages or recreational drugs in the past 24 hours, or took sleeping medicines last night which you do not routinely take every night, or smoked tobacco products within four hours prior to testing procedures.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 11 adults with primary brain tumors and 11 healthy adults in this research study.

How long will your part in this study last?

The study will take no more than 3 hours to complete.

What will happen if you take part in the study?

After you review this consent form and have opportunity to ask questions about the testing procedures, you will have your vital signs measured (heart rate, blood pressure, blood oxygen levels in your finger) Next you will be asked to complete a questionnaire about depression and a second questionnaire about your ability to take care of yourself. You will then be asked to take a brief neurological test. This test will be videotaped so that a reviewer will independently score the results. The video camera will include your face. The video recordings will be kept in a locked cabinet. You may opt not to allow the video taping without any affect on participation in the study. Please check the line that best matches your choice:

- ☐ OK to record me during the study
☐ Not OK to record me during the study

Afterwards you will undergo the test that will measures your ability to perceive touch. In this test, you will place your hand under two plastic tips that touch or vibrate on the back of your hand. You will be asked to use the computer mouse with your left hand to indicate when you felt the touch, which tip you felt first, or which tip had the stronger pressure. In the last test, we will ask you to connect consecutive numbers or letters in alternating order. In this test we will be measuring how fast and how accurate you are in connecting the dots. You will be provided opportunities during all the testing procedures to have breaks for food and bathroom use. Upon completion of the study, we will provide you another snack. We will ask you to provide feedback to us regarding the tests, testing format, procedures, and breaks. You will be provided another snack and you may go home.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You may not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

There are no major risks to you as a subject in this study. It is possible that you may feel uncomfortable with some of the tasks that we ask you to do. For example, the memory test may make you feel anxious because some of the answers will be very easy and some will be very hard. We do not expect you to know all the answers. Please do not hesitate to ask any member of the research team any question, and we want you tell us about any problems you may be having.

Because we are taking a lot of measurements, we may find people who may have a condition that requires medical attention. Examples of conditions that require medical attention include findings like a high pulse rate, high or low blood pressure, below normal measures on a memory test, or the inability to perceive certain kinds of tactile stimulation. If this is detected, Ms. Allen or Dr. Carlson will talk to you directly. In this case, you will be given a form that (1) tells you what the test measures, (2) tells you what results we got, and (3) tells you to share this information with your doctor. Lastly, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

How will your privacy be protected?

Every effort will be taken to protect your identity. Only Ms. Allen, Dr. Carlson, the other study investigators, and their research assistants will have access to your data. All data (paper forms and compact discs) will be kept under lock and key at the School of Nursing. The videotape will be kept in a locked file cabinet until completion of the study. Once the study is completed and the videotape has been scored, the videotape will be destroyed.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

Will you receive anything for being in this study?

You will be receiving \$25.00 for taking part and completing the procedures in this study. You will also receive a parking voucher.

Will it cost you anything to be in this study?

There will be no costs for being in the study

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or concerns, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Title of Study: Pilot Study of Sensory Information Processing and Motor Processing: Relationship to Executive Control in Adults with Primary Brain Tumors

Principal Investigator: Deborah Allen. RN, MSN

Participant’s Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____	_____
Signature of Research Participant	Date

Printed Name of Research Participant

_____	_____
Signature of Person Obtaining Consent	Date

Printed Name of Person Obtaining Consent

IRB 08-1888: Pilot Study of Sensory Information Processing and Motor Processing:
Relationship to Executive Control in Adults with Primary Brain Tumors

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Date ____/____/____

ID: _____

Appendix A: Screening Instruments

1. Telephone Screening
2. Subject Information Packet
3. Subject Scheduling Form
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5. Mini Mental Status Examination
6. Eligibility Form

Date ____/____/____

ID: _____

Appendix A.1

TELEPHONE SCREENING INSTRUMENT

I. PHONE RECRUITMENT SCRIPT

A. Introductory Remarks:

“Hello, this is Debbie Allen, from the University of North Carolina School of Nursing. I understand that you would like to learn more about participating in a research study involving your ability to feel touch or vibration and your movements in drawing as it relates to thinking and memory. Is this a good time to talk?” If not, ask the potential participant “when is a good time to call you?”

If we need to call again, date/time agreed upon: _____

B. Brief Description of the Study

“I thank you for your interest and calling us to discuss this study more. The purpose of this research is to compare the ability to perceive touch as well as the ability to initiate and sustain movements as it differs in persons who have undergone treatment for a primary brain tumor as to persons who have not had a brain tumor.”

“We will ask you questions about your health, how well you think, measure your writing ability, and your sense of touch. It is our aim to use this information to design better methods to detect early changes in cognition and design interventions to decrease the risk of further decline. We are testing this only in adults with primary brain tumors and healthy adults. The total time to complete the study will be around three hours and we will compensate you for your time and travel with \$25.00 cash. Does this sound like something you might be interested in?”

Response:	Yes	No
------------------	------------	-----------

If they say yes, go to the Mini-Consent for Telephone Screening.		
---	--	--

If they say no, thank them for their time and interest in speaking with you.		
---	--	--

Date ____/____/____

ID: _____

C. Mini-Consent for the Telephone Screen

After the respondent tells you that they are interested in participating, ask them
“Is it okay to ask you a few questions about your health and the medications you take? It
should take no more than 15 minutes.”

If they say yes, go to Health Screening Questionnaire.

If they need to reschedule, ask them for preference of contact phone numbers
and a date/time to call.

Phone number 1: (____) ____ - _____

Phone number 2: (____) ____ - _____

Date & Time: _____, _____ AM/PM

Date ____/____/____ ID: _____

II. RESPONDENT TELEPHONE SCREENING

A. Tracking Information

Date participant called us: ____/____/____
Date call was returned: ____/____/____

B. Group Assessment

1. Have you had a brain tumor?

If they say yes, they are assigned to the brain tumor subject group.
Proceed to ask questions **a** and **b** below.

If they say no, they are assigned to the control group.
Proceed to question 2.

- a. Have you had surgery, chemotherapy, or radiation therapy as treatment for your brain tumor?
- | | Yes | No | | |
|--------------------------------|----------------|----------------|----|----|
| i. Date of surgery | ____/____/____ | ____/____/____ | or | NA |
| ii. Date of chemotherapy | ____/____/____ | ____/____/____ | or | NA |
| iii. Date of radiation therapy | ____/____/____ | ____/____/____ | or | NA |

Subtract date of last procedure from the current date: ____/____/____ - ____/____/____

That means that it has been _____ months/years since your last treatment.

If > 12 months (1 year), proceed with question **b** below.

If < 12 months (1 year), stop interview and go to **NOT ELIGIBLE** section on the last page.

b. Do you have any problems with movement, speech or touch? **Yes** **No**

If YES, stop interview here and go to **NOT ELIGIBLE section** on the last page

Date ____/____/____

ID: _____

2. Medications

Are you taking medications (including prescription & over-the-counter)?

Yes No

If they say yes, ask “What medications are you taking?”

If they do not know, ask them to read all medication bottles to you that they have.

Record below:

Medication Name	Reason for taking
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	

Compare the list of medications to the Medication Exclusion Card. Exclude the subject if she or he is taking any of the medications listed on the Medication Exclusion Card. Put a check next to the name of any drug that excludes the subject from participating.

MEDICATION EXCLUSION

Changes in seizure medications in the last six months	YES	NO
Dopaminergics	YES	NO
Major anticholinergics	YES	NO
Alzheimer’s drugs	YES	NO
Cold medications, sedative hypnotics in past 48 hours?	YES	NO

Medication Exclusion:

Taking a medication on the Medication Exclusion Card? Yes No

If YES, STOP interview here.
Go to **Not Eligible** section on last page.

Date ____/____/____

ID: _____

3. Neurological Conditions

I'm now going to read a list to you. Please wait until I have read the entire list, and then say 'yes' if you have been diagnosed with any of these conditions, or say 'no' if you have not.

- a. Alzheimer's Disease
- b. Dementia
- c. Parkinson's Diseases
- d. Schizophrenia
- e. Mania
- f. Bipolar Disorder
- g. Unstable Seizure Disorder requiring antiepileptic changes in the last six months
- h. Any problems with numbness or tingling in your arms or legs
- i. Any problems moving your arms or legs
- j. Had any surgery requiring general anesthesia in the last two weeks

Neurological Disease Exclusion:

Answer of "Yes" to any of the neurological conditions?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

4. Other Neuroimmune Disorders

For this next list, again, please wait until I have read the entire list, and then say 'yes' if you have been diagnosed with any of these conditions, or say 'no' if you have not.

- a. Tuberculosis
- b. Hepatitis
- c. HIV or AIDS
- d. Herpes
- e. Syphilis

Neuroimmune Disorder Exclusion:

Answer of "Yes" to any of the neuroimmune disorders?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

5. Cerebrovascular Events

For this next list, please wait until I have read the entire list, and then say 'yes' if you have had any of these conditions **in the past 6 months** or say 'no' if you have not.

- a. Stroke or Transient Ischemic Attack
- b. Hit your head and lost consciousness

Cerebrovascular Event Exclusion:

Answer of "Yes" to any of the cerebrovascular events?	Yes	No
If YES, STOP interview here.		
Go to "Not-Eligible" section on last page.		

6. Sleep-Related Symptoms

After I have read the next list, please say ‘yes’ if you have had any of the following problems **in the past month**, or say ‘no’ if you have not.

- a. Pain so bad it keeps you awake
- b. Having to get up and urinate 3 or more times a night
- c. Being easily awakened by sounds
- d. Having difficulty sleeping when away from home
- e. Walking in your sleep
- f. Falling out of bed
- g. Waking from sleep violent or confused

<u>Sleep-Related Exclusions:</u>		
Answer of “Yes” to any of the sleep-related symptoms questions?	Yes	No
If YES, STOP interview here.		
Go to “Not-Eligible” section on last page.		

7. Alcohol & Drug Exclusions

These next questions are about alcohol and illegal drugs. Please wait until I have read the entire list, and then just say ‘yes’ if you do any of the following or ‘no’ if you do not:

- a. Have more than 3 cans of beer on more than 3 nights/week
- b. Have more than 3 glasses of wine on more than 3 nights/week
- c. Have more than 3 shots of distilled liquor on more than 3 nights/week
- d. Currently smoke marijuana or use illegal drugs

<u>Alcohol and Drug Exclusion:</u>		
Answer of “Yes” to any of the alcohol/drug questions?	Yes	No
If YES, STOP interview here.		
Go to “Not-Eligible” section on last page.		

Date ____/____/____ ID: _____

8. What is your date of birth ____/____/____

Subtract date of last procedure from the current date: ____/____/____ - ____/____/____

“Then that would mean that you are: ____ ____ years old.

<u>Age exclusion:</u>			
Age < 30 years	OR	Age > 55 years	Yes No
If YES, STOP interview here. Go to “Not-Eligible” section below.			

Not-Eligible Section

If the subject is deemed ineligible for study, state:

“Thank you for you time today. We appreciate your interest. However some health conditions or medications may interfere with the results with the study tests. We are not able to enroll you in the study, but greatly appreciate your time and effort.”

Date ____/____/____

ID: _____

COMPLETION OF PHONE ELIGIBILITY

Script

Thank you for answering all of these questions. You may enroll to participate in the study by completing more study questions that will be done at the UNC School of Nursing. What days of the week are you able to come to the School of Nursing?

Date 1: ____/____/____

Time: ____:____

Date 2: ____/____/____

Time: ____:____

Enter these dates to schedule the study procedures to check for availability with the UNC SON BBL calendar on the Scheduling Form, next page.

Instructions to the Participant

You will receive a subject information packet that provides a letter telling you the scheduled study date and time, instructions for transportation and parking with a map, an overview of the study and things you will need to do the night before the study. I want you to read over all these instructions when you received them in the mail and call me if you have any questions.

What address would you like for us to mail this information packet to?

Street or Box: _____

City: _____

State: _____ Zip: _____

It is expected that you will be with us for three to four hours depending on your needs. While you are with us, you will be provided some nourishing refreshments. Please bring any medications that you need to take during those times with you. Would you like to have a reminder call the day before you come in for the research study?

Yes

No

If yes, ask them for two phone numbers of their choice to contact them.

Contact 1: (____) _____ - _____

Contact 2: (____) _____ - _____

We thank you for your interest in this study and your willingness to participate. I look forward to working with you in this research study at the UNC School of Nursing.

Date ____/____/____

ID: _____

A.2 Subject Information Packet

SUBJECT INFORMATION PACKET

Instructions for sending the Subject Information Packet

1. After consulting with the UNC SON Biobehavioral Laboratory calendar to schedule the subject, you will send the Subject Information Packet to the subject.

This packet contains:

1. Letter to subject with their scheduled study date and time
2. Instructions sheet labeled “What they should do now”
3. Instructions sheet labeled “Overview of the study”
4. Instruction sheet labeled “Directions”
5. Map of the UNC Campus

2. Be sure to address the letter to the subject.

3. Be sure to insert in the letter (Item #1) the scheduled date and time.

4. Make a copy of the letter to be retained in the subject file which will be kept in the locked cabinet.



April 12, 2014

«Title» «First» «MidI» «Last»
«Street_1»
«City», «State» «Zip5»«Zip9»

Dear «Title» «Last»:

Thank you again for participating in our research study titled “Pilot Study of Sensory Information Processing and Motor Processing: Relationship to Executive Control in Adults with Primary Brain Tumors.” We’re very excited that you called us about this important study and we’re looking forward to seeing you for your scheduled appointment in the University of North Carolina School of Nursing Biobehavioral Laboratory. We presently have you scheduled to come in as follows:

**Date: «BDay1», «BDate1», at
Time: «BTime2»**

I have enclosed materials that provide more detailed information that I hope you will find helpful. Please pay special attention to the page entitled, “What you should do now.”

I will call you the day before your study to make sure you’ve received this packet and to answer any questions you may have. Please bring this packet with you when you come for your study, because you will be receiving other information that you may want to keep together. In the meantime, please feel free to phone me (919-883-7002) with any questions or concerns you might have. We’ll look forward to seeing you then!

Sincerely,

Deborah H. Allen, RN, MSN, FNP-BC, AOCNP
Predoctoral Student, School of Nursing
University of North Carolina at Chapel Hill

What You Should Do Now

1. Please let us know if you have any food allergies or other dietary requirements of which we might not already be aware. You may call us at (919) 883-7002 to so advise.
2. Please let us know if you plan to drive so that we can reserve a parking space for you. You may reach us by telephone at (919) 883-7002. Parking is limited to the Bell Tower parking lot, which is located down the hill from the School of Nursing. If you choose to drive, one of my research assistants will meet you at the Bell Tower parking lot entrance to give you the permit and assist you with gaining access to the parking area (see the directions on the following page).

If you would prefer not to drive, you may ride one of the Chapel Hill Transit busses free of charge. There is a bus stop located directly in front of the School of Nursing. If you are having difficulty in arranging for transportation, please call so that we may help. If you would like for us to do this, please call us as soon as possible (919-883-7002) so we may have enough time to make plans for your transportation.

On the day of your appointment:

If you are going to be late or need to cancel your study,
Please call Deborah Allen directly.
At phone number 919-883-7002.

**A MAP AND DIRECTIONS TO THE PARKING AREA
ARE INCLUDED LATER IN THE PACKET.**

Date: ____/____/____

ID: _____

OVERVIEW OF THE STUDY PROTOCOL

The study will be conducted at the Biobehavioral Laboratory (Room 10) at the UNC School of Nursing, located in Carrington Hall. We will ask that you report to the lab at the scheduled time of _____ as indicated in your letter. The study will take 3 hours. You will be given time for breaks, as well as snacks and drinks. You may opt to bring in food, drinks, or items like pillows to make sitting more comfortable. Let us know if you have any allergies, require special foods or drinks, or have special needs that we should know; you may call us at 919-883-7002.

WHAT YOU SHOULD KNOW BEFORE COMING IN FOR YOUR STUDY

1. On the day before the study, you should do the things that you would regularly do. This includes going to bed and getting up at your usual times, eating what you usually eat, and taking your medications as prescribed by your doctor. (The exceptions to this are listed below under the heading “What we ask you to avoid.”)
2. If you have been taking cold medicines the week before the study, please call us to discuss rescheduling the study procedures.
3. Do not bring any valuables (large amounts of money or jewelry) that could be stolen. Although this is unlikely to occur, it is better to be safe than sorry.
4. Your family or friends may come with you to see the laboratory.

What We Ask You To Avoid

We would ask that you avoid the following so we get the best recordings possible:

- a. Any alcoholic beverages after dinner (including wine and beer) on the night before coming in for your study,
- b. Medications that help you sleep or cold medications for 24 hours before coming in for your study, and
- c. Do not smoke any tobacco products for 4 hours before coming in for your study.

Date: ____/____/____

ID: _____

Directions to the Bell Tower Parking Lot/School of Nursing

1. North on 15-501 Bypass (from Burlington/Carrboro): Take the Chapel Hill-Pittsboro exit. At the stoplight, make a left onto South Columbia Street. Follow the road up the hill and go through the intersection of South Columbia and Manning Drive. Start to get into the right lane. After you pass the School of Nursing (which will be located on your right), make a right turn at the next stoplight (which is at South Road). Stay to the right again and make a right-hand turn at the next stop light, which is Bell Tower Drive (this will take you into the Bell Tower parking area).

2. South on 15-501 Bypass (from University Mall/Durham): From University Mall, get ready to make a right turn at the Highway 54 exit (as you head into campus this becomes South Road). At the first stoplight at the top of the hill you will see the Institute of Law to your left. Continue going straight on South Road. At the second stoplight you will see Fetzer Gymnasium to your left and Raleigh Road to your right. You'll next see Student Stores on your right, followed by Stadium Drive and the Bell Tower on your left. Continue to the next stoplight and make a left turn onto Bell Tower Drive (this will take you into the Bell Tower parking area).

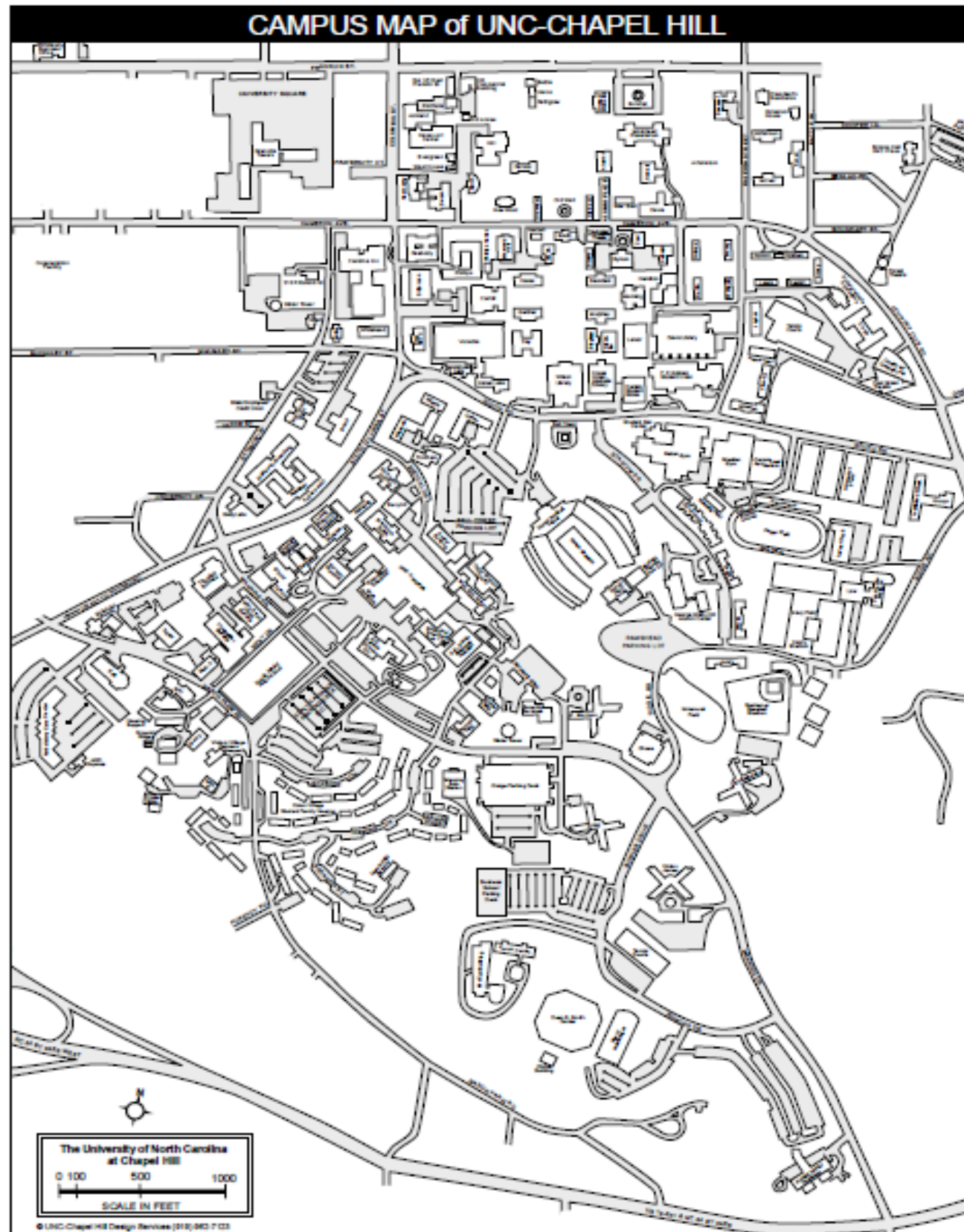
3. From Highway 54 (RTP or Raleigh): Take Highway 54 toward campus, go under the 15-501 bypass, and continue up the hill (as you head into campus, Hwy 54 becomes South Road). At the first stoplight at the top of the hill you will see the Institute of Law to your left. Continue going straight on South Road. At the second stoplight you will see Fetzer Gymnasium to your left and Raleigh Road to your right. You'll next see Student Stores on your right, followed by Stadium Drive and the Bell Tower on your left. Continue to the next stoplight and make a left turn onto Bell Tower Drive (this will take you into the Bell Tower parking area).

4. From Downtown Chapel Hill (Coming from Franklin Street): From the intersection of Franklin and South Columbia Streets (Spanky's is on this corner), take South Columbia into campus. At the second stop light, make a right onto Cameron Avenue and get into the left lane. At the next stoplight, make a left onto Pittsboro Street. Then make a left again at the next stop light, which will be at McCauley Street. Cross South Columbia Street (at this point McCauley Street becomes South Road). Make a right at the next stop light, which is Bell Tower Drive (which will take you into the Bell Tower parking area).

PLEASE REFER TO THE MAP ON THE NEXT PAGE.

Date: ____/____/____

ID: _____



Date: ____/____/____

ID: _____

A.3 Scheduling Form

SCHEDULING FORM

INSTRUCTIONS TO RECRUITER:
Add new participant name to this form when recruiting. After completing this form and confirming the schedule with the SON BBL, file in the Scheduling Folder and keep stored in locked file cabinet.

Adults with Primary Brain Tumors:

Subject Name	Age	Gender	Study Date 1	Study Date 2
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				

Healthy Adult Controls

Subject Name	Age	Gender	Study Date 1	Study Date 2
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				

Date: ____/____/____

ID: _____

A.4 Laboratory Intake Screen & Mini-Consent

LABORATORY INTAKE SCREEN

Subject Preparation

Give the subject a tour of the BBL including the test area, bathroom, and nourishment station. Offer them something to drink and have them seated in the testing interview area. Make sure the door is closed to the BBL and the interview room prior to proceeding with the Laboratory Intake Screen.

Mini Consent

Ask them:

“Before we start, I’d like to ask you a few questions and would like to perform a brief exam on your ability to process and think. This is to make sure that you have had not changes in your health status since we spoke on the telephone. There are some health conditions or problems with thinking that may keep you from participating in the study. If you are not eligible to be involved in the study, I will shred all of the information that you have given me over the phone and what we have done today and you will not receive the \$25 for your time and travel. Is it okay to proceed with the questions and test now?”

If yes, proceed with the four questions below.

If no, stop the interview and thank the subject for coming.
Escort the subject and ask if they need directions back to their parking area.

Adjunct to Pre-Study Instrument

“Since we’ve last talked have you had any of the following:

1. Surgical procedures requiring general anesthesia? **Yes** **No**

2. Please tell me about any new medicine you are taking.

List the medications: _____

Are any of these drugs a sedative hypnotic or cold medication? **Yes** **No**

3. Have you had alcohol in the last 24 hours? **Yes** **No**

4. Have you smoked in the last 4 hours? **Yes** **No**

If yes to any of the question, reschedule the research study time.

Date: ____/____/____ Time: ____:____

If no, proceed to the Mini-Mental Status Examination, next page.

Date: ____/____/____

ID: _____

A.5 Mini-Mental Status Examination

The Mini-Mental State Examination
(Folstein et al., 1975)

Instructions to Patient: “Now I’d like you to answer some questions and follow some Instructions. Do your best to respond to each question or instruction. Some will seem very simple and some will be more difficult.”

Code in margin any question that patient refuses to answer (9) or is physically unable to answer (8). Do not include the 8’s and 9’s in the total score, but do indicate reason code was used (where applicable).

	Points Avail.	Points Earned
Orientation		
1. Ask first: “What is the day, date and season?”		
If information is omitted, ask as needed:		
Year	1	_____
Season?	1	_____
Date?	1	_____
Day?	1	_____
Month?	1	_____
If patient can’t answer three of these correctly ask, “What part of the day is this?” (morning, afternoon, evening, night). Code response at end of MMSE total (see item #13)		
2. Ask: “What is the name of this place and where is it located?”		
If information is omitted, ask as needed:		
State?	1	_____
County?	1	_____
Town or City?	1	_____
Building?	1	_____
Floor?	1	_____
Registration		
3. Name three objects, taking one second to say each.		
“I am going to give you a list of 3 words. I want you to listen carefully then repeat them back to me. The words are book, house, candle . Please tell me the three words.”		
Book	1	_____
House	1	_____
Candle	1	_____
(Score responses on first try. Then repeat objects until all are learned.)		
Tell patient, “Try to remember those objects because I’m going to ask you to repeat them from memory later.”		
Attention and Calculation		
4. Serial Sevens. Give one point for each correct answer.		

Date: ____/____/____ ID: _____

“I want you to start with the number 100, subtract 7, and tell me your answer. So how much is 7 from 100? ____ (93)
Now keep subtracting seven until I tell you to stop.”
(Stop after five answers; you may prompt after each answer.)
Record responses: ____
Correct Responses: 93 86 79 72 65 5 _____

If patient missed any calculation, then ask the following:
“Now I am going to spell a word forward and I want you to spell it backwards. The word is ‘world,’ W-O-R-L-D. Spell ‘world’ backwards.”
(Answer: D-L-R-O-W; repeat if necessary but not after spelling starts.)
Record responses: ____

Recall
5. Ask for the names of the three objects learned in Question 3.
(Give 1 point for each correct answer.)
(book, house, candle) : _____ 3 _____

Language
6. Point to a pencil & a watch. Have patient name them as you point.
“What do you call this?” “What is this?” 2 _____
7. Have the patient repeat: “No ifs, ands, or buts.” 1 _____
(Stress s’s when you say it, s’s must be repeated back for a correct response.)
8. Have the patient follow a three-step command (using next page):
“Take this paper in your right hand, fold the paper in half with both hands, and put the paper on the bed (floor, etc.).” 3 _____
9. Have the patient read and obey the following from the next page:
“CLOSE YOUR EYES.” 1 _____
10. Have the patient write a simple sentence of his or her choice. 1 _____
(The sentence should contain a subject and a verb and should make sense. Ignore spelling errors when scoring.)
11. Put the Bender Gestalt design before patient and ask patient to,
“Copy this shape.” 1 _____
(Give one point if all sides and angles are preserved and if the intersecting sides form a quadrangle.)
12. Total Score (sum 0’s & 1’s). 30 _____

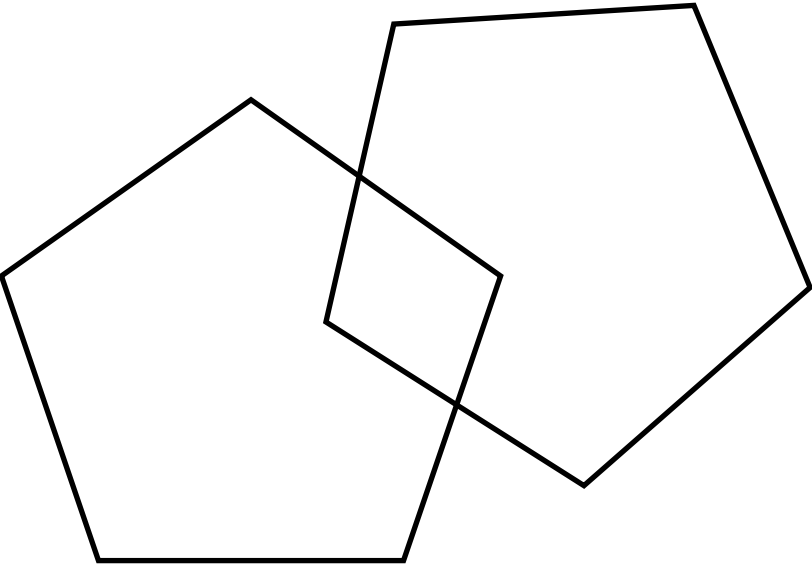
Date: ____/____/____

ID: _____

Close your eyes.

Date: ____/____/____

ID: _____



Date: ____/____/____

ID: _____

A.6 Subject Eligibility Form

SUBJECT ELIGIBILITY FORM

Eligibility Criteria for Adults Subject with Primary Brain Tumor	Screen TS/Lab	YES	NO	N/A
Age 30 to 55 years old	TS			
Primary Brain Tumor treated with chemotherapy or radiation therapy (completed therapy at least one year prior to enrollment)	TS			
Read and write English language	TS			
Stable seizure status for last six months with no antiepileptic medication changes in the last six months	TS			
MMSE \geq 24 points	Lab			
Signed informed consent	Lab			
<i>Exclusion Criteria</i>				
General anesthesia within the last six months	TS			
Paresis or Aphasia	TS			
Unstable seizure disorder requiring antiepileptic medication adjustments	TS			
Known neuro disorders listed in Appendix A.1 (Example: Parkinson's disease, multiple sclerosis, Alzheimer's disease, CVA, immune disorders)	TS			
Sleep disorder/apnea or sedative hypnotic the night before	TS & Lab			
Had cold meds, alcohol night before; tobacco 4 hr before	Lab			

Exclude subject if yes to any of these exclusions.

TS=telephone screen

Eligibility Criteria for Healthy Control Subjects	Screen TS/Lab	YES	NO	N/A
Age 30 to 55 years old	TS			
No seizures	TS			
Read and write English language	TS			
MMSE \geq 24 points	Lab			
Signed informed consent	Lab			
<i>Exclusion Criteria</i>				
General anesthesia within the last six months	TS			
Paresis or Aphasia	TS			
Unstable seizure disorder requiring antiepileptic medication adjustments	TS			
Known neuro disorders listed in Appendix A.1 (Example: Parkinson's disease, multiple sclerosis, Alzheimer's disease, CVA, immune disorders)	TS			
Sleep disorder/apnea or sedative hypnotic the night before	TS & Lab			
Had cold meds, alcohol night before; tobacco 4 hr before	Lab			

Exclude subject if yes to any of these exclusions.

TS=telephone screen

Date: ____/____/____

ID: _____

Appendix B: Informed Consent

1. Informed Consent Protocol
2. Informed Consent for the study

Date: ____/____/____

ID: _____

B.1. Informed Consent Protocol Checklist

Informed Consent Protocol

Informed Consent:

1. Allow subject to read consent or read it to them
2. Allow subject time to ask questions
3. Review the three hour schedule
4. Have subject sign the consent and researcher cosign the consent
5. Make a copy for subject, place original in file

Date: ____/____/____

ID: _____

Appendix C: Evaluations

1. Subject Packet

- a. Demographic Information
- b. Older Adults Resource Services Activities of Daily Living Scale
- c. Center for Epidemiological Studies Depression Scale

2. Investigator Packet

- a. Health Information Form
- b. EXIT-25
- c. Quantitative Sensory Test
- d. Trails-Making Test B on the OASIS Digitizer Writing Tablet

Date: ____/____/____

ID: _____

C.1 Subject Packet

Instructions for Subject Packet

The following questionnaires are to be completed by the subject:

Demographic Information Sheet

Older Adults Resource Services Activities of Daily Living Scale

Center for Epidemiological Studies Depression Scale

Provide a pencil with the forms for the subject.

Be available to answer any questions.

When the subject indicates that they are done, review the form to make sure all items are answered.

Record scores on data collection forms for data entry.

Check the data collection forms for accuracy.

File in subject record and store in locked file cabinet.

Date: ____/____/____

ID: _____

C.1.a. Demographic Information

DEMOGRAPHIC INFORMATION
(Carlson, 1999)

1.

Race

1=Caucasian/white

2=African American

3=American Indian

4=Hispanic

5=Asian/Pacific islander

6=Other
2.

Gender (1=male, 2=female)
3.

How many grades did you complete in school?

(Record highest grade)

1-12=Grade school/High school

12=GED/High school diploma

13=Technical only

14=Baccalaurean only

15=Graduate School

16=Doctorate
4.

What activities best describe what you typically do:

1=employed, full time

2=employed, part time

3=retired

4=never had a job outside home

5=disabled

6=other
5.

Marital Status

1=married, living with spouse

2=married, separated

3=single, living alone

4=single, living with someone

5=single, recently widowed (2 years)
6.

Age (rounded to the nearest year)
7.

What types of jobs have you had?

Date: ____/____/____

ID: _____

C.1.b Older Adults Resource Services Activities of Daily Living Scale

Older Adults Resource Services Activities of Daily Living Scale

(Fillenbaum, 1978)

Instructions: The following questions are about some of the activities of daily living (ADLs), the things that we all need to do as part of our daily lives. I would like to know if, within the last month, you could do these activities without any help at all, or if you needed some help to do them, or if you couldn't do them at all. Please write the number for the best answer in the space provided.

Physical ADLS

1. Can you eat . . . _____
2 = without help (able to feed yourself completely),
1 = with some help (need help with cutting, etc.),
0 = or are you completely unable to feed yourself?
2. Can you dress and undress yourself . . . _____
2 = without help (able to pick out clothes, dress and undress yourself),
1 = with some help,
0 = or are you completely unable to dress and undress yourself?
3. Can you take care of your own appearance, for example combing your hair or shaving . . . _____
2 = without help,
1 = with some help,
0 = or are you completely unable to maintain your appearance yourself?
4. Can you walk . . . _____
2 = without help (except for a cane),
1 = with some help from a person or using a walker, crutches, etc.,
0 = or are you completely unable to walk?
5. Can you get in and out of bed . . . _____
2 = without any help (without grabbing hold of the bedstand or aids),
1 = with some help (either from a person, grabbing hold of a bedstand or with the aid of some device),
0 = or are you totally dependent on someone else to lift you?
6. Can you take a bath or shower . . . _____
2 = without help,
1 = with some help (need help getting in and out of the tub, or need special attachment on the tub),
0 = or are you completely unable to bathe yourself?

Date: ____/____/____

ID: _____

7. Do you ever have trouble getting to the bathroom on time? _____
2 = no
1 = yes
- a. If yes, how often do you wet our soil yourself? _____
1 = once or twice a week?
0 = three times a week or more?

Independent ADLS

8. Can you use the telephone . . . _____
2 = without help, including looking up the number and dialing,
1 = with some help (could answer phone or dial operator in an emergency, but need a special phone or help),
0 = or are you completely unable to use the telephone?
9. Can you get to places out of walking distance . . . _____
2 = without help (travel alone on buses, taxis, or drive your own car),
1 = with some help (need someone to help you or be with you when traveling),
0 = or are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?
10. Can you go shopping for groceries or clothes (assuming you have transportation) . . . _____
2 = without help (take care of all shopping needs yourself),
1 = with some help (need someone to go with you on all shopping trips),
0 = or are you completely unable to do any shopping?
11. Can you prepare your own meals . . . _____
2 = without help (plan and cook full meals yourself),
1 = with some help (could prepare something but unable to cook full meals yourself),
0 = or were you completely unable to prepare your meals?
12. Can you do your housework or yardwork . . . _____
2 = without help (scrub floors, cut grass, etc.),
1 = with some help (could do light work but need help with heavy work),
0 = or are you completely unable to do any of this type of work?

Date: ____/____/____

ID: _____

13. Can you take your own medicine . . . _____
- 2 = without help (in the right dose, at the right time),
 - 1 = with some help (able to take medicine if someone prepares it for you or reminds you to take it),
 - 0 = or are you completely unable to take your medicine?
14. Can you handle your own money... _____
- 2 = without help (write checks, pay bills, etc.),
 - 1 = with some help (could manage day-to-day buying but need help with managing your checkbook or paying your bills),
 - 0 = were you completely unable to handle money?

Date: ____/____/____

ID: _____

C.1.c Center of Epidemiology Screen for Depression

Mood Screen

Please indicate how often in the past seven days you have agreed with the following statements

During the past week:	Rarely (<1 day)	Some of the time (1-2 days)	Occasionally (3-4 days)	Most of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I did not feel like eating; my appetite was poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt that I was just as good as other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I had trouble keeping my mind on what I was doing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I felt depressed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I felt that everything I did was an effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I felt hopeful about the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I thought my life had been a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I felt fearful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. My sleep was restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I was happy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I talked less than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I felt lonely.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. People were unfriendly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I enjoyed life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I had crying spells.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I felt sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I felt that people disliked me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I could not get "going."	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date: ____/____/____

ID: _____

C.2 Investigator Packet

Instructions for Investigator Packet

The following evaluations are to be completed by the researcher:

Health Information Form

EXIT-25

Quantitative Sensory Test

Trails-Making Test B on the OASIS Digitizer Writing Tablet

Date: ____/____/____

ID: _____

C.2.a Health Information Form

Health Information

I. Vital Signs

Have the subject sitting comfortably. Inform the subject that you are going to take their vital signs, starting with their blood pressure in their right arm. Loose any restrictive clothing on the right arm (roll up sleeve of shirt if necessary).

- 1. Place the Dynamap 1846 SX cuff on the right arm and begin the machine.
- 2. Place the Nonin1500 pulse oximeter on the middle finger of the left hand.
- 3. Take oral temperature with the IVAC thermometer.
- 4. Record vital signs below.

Heart rate	_____	_____	_____
Systolic blood pressure	_____	_____	_____
Diastolic blood pressure	_____	_____	_____
Respiratory rate	_____	_____	
Oral Temperature to nearest .1 degree Fahrenheit	_____	_____	_____
Oxyhemoglobin saturation:	_____	_____	%

Date: / /

ID:

II. Key Medical-Related Events

Ask the subject the following:
“Over the past three months, have you had any of the following?”

KEY MEDICAL RELATED EVENTS	YES	NO
General:		
Falls		
Fainting spells /blacking out		
Dizziness		
Numbness/weakness		
Chills/fever		
Headaches or migraines		
Seizures		
Orthnopnea		
Shortness of breath		
Chest pain		
Tachycardia		
Leg swelling		
#Pillows to sleep		
Numbness/weakness		
Upper respiratory infection in past week?		
Coughing		
Hemoptysis		
Wheezing		
Shortness of breath in the past week		
Weakness of any extremity		
Problems walking		
Joint problems		
Difficulty with dexterity (button clothes, etc)		
Self-Report Health Rating: How would you say that your health at this time compares with your health one month ago? Is it: 3=better than 1 month ago 2=about the same as 1 month ago 1=worse than 1 month ago		

If subject is in the healthy control group, begin the EXIT-25 examination.

If subject is in the primary brain tumor group, complete the following set of questions below. Upon completion, proceed to the EXIT-25 examination.

Date: ____/____/____

ID: _____

III. Primary Brain Tumor Treatment Information

1. When were you diagnosed with your tumor? _____

2. What kind of tumor was it?
____ astrocytoma
____ oligodendroglioma
____ anaplastic astrocytoma
____ glioblastoma multiforme
____ other: _____

3. Do you know the location of the tumor?
____ right side ____ frontal
____ left side ____ parietal
 ____ temporal
 ____ occipital
 ____ cerebellum
 ____ brain stem

4. What kind of surgical procedure did you have when you were diagnosed?
____ biopsy
____ partial surgical resection
____ gross total resection

5. Date of surgery or surgeries: _____

6. What kind of treatments did you have for your tumor?
____ radiation therapy
____ stereotactic radiosurgery
____ stereotactic radiotherapy

7. Date of radiation therapies: _____

8. Did you have chemotherapy? _____ yes _____ no
If yes, duration _____

Date: ____/____/____

ID: _____

C.2.b EXIT-25

EXIT-25 (Royall, 1995)

EXIT EXIT25 (page 1 of 11)																	
<p>INDICATE ONE RESPONSE FOR EACH QUESTION BY PLACING A MARK IN THE APPROPRIATE NUMBERED BOX.</p> <div style="border: 1px solid black; padding: 2px; width: fit-content; margin-bottom: 10px;"> Mark appropriate box</div> <p>1. NUMBER-LETTER TASK</p> <p>"I'd like you to say some numbers and letters for me like this."</p> <p style="padding-left: 40px;">"1-A, 2-B, 3-what would come next?"</p> <p style="padding-left: 40px;">"C"</p> <p>"Now you try it starting with the number 1. Keep going until I say "stop".</p> <table style="margin-left: auto; margin-right: auto; border-collapse: collapse;"><tr><td style="padding: 0 10px;">1</td><td style="padding: 0 10px;">2</td><td style="padding: 0 10px;">3</td><td style="padding: 0 10px;">4</td><td style="padding: 0 10px;">5</td><td style="padding-left: 20px;">"Stop"</td></tr><tr><td style="padding: 0 10px;">A</td><td style="padding: 0 10px;">B</td><td style="padding: 0 10px;">C</td><td style="padding: 0 10px;">D</td><td style="padding: 0 10px;">E</td><td></td></tr></table> <p>SCORE:</p> <p>0 <input type="checkbox"/> No errors</p> <p>1 <input type="checkbox"/> Complete task with prompting (or repeat instruction)</p> <p>2 <input type="checkbox"/> Doesn't complete task</p>	1	2	3	4	5	"Stop"	A	B	C	D	E		<p>Examiner's Initials</p> <div style="border: 1px solid black; width: 100px; height: 40px; margin: 0 auto; position: relative;"><div style="position: absolute; top: -10px; left: 0; right: 0; border-top: 1px solid black;"></div><div style="position: absolute; bottom: -10px; left: 0; right: 0; border-bottom: 1px solid black;"></div></div> <p><small>Print Initials</small></p>				
1	2	3	4	5	"Stop"												
A	B	C	D	E													
<p>2. WORD FLUENCY</p> <p>"I am going to give you a letter. You will have one minute to name as many words as you can think of which begin with that letter."</p> <p>"For example, with the letter 'P' you could say 'people, pot, plant'... and so on. Are you ready?"</p> <p>"Do you have any questions?"</p> <p>"The letter is - A -. Go!"</p> <table style="width: 100%; border-collapse: collapse;"><tr><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td><td style="border-bottom: 1px solid black; width: 25%;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr><tr><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td><td style="border-bottom: 1px solid black;"></td></tr></table> <p>SCORE:</p> <p>0 <input type="checkbox"/> 10 or more words</p> <p>1 <input type="checkbox"/> 5 - 9 words</p> <p>2 <input type="checkbox"/> Less than 5 words</p>																	

Date: ____/____/____

ID: _____

EXIT	EXIT25 (page 2 of 11)
3. DESIGN FLUENCY	
"Look at these pictures. Each is made with only four (4) lines. I am going to give you one minute to draw as many DIFFERENT designs as you can. The only rules are that they must each be different and be drawn with four lines. Now go!"	
SCORE:	0 <input type="checkbox"/> 10 or more unique drawings (no copies of examples)
	1 <input type="checkbox"/> 5 - 9 unique drawings
	2 <input type="checkbox"/> Less than 5 unique drawings

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 3 of 11)

4. THEMATIC PERCEPTION

(Patient shown picture by examiner)

"Tell me what is happening in this picture."

- SCORE:**
- 0 ☐ Tells spontaneous story (story = setting, 3 characters, action)
 - 1 ☐ Tells story with prompting x 1 ("anything else?")
 - 2 ☐ Fails to tell story despite prompt





Date: ____/____/____

ID: _____

EXIT EXIT25 (page 4 of 11)	
5. ANOMALOUS SENTENCE REPETITION	
<div>✕ Mark appropriate box</div>	
"Listen very carefully and repeat these sentences exactly..."	
(Read the sentence in the usual tone of voice.)	
<div>1. "I pledge allegiance to those flags." 2. "Mary fed a little lamb." 3. "Throw, throw, throw your boat." 4. "Tinkle tinkle little star." 5. "A B C D U F G"</div>	
SCORE:	<div>0 <input type="checkbox"/> No errors 1 <input type="checkbox"/> Fails to make one or more changes 2 <input type="checkbox"/> Continues with one or more expressions (e.g. "Mary had a little lamb whose fleece was white as snow")</div>
6. MEMORY/DISTRACTION TASK	
"Remember these three words:"	
"APPLE, TABLE, PENNY"	
(Patient repeats words until all three are registered.)	
"Remember them - I'll ask you to repeat them for me later."	
"Now - spell CAT for me..."	
"Good. Now spell it backwards..."	
"OK. Tell me those three words we learned."	
<div>_____</div>	
SCORE:	<div>0 <input type="checkbox"/> Patient names some or all of the three words correctly without naming CAT (Examiner may prompt: "Anything else?") 1 <input type="checkbox"/> Other responses, Describe: <div></div> 2 <input type="checkbox"/> Patient names CAT as one of the three words (intrusion)</div>

Date: ____/____/____

ID: _____

EXIT		EXIT25 (page 5 of 11)	
7. INTERFERENCE TASK		<div> Mark appropriate box</div>	
<p>"What color are these letters?"</p> <p>(Examiner shows patient and sweeps hand back and forth over all letters.)</p>			
SCORE:	0	<input type="checkbox"/>	"black"
	1	<input type="checkbox"/>	"brown" (prompt "Are you sure?") > "black"
	2	<input type="checkbox"/>	"brown" (prompt) "brown" (intrusion)
<div></div>			
8. AUTOMATIC BEHAVIOR I			
<p>(Patient holds hands forward palms down.)</p> <p>"Relax while I check your reflexes..."</p> <p>(Rotate patient's arms one at a time at the elbow as if to check for cogwheeling. Gauge patients <u>active</u> participation/anticipation of the <u>rotation</u>.)</p>			
SCORE:	0	<input type="checkbox"/>	Patient remains passive
	1	<input type="checkbox"/>	Equivocal
	2	<input type="checkbox"/>	Patient actively copies the circular motion

Date: ____/____/____

ID: _____

EXIT	EXIT25 (page 6 of 11)
9. AUTOMATIC BEHAVIOR II (Patient holds hands out palms <u>up</u> .) "Just relax." (Examiner pushes down on patient's hands - gently at first, becoming more forceful. Gauge patient's active participation in the response.) SCORE: 0 <input type="checkbox"/> Patient offers no resistance (remains passive) 1 <input type="checkbox"/> Equivocal response 2 <input type="checkbox"/> <u>Actively</u> resists (or complies) with examiner	
10. GRASP REFLEX (Patient holds hands out with open palms <u>down</u> .) "Just relax." (Both palms are lightly stroked simultaneous by the examiner, who looks for grasping/gripping actions in the fingers.) SCORE: 0 <input type="checkbox"/> Absent 1 <input type="checkbox"/> Equivocal 2 <input type="checkbox"/> Present If present, does the patient grasp firmly enough to be drawn up and out of chair by examiner? 1 <input type="checkbox"/> NO 2 <input type="checkbox"/> YES	
11. SOCIAL HABIT I Fix patient's eyes. Silently count to three while maintaining patient's gaze, then say "Thank you." SCORE: 0 <input type="checkbox"/> Replies with a question (e.g. "Thank you for what?") 1 <input type="checkbox"/> Other responses, Describe: <input type="text"/> 2 <input type="checkbox"/> "You're welcome."	
12. MOTOR IMPERSISTENCE "Stick out your tongue and say 'aah' till I say stop... Go!" (count to three silently) (Subject must sustain a constant tone, not "ah...ah...ah...") SCORE: 0 <input type="checkbox"/> Completes task spontaneously 1 <input type="checkbox"/> Completes task with examiner modelling task for patient 2 <input type="checkbox"/> Fails task despite modelling by examiner	

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 7 of 11)	
13. SNOUT REFLEX	
"Just relax."	
(Examiner slowly brings index finger towards patient's lips, pausing momentarily 2" away. Finger is then placed vertically across lips and then is lightly tapped with the other hand. Observe lips for puckering.)	
SCORE:	0 <input type="checkbox"/> Not present
	1 <input type="checkbox"/> Equivocal
	2 <input type="checkbox"/> Present
	If present, does the patient pucker lips while examiner is pausing 2" away? 1 <input type="checkbox"/> NO 2 <input type="checkbox"/> YES
14. FINGER-NOSE-FINGER TASK	
(Examiner holds up index finger.)	
"Touch my finger."	
(Leaving finger in place, examiner says...)	
"Now touch your nose."	
SCORE:	0 <input type="checkbox"/> Patient complies, using same hand
	1 <input type="checkbox"/> Other response, Describe: <input type="text"/>
	2 <input type="checkbox"/> Patient complies, using other hand while continuing to touch examiner's finger
15. GO/NO-GO TASK	
"Now..."	
"When I touch my nose, you raise your finger like this." (Examiner raises index finger.)	
"When I raise my finger, you touch your nose like this." (Examiner touches nose with index finger.)	
Have patient repeat instructions if possible. The examiner should put their finger in their lap between instructions to reduce the potential for confusion.	
(Examiner begins task. Leave finger in place while awaiting patient's response. Put your finger back in your lap between trials to reduce the potential for confusion)	
Examiner	Patient
F	N F
N	F N
F	N F
F	N F
N	F N
SCORE:	0 <input type="checkbox"/> Performs bold sequence correctly
	1 <input type="checkbox"/> Correct, requires prompting/repeat instructions
	2 <input type="checkbox"/> Fails sequence despite prompting/repeat instructions

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 8 of 11)

16. ECHOPRAXIA I

"Now listen carefully. I want you to do exactly what I say. Ready?"

"Touch your ear." (Examiner touches his nose and keeps finger there.)

- SCORE: 0 ☐ Patient touches his ear
- 1 ☐ Other response, Describe:
(look for "mid-position" stance)
- 2 ☐ Patient touches his nose

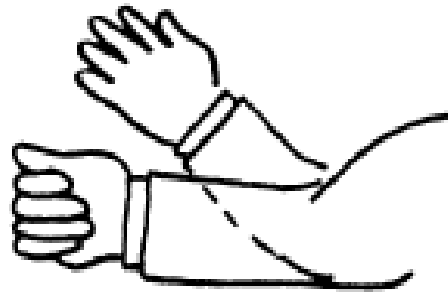
17. LURIA HAND SEQUENCE I

☒ Mark appropriate box

Palm/Fist

"Can you do this?"

(Invite patient to watch while alternating palm/fist with either hand. Once the patient appears to have mastered the task, have them demonstrate it. Ask the patient to "**keep going**" while the examiner stops. Count the number of successive palm/fist cycles.)



- SCORE: 0 ☐ 5 cycles without error after examiner stops
- 1 ☐ 5 cycles with additional verbal prompt
- 2 ☐ Unsuccessful despite prompting/modeling (watch for "mid-position" stances)

Date: ____/____/____

ID: _____

EXIT EXIT25 (page 9 of 11)

18. LURIA HAND SEQUENCE II

3 Hands

"Can you do this?"

(Examiner models: a) slap, b) fist, c) cut - while patient imitates each step)



"Now follow me." (Examiner begins to repeat sequence.)

Once the patient appears to have mastered the task, have them demonstrate it. Ask the patient to "keep going" while the examiner stops. Count the number of successive cycles.

Prompting is allowed at thirty seconds "are you sure you got it?"

Terminate the procedure after one minute has elapsed.

- SCORE:**
- 0 ☐ 4 cycles without error after examiner stops
 - 1 ☐ 4 cycles with additional verbal prompt ("Keep going") or modeling
 - 2 ☐ Unsuccessful

19. GRIP TASK



"Squeeze my fingers."

- SCORE:**
- 0 ☐ Patient grips fingers
 - 1 ☐ Other response, Describe:
 - 2 ☐ Patient pulls examiner's hands together

20. ECHOPRAXIA II

(Suddenly and without warning, the examiner slaps his hands together.)

- SCORE:**
- 0 ☐ Patient does not imitate examiner
 - 1 ☐ Patient hesitates, uncertain
 - 2 ☐ Patient imitates slap

Date: ____/____/____

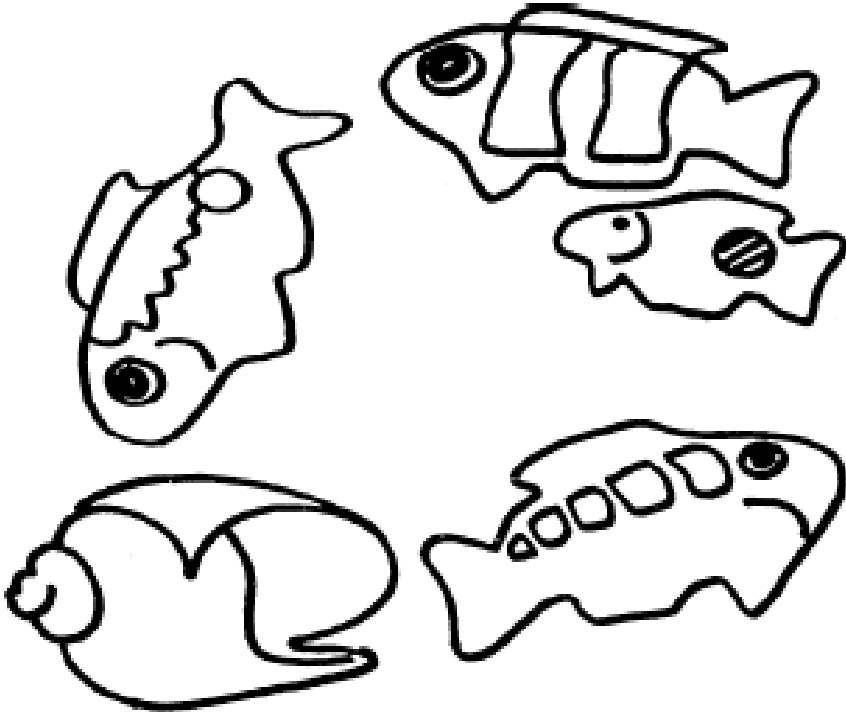
ID: _____

EXIT EXIT25 (page 10 of 11)	
<div>21. COMPLEX COMMAND TASK<div>Mark appropriate box</div><p>"Put your left hand on top of your head and close your eyes. That was good..."</p><p>(Examiner remains aloof, Quickly go onto next task.)</p><p>SCORE: 0 <input type="checkbox"/> Patient stops when next task began</p><p>1 <input type="checkbox"/> Equivocal - holds posture during part of next task</p><p>2 <input type="checkbox"/> Patient maintains posture through completion of next task - has to be told to cease</p></div>	
<div>22. SERIAL ORDER REVERSAL TASK<p>(Have patient recite the months of the year.)</p><p>"...Now start with January and say them all <u>backwards</u>..."</p><p>SCORE: 0 <input type="checkbox"/> No errors, at least past September</p><p>1 <input type="checkbox"/> Gets past September but requires repeat instructions ("Just start with January and say them all backwards.")</p><p>2 <input type="checkbox"/> Can't succeed despite prompting</p></div>	
<div>23. UTILIZATION BEHAVIOR<p>(Examiner holds pen near point and dramatically "presents" it to the patient asking:)</p><p>"What is this called?"</p><p>SCORE: 0 <input type="checkbox"/> Doesn't reach</p><p>1 <input type="checkbox"/> Reaches, hesitates</p><p>2 <input type="checkbox"/> Patient takes pen from examiner (utilization behavior)</p></div>	
<div>24. IMITATION BEHAVIOR<p>(Examiner flexes wrist up and down and points to it asking:)</p><p>"What is this called?"</p><p>SCORE: 0 <input type="checkbox"/> "Wrist"</p><p>1 <input type="checkbox"/> Other response, Describe: <input type="text"/></p><p>2 <input type="checkbox"/> Patient flexes wrist up and down (echopraxia)</p></div>	

EXIT EXIT25 (page 11 of 11)

25. COUNTING TASK 1
"Please count the fish in this picture out loud."

SCORE: 0 ☐ Four
1 ☐ Other
2 ☐ More or less than four



Date: ____/____/____

ID: _____

C.2.c Quantitative Sensory Testing (QST) Protocol

Instrument Prep (prior to subject arrival)

1. Turn on the computer
2. Make sure the cables from the QST to the computer is intact
3. Turn on the QST
4. Locate the QST program icon on the laptop screen
5. Double click to enter into the program
6. On the left side of the screen find the calibration program, highlight and click
7. Observe the tips beginning to move, place your finger tips (second and third tips) over the finger tip holes and feel the tips touch; once completed the machine is calibrated.
8. Find the SON program on the right side of the program options, highlight it and click.
9. Enter subject number and date into the program
10. Click on UL D2D3 for the stimulus location
11. Save this program and exit out until ready for subject to begin the study

Initiation of the Trial

1. To begin study, find subject data
2. Click on SON program, UL D2D3
3. Have subject sit comfortably in a chair in front of the computer scan
4. Show the subject the device and the 2 finger tip holes
5. Offer the bean bag on top of the device in order to rest their wrist
6. Show them the two button mouse which they will use with their left hand to indicate their choices
7. Ask them if they are ready for a demonstration
8. Press GO

Date: ____/____/____

ID: _____

Subject Instructions

1. Get the subject to place their arm on the device with their wrist on the top of the device and the fingertips over the applicator holes. Say to the subject “Place your finger tips against the holes. Do not press too hard against the holes as the device is sensitive to the pressure. Be sure to relax your arm and wrist.”

Practice Session

2. Prepare to begin the demonstration program and say “This first test is one that is a reaction time test so as soon as you feel the tip against your finger, press the right button here with your left hand.”
3. Start the program and as the applicators extend to make contact the subject say “Do you feel it?”
4. As the subject indicates that they successfully felt the applicator, say “Good. Are you ready to start the first program?”
5. As the subject indicates that they are ready, press start and say “Let’s start the training session.”
6. Stay with the subject as they are completing the first series in case they have questions or to troubleshoot any technical difficulties with the equipment. At the end of the program, say “Now you can relax.” Point to the computer screen and explain it to the subject by saying “This screen shows your reaction times when you felt the tip against your finger. The average is 150 milliseconds.”

Series One

7. To prepare for the first study series, explain to the subject “This next test is a little different. The touch that you will feel will be on either finger, the right one or the left one. You will need to indicate where you feel it by pressing the right or left button here with your left hand. There is a training here with 3 tries. So let’s start that to see if you have questions.”
8. Make sure that their arm is back in position. Press GO to start the training session.
9. As they are completing the training, ask “Did you feel that? How was it to press the right or the left button.” Listen to their comments to see if they need a more comfortable seat, hand position, different mouse for their left hand.
10. When they are finished responding to you, ask “Are you ready to start the session on this test?” As they indicate that they are ready, press GO.
11. Stay with the subject as they are completing the first series in case they have questions or to troubleshoot any technical difficulties with the equipment. At the end of the program, say “Now you can relax.” Point to the computer screen and explain it to the subject by saying “This screen shows your reaction times again and it does take longer for you to distinguish between right and left. That is normal.”

Series Two

12. To prepare the subject for the second series, explain to them “This next test is again different. You will feel 2 taps and you need to determine which one is first. The point of this test is to be correct with where you felt it first, not how fast you are.

Date: ____/____/____

ID: _____

There will be a 'choose' screen after the taps have been done and that is when you press the right or the left button. Are you ready?"

13. As they have their fingers in position and their arm rested on top of the device, press GO.
14. At the end of the program, state "You can relax your arm now. This shows your tracking with the tap. The taps did occur faster and that makes it more difficult to judge where you felt them."

Series Three

15. Prepare the subject for the third series, and say "This next test is using vibration instead of the light touch or tap. You will feel the vibration on both fingertips. You will need to indicate where you feel the strongest vibration. There is training with this one so let's begin that with three test trials. Ready?"
16. As they indicate that they are ready, check their arm positioning and make sure the arm is relaxed. Press GO.
17. At the end of the program, say "You can relax now. How are you doing? Are you ready for the next one?"

Series Four

18. Continue to make sure that the subject is comfortable. Say "For this fourth test, it is similar to the last one but you will feel the vibration on one finger. Ignore this vibration. There will be a short interval and then you will feel vibration on both fingertips. You will need to pick which vibration is stronger. You will have the CHOOSE screen come up when it is time for you to make your choice. Are you ready? Good."
19. As they indicate that they are ready, press GO.
20. At the end of the program, make sure they relax their position "You can relax now."

Series Five

21. For the last test, say "This last test is similar. There is a short delay in between the vibrations. One will be weak and one will be strong. Press the button when they feel the same to you. Ready?"
22. When the subject is ready, press GO.
23. As the program ends, reassure them that they are now completed with this session. "You can relax your arm now and get up to move around if you prefer. You have completed the tests with this instrument. Do you have any questions? It is now time for a break."

Instructions to end the program

After the subject has completed the test, press end to save the data to the hard drive. Do not turn off the computer as you will need to copy and back up the data after the subject has left the lab.

Date: ____/____/____

ID: _____

C.2.d Writing Board/Trails Making Test B Protocol

Instrument Prep (prior to subject arrival)

- a. Review the purpose of the instrument with the subject
- b. Show the subject the conventional Trails Making Test paper and pen
- c. Show the subject the OASIS digital writing tablet
 - i. Place the Trails Making Test A sample on the digital writing tablet on the board and turn on the magnetization to keep the paper secured
 - ii. Demonstrate how the pen writes on the paper
 - iii. Do not start the computerized program
- d. Review the Trails Making Test B by removing sample A from the board and placing sample B on the board
 - i. Review the instructions of sample B
 - ii. Have them perform the sample B on the writing board
 - iii. Do not start the computerized program
- e. Ask if they have any questions
- f. Remove sample B and place test B on the board, magnetize
- g. Begin the subject's computerized program
 - i. Read the instructions to the subject
 - ii. Start the computerized program when they are ready to start drawing
 - iii. Stop the computerized program when they stop the drawing process at number 13
 - iv. Record total time on the data collection form
 - v. Save the subject data and close the program
 - vi. Leave the computer on so that at completion of this session and subject has left, the PI can go back in to the program to record the data on the data collection forms and save to a CD

Date: ____/____/____

ID: _____

C.2.d Trails-Making Test, Parts A & B

Instructions for Administering the Trails A & B

Part A

1. Tell the subject “For this test I want you to work as quickly as possible but try to avoid making mistakes.”
2. Place the example for Trails A in front of the participant, the bottom of the test should be about 6 inches from the edge of the table.
3. Give the participant a pencil and say: “On this page are some numbers” (Point at the numbers). Begin at number 1 (point to 1) and draw a line from 1-2 (point to 2), 2 to 3 (point to 3), 3-4 (point to 4) and so on, in order, until you reach the end (point to the circle marked ‘end’) Draw the lines as fast as you can. Ready—Begin.”
4. If the participant completes the sample and shows he/she understands the instructions then say: “Good! Why don’t you try this next one.”
5. Turn the page over and give Part A of the test and say: ”On this page are some more numbers. Begin with the number 1 (point to 1) and draw a line from 1 to 2 (point to 2) and so on, until you reach the end (point to end). Remember to work as fast as you can.”

Start timing as soon as the subject moves the pencil toward the number 2. Watch the participant closely in order to catch any errors as soon as they are made. If the subject makes any errors, call it to her/his attention immediately, return the subject’s pencil to the last correct circle and continue the test from that point. Do not stop timing while correcting the subject’s error.

6. After the subject completes Part A, take the test sheet and record the time as it is shown on the stop watch.
7. Then say “That’s fine. Now we’ll try another one.”
8. Write down the stopwatch time in the upper right hand corner 00:00:00

Part B

1. Place the sample side of Part B on the table in front of the subject in the same position as the sheet for Part A.
2. Point to the sample and say “On this page are some numbers and letters. Begin at 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end. Ready ---Begin.”
3. When the subject completes Sample B, say. On this page are both number and letters. Please do this the same way. Begin at 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end. Ready ---Begin.”

Start timing as soon as the subject moves the pencil toward the letter ‘A’. Watch the participant closely in order to catch any errors as soon as they are made. If the subject makes any errors, call it to her/his attention immediately, return the subject’s pencil to the last correct circle and continue the test from that point. Do not stop timing while correcting the subject’s error.

4. Write down the stopwatch time in the upper right hand corner 00:00:00

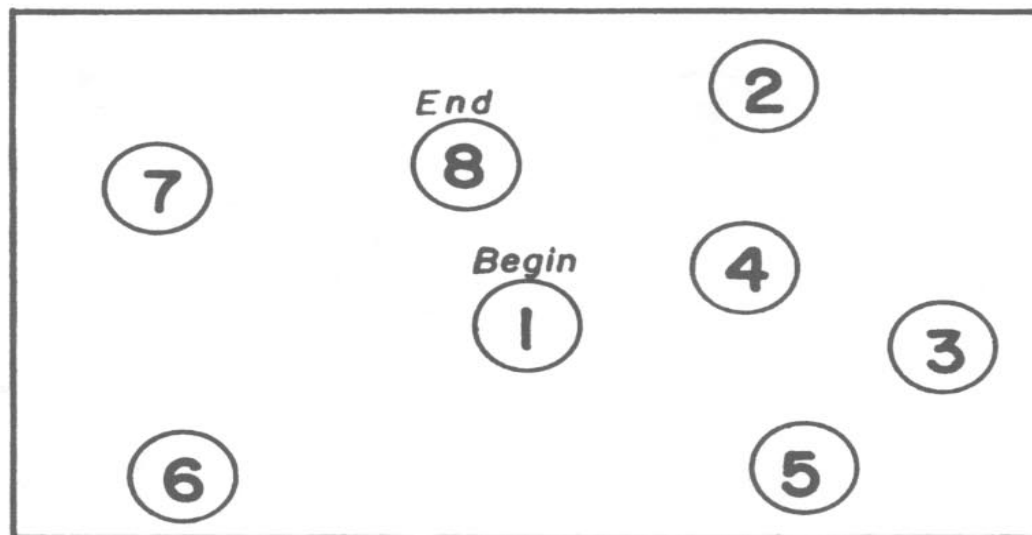
Date: ____/____/____

ID: _____

TRAIL MAKING

Part A

SAMPLE

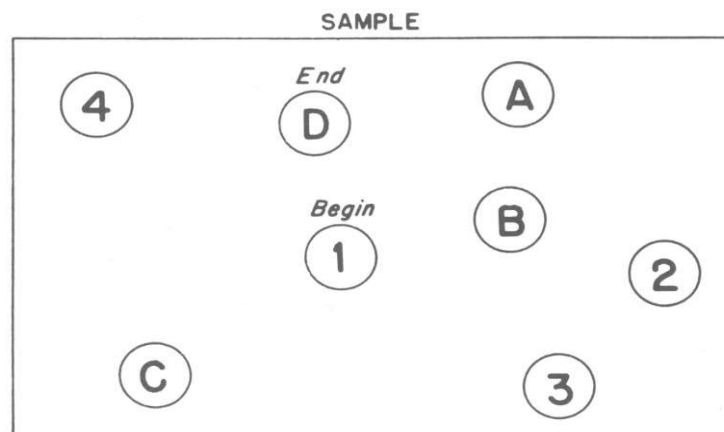


Date: ____/____/____

ID: _____

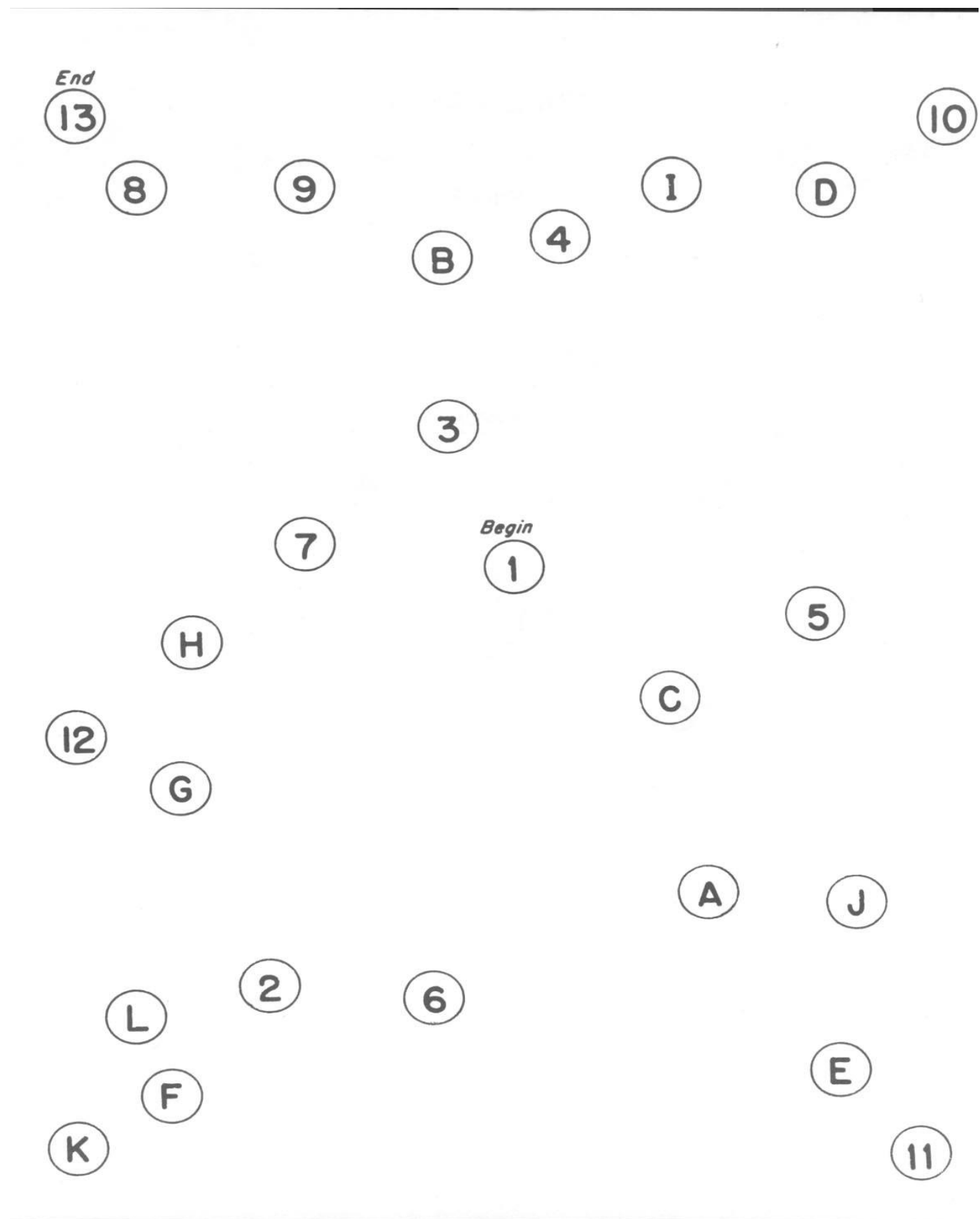
TRAIL MAKING

Part B



Date: ____/____/____

ID: _____



Date: ____/____/____

ID: _____

- Appendix D: Subject Debriefing
1. Qualitative Assessment Questionnaire
 2. Participation Packet

Date: ____/____/____

ID: _____

D.1 Qualitative Assessment Questionnaire

QUALITATIVE ASSESSMENT QUESTIONNAIRE

1. Please tell me about today's testing experience?
May need to ask more specifically to start them talking by discussing or asking ---
Were there specifics tests or questionnaires that you did like?
What did you like about them? What did you not like? Tell me more about that.

2. Did you get enough rest and food breaks today?
What would you suggest to improve it?

3. Did any of the tests or questionnaires make you feel uncomfortable?
Were you surprised by any of the tests, for instance, did a description of the test
make you think it was going to be something different?

4. Are there any of the tests that you would not want to do again? Why?
Are there any of the test that you would do again? and why?

5. Is there anything else that you would like to tell me that I haven't asked you regarding
the testing procedure that you have done today?

Thank you for your participation today. You may contact me at any time if you have any further questions that you may want to ask or any other forms of feedback about these tests that you would like to suggest.

Date: ____/____/____

ID: _____

D.2 Debriefing Protocol Checklist

Instructions for the final debriefing prior to subject departure

1. Perform Qualitative Assessment Questionnaire
2. Thank subject for their participation, time, travel.
3. Offer more nourishment.
4. Make sure they have their copy of the consent, card for future questions.
5. Provide them their cash for participation.
6. Have the subject sign a receipt.
7. Escort the subject to the door and make sure they have directions for their parking area.

Date: ____/____/____

ID: _____

Appendix E: Additional Materials

1. Referral Protocol and Letters for Subjects
2. Recruitment Flyers
 - a. Tear-off Flyer
 - b. Handout Flyer
3. Recruitment Email

Date: ____/____/____

ID: _____

E.1 Referral Protocol and Letter for Subjects

Instructions for Referring Subjects based on the findings from this study

A referral letter must be given to all subjects who *attains*:

1. a MMSE score < 24 points,
2. an EXIT-25 score of > 20,
3. Trails Making Test B time > 3 minutes,
4. an OARS score of < 20,
5. a CESD score of > 15,
6. a blood pressures over 140 systolic or 90 diastolic,
7. has a heart rate > 120 bpm,
8. a low arterial oxygen desaturation of < 90%,
9. prolonged anxiety or fear during testing procedure of > 10 minutes.

All of these conditions are serious and the lab director should be notified for adverse events requiring emergency personnel.

Attached are two major types of study referral letters: one for cognitive impairments and one for vital signs.

Please make sure that a copies of each form are on file in the research office under subject referrals.

Date: ____/____/____

ID: _____



Date: January 8, 2009

To: Mr. XXX
Address

From: Deborah Allen
Principal Investigator
School of Nursing
University of North Carolina at Chapel Hill

RE: Results of test here

Dear Mr. XXX,

As one of my study participants, you underwent a battery of health, memory and functional tests at the University of North Carolina, School of Nursing Biobehavioral Laboratory. In the process of our evaluation, we found that you are having difficulties with _____ and thought that it would be good for you to tell your doctor.

Specifically, you scored below normal on the Mini-Mental Status Exam. The Mini-Mental Status Exam is a test of overall cognitive function. The average passing score on the Mini-Mental Status Exam is 24 and you scored a __ on this test. You may also want to tell your doctor about these problems. Please let your doctor know that I would be happy to talk with him/her about the findings of this study. I can be reached at (919) 883-7002.

Sincerely,

Deborah Allen
Principal Investigator
UNC School of Nursing

Date: ____/____/____

ID: _____



Date: January 8, 2009

To: Mr. XXX
Address

From: Deborah Allen
Principal Investigator
School of Nursing
University of North Carolina at Chapel Hill

RE: Results of test here

Dear Mr. XXX,

As one of my study participants, you underwent a battery of health, memory and functional tests at the University of North Carolina, School of Nursing Biobehavioral Laboratory. In the process of our evaluation, we found that you are having difficulties with one of your vital signs and thought that it would be good for you to tell your doctor.

Specifically, you had a blood pressure that was very high. Your blood pressure was ____ systolic / ____ diastolic. The average blood pressure is below 120 systolic / 80 diastolic. You may also want to tell your doctor about these problems.

Please let your doctor know that I would be happy to talk with him/her about the findings of this study. I can be reached at (919) 883-7002.

Sincerely,

Deborah Allen
Principal Investigator
UNC School of Nursing

**ARE YOU A SURVIVOR OF A BRAIN TUMOR
and Interested in Participating in Research?**

If you are between 30 & 55 years of age and have undergone treatment for a primary brain tumor, you may be eligible to participate in a research study that is examining in tactile perception and motor control in survivors of primary brain tumors.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, sense different types of touch, and ability to connect numbers and letters on a digital writing board,

We will provide you with free parking and \$25 for your time upon completion of testing procedures.

There are no needles or blood draws!!!!

For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

Supported by the Biobehavioral Laboratory at

The School of Nursing, The University of North Carolina at Chapel Hill

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 08-1888

Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002
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ARE YOU A HEALTHY ADULT
and Interested in Participating in Research?

If you are between 30 & 55 years of age and have no neurological disorders, you may be eligible to participate in a research study that is examining tactile perception and motor control in relationship to cognitive processing.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, sense different types of touch, and ability to connect numbers and letters on a digital writing board,

We will provide you with free parking and \$25 for your time upon completion of testing procedures.

There are no needles or blood draws!!!!
For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

Supported by the Biobehavioral Laboratory at
The School of Nursing, The University of North Carolina at Chapel Hill
This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 08-1888)

Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002	Brain tumor study 919-883-7002
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Date: ____/____/____

ID: _____

E.3 Information flyer -- handout

Are You Interested in Participating in a Research Study?

If you are 30-55 years of age and have undergone treatment for a primary brain tumor OR 30-55 years of age with no known neurological disorder and willing to serve as a healthy adult control, then you may be eligible to participate in a research study that is examining touch and motor control in survivors of primary brain tumors.

If you chose to participate, you will come to the School of

Nursing in the morning to early afternoon. While there,

you will complete:

- Questionnaires about your health and ability to care for yourself,
- Heart rate, blood pressure, oxygen level measured,
- Tests that will measure your ability to think, sense different types of touch, and ability to connect numbers and letters on a digital writing board,

We will provide you with free parking and \$25 for your time upon completion of the testing procedures.

There are no needles or blood draws!!!!

For more information, please call...

Deborah Allen, RN, MSN at 919-883-7002

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 08-1888)

Date: ____/____/____

ID: _____

E.4 Email Information Flyer

Subject: INFORMATIONAL: Interested in research on touch or motor control?

From: Deborah Allen, Principal Investigator

If you are between 30 & 55 years of age and have undergone treatment for a primary brain tumor OR if you are between 30 and 55 years of age and have no known neurological disorder and willing to serve as a healthy adult control then you may be eligible to participate in a research study that is examining in tactile perception and motor control in survivors of primary brain tumors.

If you chose to participate, you will come to the School of Nursing in the morning to early afternoon. While there, you will complete: (1) Questionnaires about your health and ability to care for yourself, (2) Heart rate, blood pressure, oxygen level measured, and (3) Tests that will measure your ability to think, sense different types of touch, and ability to connect numbers and letters on a digital writing board. There are no needles or blood draws!!!!

All participants will be provided with free parking and \$25 for your time upon completion of the testing procedures. For more information, please call **Deborah Allen, RN, MSN** at 919-883-7002.

This study has been reviewed and approved by the UNC-Chapel Hill IRB (IRB# 08-1888)

APPENDIX J: PROXIES OF COGNITIVE RESERVE

Premorbid intelligence (IQ), educational achievement, and occupational attainment are the most commonly used proxies of cognitive reserve in subjects with dementia, traumatic brain injury, psychiatric disorders, and healthy aging. However, these proxies have not previously been explored for use with survivors or primary brain tumors. Thus, the measures for the CR proxies were first examined for suitability as a proxy of cognitive reserve in this sample.

Premorbid intelligence: the North American Adult Reading Test (NAART).

Premorbid intelligence was estimated by calculating the Full Scale Intelligence Quotient (FSIQ) from performance scores on the North American Adult Reading Test ([NAART]; Blair & Spreen, 1987, 1989). The NAART is reading test of 61 words that do not follow normal pronunciation procedures and requires previous exposure for its correct pronunciation. Population-based FSIQ scores for an average intelligence ranges from 90 to 110 with higher scores indicating higher IQ.

This sample had correct pronunciations on the NAART that ranged from 5 to 59 words for a median of 40.5 words (M 38.4, SD 12.7). Using the correct scores then produced FSIQ estimations of premorbid intelligence that ranged from 84.1, or slightly below average intelligence, to 126.2, or slightly above average intelligence. The sample mean was 110.0 (SD 9.8) reflecting average intelligence.

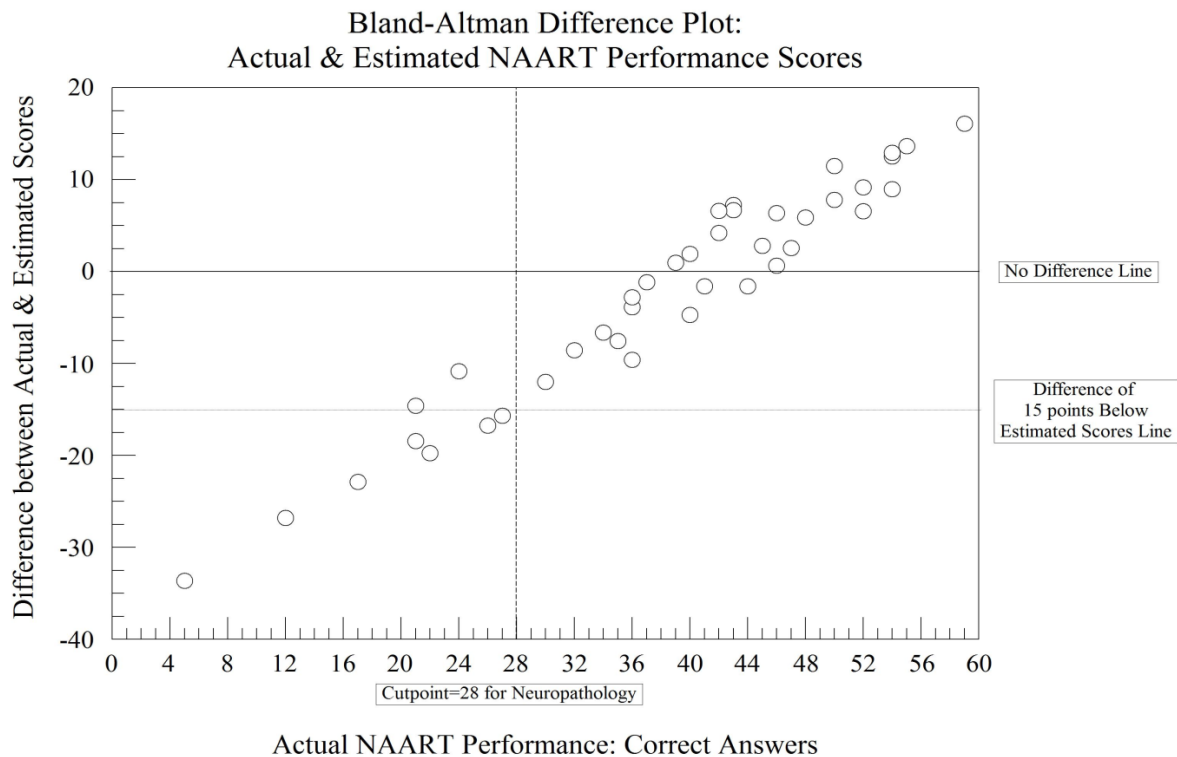
Age, $t(39)=-20.45, p<.001$, and education, $t(39)=-9.10, p<.001$, were associated with lower NAART performance scores. Thus, subjects who were older or had less education were more likely to have lower performance scores on the NAART. Those with longer survival times since diagnosis were more likely to have lower NAART performance scores, $t(39)=8.05, p<.001$.

There were no significant effects observed from tumor-related variables on NAART performance.

Spreeen and Strauss (2006) recommend using two determinations to ensure that the FSIQ estimation of premorbid intelligence is reliable in samples containing subjects with extensive neuropathology: (1) use of cutpoint score of 15 calculated from the difference between actual NAART performance and expected performance using age and education-based normative data, and (2) use of a cutpoint score of 28 for correct pronunciations.

The difference between actual and estimated NAART performance scores in this sample ranged from -33.7 to 16.1 and averaged -2.1 (SD 12.1). Eight subjects (20%) performed ≥ 15 points below the estimated NAART scores based on the education and age-adjusted calculations. All 8 subjects also performed > 28 correct pronunciations. There were a total of 9 subjects (22.5%) who had actual NAART performance scores of less than 28 as observed on Figure AJ.1.

Figure AJ.1. Bland-Altman Difference Plot of Actual & Estimated NAART Performance Scores ($n=40$).



The magnitude of the difference scores in relationship to actual performance on the NAART is demonstrated on the Bland-Altman plot, Figure 1. For every correctly pronounced word on the NAART, the difference between expected and actual performance improves by 0.97 ($R^2=0.94$, $p<.001$). While the majority of subjects performed within acceptable parameters according to Spreen and Strauss, the bias plot shows that half of the subjects in this sample performed below expected ranges based on their age and education. In addition, the magnitude of those performing below their expected scores is greater than those performing well.

To further describe differences observed in performances on the NAART, two groups were formed using the NAART difference cutpoint of ≥ 15 , Table 1. Subjects with more

education and held more professional job categories, as measured by the Hollingshead Index, were more likely to perform better on the NAART, $t(38)=2.64$, $p=.01$.

Table AJ.1.

Subject characteristics by difference scores between actual and expected NAART performance (n=40).

Characteristics	Difference < -15 (n=8)	Difference > -15 (n=32)	Group Comparisons t-test or χ^2
Age in years	54.5 (7.4)	49.0 (9.9)	$t(38)=1.45$, $p=.16$
Education in years	14.5 (1.4)	15.3 (2.0)	$t(38)=-1.02$, $p=.32$
Hollingshead Index	40.8 (8.9)	29.5 (11.2)	$t(38)=2.64$, $p=.01^*$
Time since diagnosed, in years	126.0 (83.5)	95.0 (79.6)	$t(38)=0.98$, $p=.36$
WHO Grade			Fisher's exact $p=.65$
Low Grade	1 (12.5%)	9 (28.0%)	
High Grade	7 (88.5%)	23 (72.0%)	
Tumor stability			Fisher's exact $p=.24$
No recurrence	7 (88.5%)	20 (62.5%)	
Any recurrence	1 (12.5%)	12 (37.5%)	
Tumor Hemisphere			$\chi^2(1)=0.63$, $p=.43$
Right	5 (62.5%)	15 (47.0%)	
Left	3 (37.5%)	17 (43.0%)	
Tumor Location			Fisher's exact $p=.05^*$
Frontal	1 (12.5%)	18 (75.0%)	
All other locations	7 (88.5%)	14 (25.0%)	

* Statistically significant difference between groups $p \leq .05$

Educational and Occupational Attainment: the Hollingshead 2-Factor Index.

The Hollingshead 2-Factor Index of Social Position ([Hollingshead Index]; Hollingshead, 1957) uses educational and occupational attainment to derive a solitary score for CR. Scores may range from 11-77 points. Lower scores on the Hollingshead Index indicate higher levels of education and occupational attainment, and thus, would reflect higher CR.

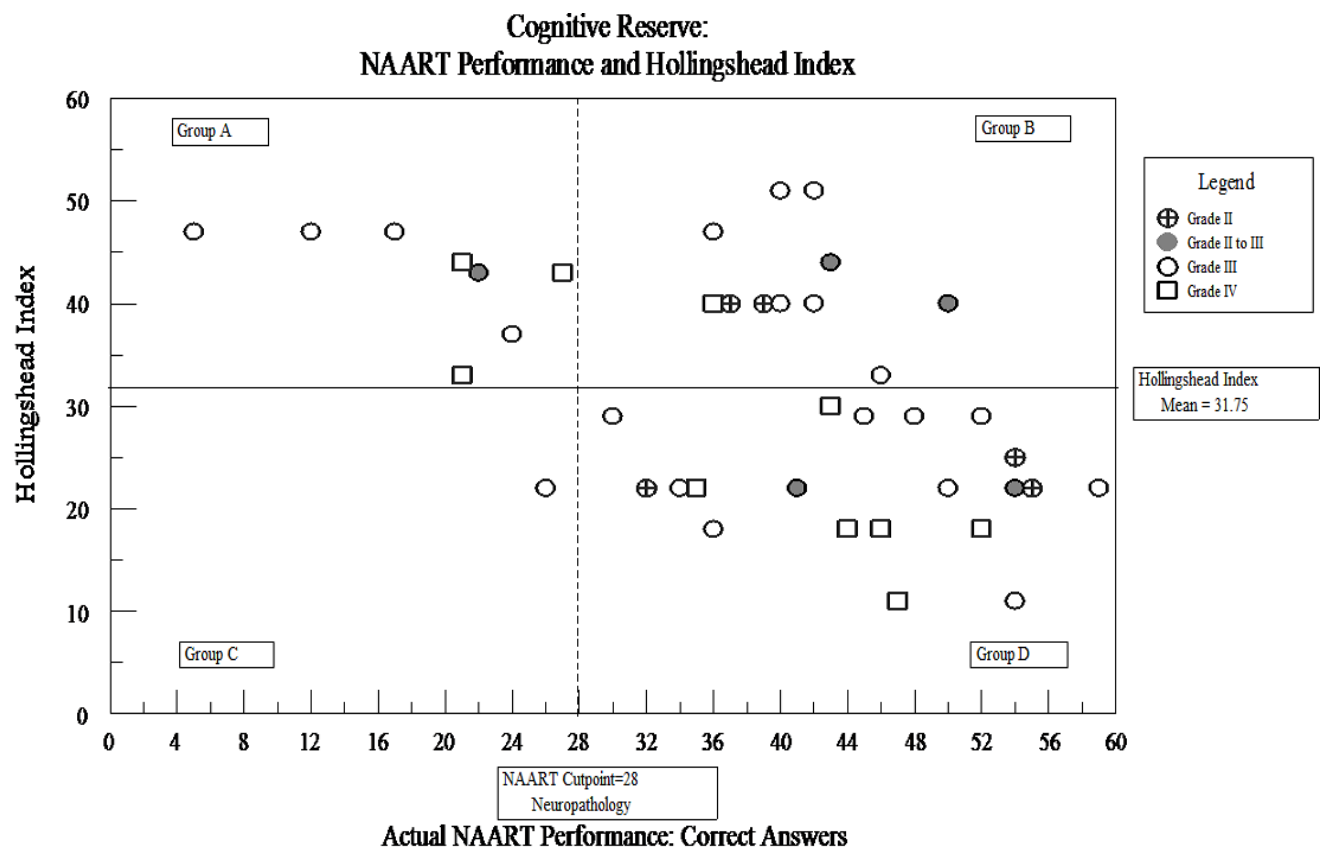
The Hollingshead Index ranged from 11 to 51 points in this sample, with a median of 29.5 points and mean of 31.75 (SD 11.56) points. These scores approach the midpoint of 33 on

the Hollingshead Index. Those with higher CR were more likely to live longer after diagnosis, $t(39)=-5.53, p<.001$. No other subject or tumor-related factors were significantly associated with the Hollingshead Index.

Figure 2 illustrates a curvilinear relationship between the Hollingshead Index and NAART performance. Those with higher educational and occupational attainment (lower Hollingshead Index scores) had higher NAART performance, and thus higher premorbid intelligence. Likewise, those with average educational and occupational attainment (higher Hollingshead Index scores) tended to have lower NAART performance. Estimated premorbid intelligence was significantly associated with the Hollingshead Index, $r = -.52, p<.001$.

Figure AJ.2.

Scatterplot of Actual NAART Performance Scores and Hollingshead Index (n=40).



To further examine differences in NAART performance as it relates to CR, the NAART cutoff score of 28 was used to distinguish normal and low performance while the Hollingshead Index mean of 31.75 for the sample was used to distinguish high and low CR, Figure 2. These two cutpoints established four quadrants, or groups, within the scatterplot. This permitted the subjects within the cells to be further described: 1) Group A has low CR and low NAART performance; 2) Group B has low CR and normal NAART performance; 3) Group C has high CR and low NAART performance; and 4) Group D has high CR and normal NAART performance.

The majority of subjects (n=20, 50%) comprised the group with high CR and normal NAART performance, Group D. There are fewer subjects in the cells for lower NAART performance (n=9), Groups A and C, than those with overall normal NAART performance (n=31), Groups B and D. There is only one subject with high CR with low NAART performance, Group C, as compared to the 8 subjects with low CR and low NAART performance, Group A. Subject characteristics were similar across the four groups, Table AJ.2, thus no significant differences were observed using Kruskal-Wallis procedures.

Table 2.*Subject characteristics by Hollingshead Index and NAART performance groupings (n=40).*

	Group A	Group B	Group C	Group D
	Low CR-Low P	Low CR-Normal P	High CR-Low P	High CR-Normal P
Characteristics	(n=8)	(n=11)	(n=1)	(n=20)
Age in years	51.3 (9.2)	46.0 (9.3)	62	51.4 (9.8)
Education in years	14.0 (1.5)	13.5 (0.9)	16	16.4 (1.4)
Hollingshead Index	42.6 (5.1)	42.3 (5.4)	22	22.0 (5.5)
Time since diagnosed, in months	113.8 (89.4)	109.0 (62.4)	132	90.4 (89.1)
WHO Grade				
Low Grade	1 (13%)	4 (36%)	0	5 (25%)
High Grade	7 (87%)	7 (64%)	1	15 (75%)
Tumor stability				
No recurrence	6 (75%)	4 (40%)	1	15 (75%)
Any recurrence	2 (25%)	6 (60%)	0	5 (25%)
Tumor Hemisphere				
Right	4 (50%)	6 (60%)	1	9 (45%)
Left	4 (50%)	4 (40%)	0	11 (55%)
Tumor Location				
Frontal	2 (25%)	5 (50%)	0	12 (60%)
All other locations	6 (75%)	5 (50%)	1	8 (40%)

CR=cognitive reserve; P=NAART performance

Summary on Proxies of Cognitive Reserve

These findings suggest that caution may be warranted when using NAART estimations of premorbid intelligence in this sample of survivors with PBT. The relationship between lower occupational and educational attainment (higher Hollingshead Index) and lower than expected NAART performance suggests that that Hollingshead Index may serve as a useful proxy for CR when limitations in using the NAART exist. Thus, for the purposes of this study, the Hollingshead Index was used to explore Specific Aim 4. The sample mean of 31.75 was used to differentiate between high and low CR.

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