LONG-TERM NEUROPSYCHOLOGICAL EFFECTS IN SURVIVORS OF PEDIATRIC LOW-GRADE GLIOMAS

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Abstract

Statement of the problem: Survival rates of low-grade gliomas (diagnosed and treated during childhood) have improved resulting in a population of long-term survivors, albeit with limited knowledge of their neurocognitive function, quality of life, and adaptive function.

Methods: Patients treated at The Children's Hospital at Westmead, Sydney, Australia during childhood (ages 6-18), and a minimum of five years post diagnosis (n = 20) participated in a neuropsychological evaluation. Demographic and tumour related variables were independently analyzed.

Results: The majority of the participants demonstrated average ability on most cognitive tasks, although we found some variability resulting in three subgroups ranging from mild to severe functioning. The lower cognitive functioning subgroup demonstrated challenges on tasks of memory, processing speed, and executive function. In addition, they self-reported sub-clinical to clinical ranges in internalizing and externalizing symptoms as well as difficulties in physical health, and social and emotional well-being. Medication consumption and less education were moderators of biological risk. None of the tumour related factors were identified as moderators, in part due to the small sample size. Positive associations between challenges in adaptive function (internalizing and externalizing symptoms) and difficulties in perceived cognitive abilities and health related quality of life were identified in the sample.

Conclusions: This study highlighted the variability in long-term outcomes of low-grade gliomas and the necessity for routine follow-up care over the course of recovery and survivorship.

I dedicate this work to my beautiful children Solana, Diyaan, and Niyaal.
Their pursuit for knowledge has inspired me to accomplish unimaginable feats.
I hope to return the favour and inspire them with this one.

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List of Abbreviations

ASR	Adult Self-Report questionnaire
BCSCs	Brain Cancer Stem Cells
BRC	Brain Reserve Capacity
CRC	Cognitive Reserve Capacity
DKEFS	Delis-Kaplan Executive Function System
FACT-Cog	Functional Assessment of Cancer Therapy- Cognitive Function
IQ	Intelligence Quotient
JOLO	Judgment of line orientation
QoL	Quality of Life
RAVLT	Rey-Auditory Verbal Learning Test
ROCF	Rey-Osterrieth Complex Figure Test
SDMT	Symbol Digit Modality Test
TMT	Trail Making Tests
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test

Overview

Brain tumours are the most common solid tumour entity in children and constitute 15-20% of all childhood cancers. Their incidence in childhood is approximately 3.3 per 100 000 per year (Kaatsch, et al.,2001). Central nervous system tumours are particularly dangerous because of their proximity to vitally important structures. Brain tumours vary by location, histology, and pathology. They are classified based on the notion that each type of tumour results from the abnormal growth of a specific cell type. The cell type predicts tumour behaviour, choice of therapy, and prognosis. By definition, high-grade tumours expand and affect healthy tissue more rapidly than low-grade tumours. Low-grade tumours are usually benign and do not typically spread to other areas of the brain and body. About 50% of all brain tumours arise from supportive tissue in the brain and are collectively called gliomas. Gliomas can be differentiated further depending on their cell of origin. Examples of gliomas include astrocytomas, oligodendrogliomas, and ependymomas. Low-grade gliomas account for 51.5% of primary central nervous system tumours in children (Ullrich & Pomeroy, 2003). The diagnosis is based on patient history, physical examination, and imaging data. Low-grade gliomas are primarily treated by surgery, but treatment can include adjuvant chemotherapy and focal radiation therapy. Survival rates in this tumour population are very favorable ranging from 50% to 95% for 5-year survival rates depending on the type of glioma (Cancer Research UK); thus leading to a population of long-term survivors of pediatric low-grade gliomas. Yet, it is unclear how this population fares in the long-term in terms of neurocognitive function, quality of life, and adaptive function. The purpose of this dissertation was to explore these outcomes in a select sample of survivors of this type of brain tumour.

Chapter 1: Background

Section 1: Theoretical models of outcomes

A number of theoretical frameworks have contributed to the field of pediatric neuropsychology. Theories relevant to the brain tumour population under study were examined and guided our exploration of protective and vulnerability factors in the research on pediatric low-grade gliomas. One of the earliest models in the prediction of neuropsychological outcome, the "Kennard Principle" was coined by neuropsychologists based on Margaret Kennard's work with animal models in the 1930s. This model suggested that greater plasticity was inversely related to younger age of brain insult, in that healthy tissue presumably adopted functions previously destined for the injured areas (Ris & Beebe, 2008). Kennard's research on brain-behaviour relationships laid the groundwork for current models of developmental neuropsychology in terms of recovery of function and how functionality was affected in the lesioned brain. She advanced the notion that brain pathology alters the developmental sequence of a skill and by studying these sequences we can better understand the typical trajectory for that skill. Her research proposed that age at lesion operated in interaction with both lesion location and behavioural task and that the lesion itself was a poor predictor of outcome. For example, she argued that age was more important for recovery of motor function than for association cortex functions, such as memory and executive functions. Early brain damage did not consistently spare function or optimize functional recovery, but could be more, less, or equally disabling than later-onset injury, depending on the features of the injury, post-injury neuroanatomical reorganization, the staging of the lesion, and how and when the outcome was assessed (Dennis, 2010).

Kennard's work on brain-behaviour relationship was oversimplified and reduced to a principle that was later refuted by most researchers as an all-encompassing theory, yet it continues to plague current understanding of plasticity. Her principle is mentioned here to eradicate notions that the pediatric low-grade brain tumour population is free from functional damage. Studies of long-term effects in survivors of brain injuries gained in popularity across the field of developmental neuropsychology following Kennard's theories. Our population of study, survivors of childhood low-grade gliomas, provides an excellent model to further understand brain plasticity within Kennard's framework of the interaction between age and associated factors, since it involves focal insults (tumour, surgery, and focal radiation therapy) of varying magnitude, at varying ages, and to different regions of the brain.

Kennard's theories paved the way for modern theories of Brain Reserve Capacity (Satz, 1993) and Cognitive Reserve Capacity (Stern, 2002) which go beyond global statements of plasticity. Brain Reserve Capacity (BRC) is based on evidence of a certain degree of redundancy (in neurons, axons, synaptic activity) in the central nervous system, with functioning preserved until such time that a critical threshold of damage is reached. Cognitive Reserve Capacity (CRC) is an extension of this theory whereby cognitive factors (i.e., intelligence and educational level) further buffer protection or vulnerability.

Satz's (1993) theory of BRC was predominately drawn from the aging and dementia literature (i.e., Alzheimer's and Parkinson's diseases) to explain threshold differences in the onset of clinical symptoms and the expression of impaired test performance after acquired brain injury. Like Kennard, Satz highlighted the importance of the timing of the injury while expanding his

model to incorporate structural differences in the brain. His model reflected two main postulates of injury based on brain reserve capacity, 1) greater brain reserve capacity acts as a protective factor, and 2) less brain reserve capacity acts a vulnerability factor. For example, in Alzheimer's disease, senile plaques and neurofibrillary tangles must exceed a quantitative threshold before clinical symptoms of dementia are expressed (Miller, Hicks, D'Amato, & Landis, 1984). Similarly, in Parkinson's disease clinical manifestations present once a proportion of neurons in the nigrostriatal areas are depleted and there is reduction in dopamine receptors (Quinn, Rossor, & Marsden, 1986). For my dissertation, the postulate that comes from this theory is that brain reserve capacity in brain tumour patients can act as either a protective or a vulnerability factor.

The BRC theory further included the following three sub-postulates of vulnerability which could alter the threshold level for symptom presentation: the effects of aggregate lesions (i.e., the presence of additional lesions decreases threshold and produces functional impairment), temporal onset (i.e., timing of the insult could result in early or delayed onset of disease progression), and task challenge factor (i.e., functional impairment is demonstrated when a challenge is presented regardless of level of BRC). Satz further theorized that inter-individual differences in brain reserve (the amount of brain tissue or neuronal loss) could alter the symptom threshold, and therefore alter the behavioural and neuropsychological outcomes when lesions were equivalent (Satz, 1993).

Although the threshold models of BRC and CRC were developed to account for the inter-individual variability in outcomes in adults, it can be extended to children with medical disorders, with additional qualifications. Children have less brain reserve than their adult

counterparts which can be accounted for by brain size and a smaller number of synaptic connections between still maturing neurons. As such, we would predict greater vulnerability with younger age of diagnosis of glioma, when exploring neuropsychological and adaptive functioning. Reserve may also differ according to brain region in children, whereby skill acquisition and skills maintenance can be affected by different patterns of injury. The temporal onset documented in the models would incorporate the rapidity of onset of symptoms and chronological age. Finally, the impact of the summation of repeated brain insults can be understood as depletion in brain reserve over time with repeated episodes of injury from primary and secondary insults, causing irreversible brain damage. Studying the long-term effects of pediatric low-grade tumours may help capture the full effects of early brain insult, particularly age-related declines in neuropsychological functioning. In addition, the current study aims to demonstrate inter-individual differences across the sample by investigating the sub-postulates of vulnerability proposed by Satz.

Maureen Dennis (2000) proposed an alternative, yet similar, model to inform the relationship between medical disorders and outcomes in children. Her model dictated that impairment or cognitive phenotype was set by a predetermined biological risk (based on the medical disorder), which was moderated by development of the child, time since onset, and reserve (See Figure 1). In order to gain an appreciation for her model, the components are explained and related to the study when applicable.

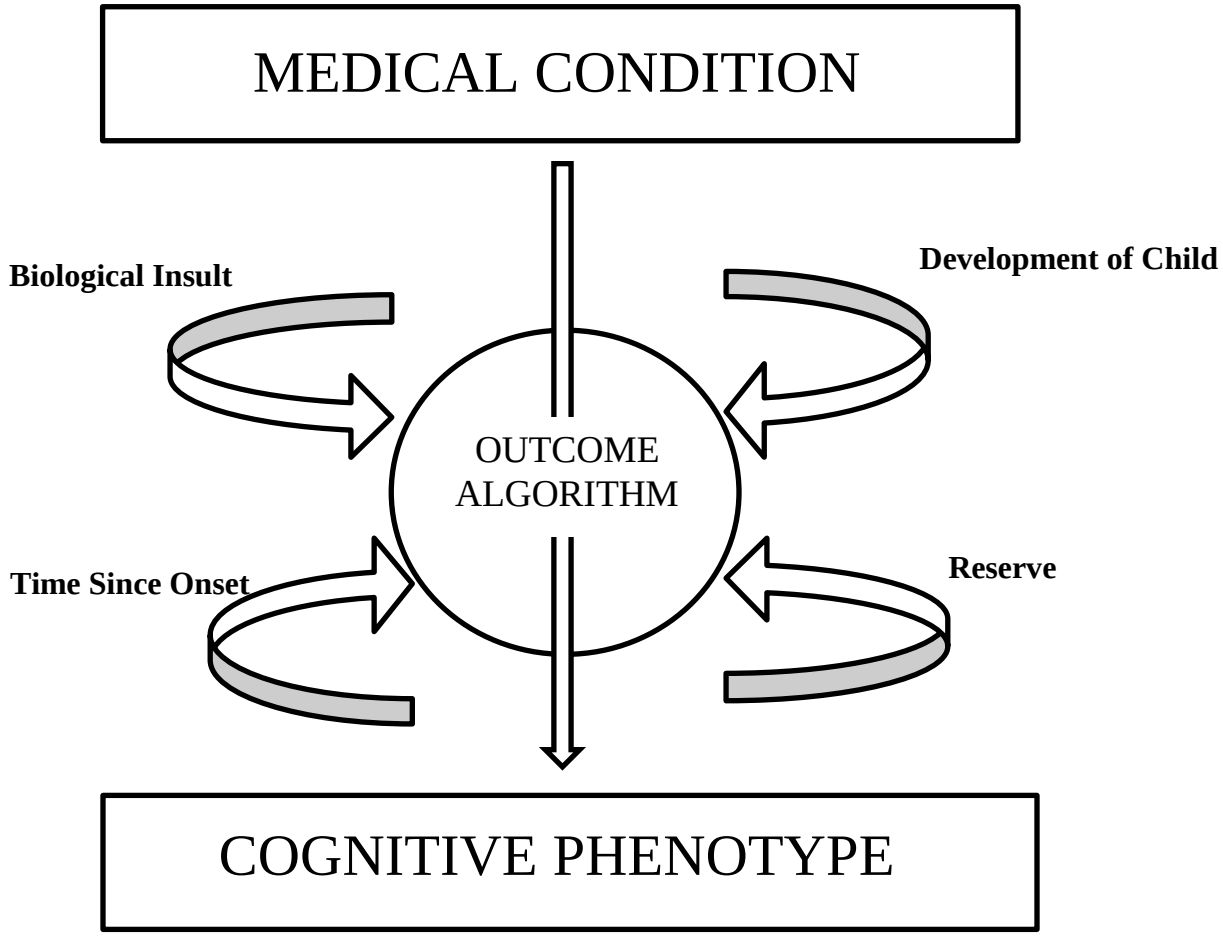

Figure 1. Dennis's model of the relationship between medical condition and cognitive phenotype (Yeates, Ris, & Taylor, 2000).

A cognitive phenotype, defined as the presentation of mental and behavioural skills, is expressed when development, time, and reserve are integrated. The cognitive phenotype involves five concepts: modal profile, variability, core deficits, challenge level, and phenocopy. The modal profile represents the typical presentation of cognitive strengths and weaknesses associated with a medical disorder. Variability in cognitive phenotype can be understood as an outcome measure. For example, the variability of performance over time can be indicative of a medical condition or the variability in a medical condition can predict variability in cognitive outcome. Core deficits relate to the cognitive phenotype of a medical condition, such that that represents an underlying cognitive impairment that is insensitive to disorder severity and intelligence. The challenge level is an important element of the cognitive phenotype, whereby children with medical conditions may demonstrate impaired performance on neuropsychological tasks as the challenge level is increased such as multi-tasking or divided attention, whereas controls may demonstrate only subclinical performance under the same challenges. Failure in performance on low-challenge tasks is observable in individuals with severe medical conditions, whereas failure on high-challenge tasks might represent individuals who appear superficially cognitively intact in daily activities. Lastly, cognitive phenocopies are expressions of similar cognitive phenotypes that arise from different underlying cognitive processes. For example, poor reading comprehension is seen in children with head injury and hydrocephalus, yet the first is related to processing speed and the latter is associated with semantic integration (Barnes, Dennis, & Wilkinson, 1999; Barnes, Faulkner, & Dennis, 1999). The cognitive phenotype examined in the current study involved the exploration of modal profile in neurocognitive, quality of life, and adaptive behaviour, anticipated variability within the group, and evaluated if the challenge level in the measures is sensitive to outcomes in this population.

As mentioned above, the cognitive phenotype is determined by biological risk factors, which can be defined by a summation of genotype, metabolism, environmental toxicity, congenital brain dysmorphologies, primary and secondary effects of acquired brain insult, and treatment comorbidity. Genotype refers to the genetic bases of a particular disorder and can account for some modal profiles. Metabolic disorders are relevant to childhood medical conditions which lead to deteriorating behaviour, dementia, severe disability, and in some cases death. Environmental toxicity refers to exposure of toxins to both mature and immature brains and can increase the risk of developmental cognitive morbidity, particularly with early exposure. Brain dysmorphologies capture medical conditions which affect myelination and white matter, such as lesions to the brain. The cognitive phenotype may be altered dependant on the type and regional distribution of brain abnormalities. For example, childhood acquired cerebellar lesions are believed to be associated with motor and cognitive dysfunctions from pediatric time of onset to early adulthood (Dennis, et al., 1999). Primary severity of acquired conditions is a significant medical risk factor, particularly for brain tumours whereby the class of tumour is dependent on the type and stage of cell development incurring a range of severity of mortality and morbidity. Secondary effects of congenital and acquired conditions can exacerbate the effects of the primary injury, although they can be reversed given accurate and timely treatment. For example raised intracranial pressure can occur secondary to medical conditions including brain tumours, altering the cognitive phenotype following shunt treatment (Raimondi & Tadanori, 1981). Treatment morbidity has the potential to treat the medical condition at the cost of functional impairment. For example, children with brain irradiation treatments have been shown to experience widespread neurocognitive deficits. Reflecting on the biological risk factors in the model, patients with brain tumours have the potential for genotype malformations (i.e., gene additions or

deletions), metabolic concerns (i.e., tumours affecting pituitary or thyroid glands), brain dysmorphologies (i.e., lesions in localized areas of the brain), primary and secondary effects of the lesion (ex. hydrocephalus, seizures, chronic medication, amongst other effects), and treatment comorbidity (i.e., surgery, chemo-, and radiation therapy). Despite advances in the molecular biology of brain tumours, the etiology remains unknown. Recent identification and isolation of brain cancer stem cells (BCSCs) have led to greater understanding of the molecular pathogenesis and possibly the catalyst of brain tumours, suggesting the presence of BCSCs would contribute to biological risk (Lee et al., 2012)

Unlike adult models of outcomes of medical disorders, Dennis's model incorporated the development of the child, which is defined as the child's chronological and functional age. This factor included the age at onset of insult (i.e., pre- or perinatal, early childhood, and late childhood), the course of skill development, mastery and maintenance, and the potential for age related skill decline. In childhood-onset disorders, children have the additional tasks of meeting developmental challenges in addition to the demands of recovery. As such, the cognitive phenotype is an expression of how the biological risk is moderated by previously acquired skills and the acquisition of new skills. Differentiating between previously acquired skills and the acquisition of new skills can be accomplished from longitudinal studies; nonetheless cross-sectional studies such as the current study offer the opportunity to review the following factors: age at insult, comparison of skill development to normative standards, and hypothesizing potential age related decline.

Dennis's model also accounted for time since onset of medical disorder, with the notion that time is not ubiquitous with recovery. In fact, cognitive deficits can emerge with time particularly with children, whereby a disorder can result in a slower rate of skill acquisition over time and residual deficits following recovery. This pattern has been documented among young head-injured children compared to older children with equally severe injuries (Anderson & Moore, 1995). The effects of time since onset on cognitive phenotype are best captured by studies of adult survivors of childhood medical disorders, such as in the design of the current study. Longitudinal studies that follow a cohort of children are particularly valuable such that they reveal cognitive morbidity of a childhood medical disorder and the developmental trajectories in children with varying medical severities and biological risk. Nonetheless, comparisons through cross-sectional studies offer valuable information to determine whether the cognitive phenotype is related to a slower rate of skill acquisition or a deficit.

Dennis's model incorporated reserve as a moderator of biological risk much like the BRC and CRC theories, although reserve in her model has been expanded to include the child's demographics, family, and social context of peers and school. Demographic variables, such as sex and socio-economic status, address pre-insult status and can influence outcomes and in some cases increase the risk of the medical disorder. Post-insult status is additionally relevant; in that a child's physical and mental health following injury can moderate outcome severity. Finally, the child's social context can ameliorate treatment compliance or hinder recovery. The current study aimed to address demographic variables of the survivor including sex and educational attainment, and investigates cognitive function, quality of life, and adaptive function as outcome measures.

A child's cognitive phenotype or outcome is in essence much more complicated than simply knowing the acquired medical condition. Each of the factors presented above can be plotted into an outcome algorithm for children. Similar to the adult threshold model, there exists a variable or "floating" threshold for impairment in which function can be buffered or exposed dependent on level of biological risk, development, time, and reserve. Figure 2 depicts a sketch of this outcome algorithm, which provides an extension of the model that Dennis proposed, as outlined above.

The first postulate suggests that children with high biological risk experience at least subclinical impairment on tasks of high challenge regardless of development, time, and reserve, whereas children with low biological risk will present with neither subclinical nor clinical impairment. The second postulate relates to the impact of the moderators of development, time, and reserve on biological risk. Each of the moderators is provided with positive or negative values dependent on whether it exacerbates or buffers the cognitive phenotype, respectively. Moderators with no impact on cognitive phenotype take a zero value. Positive values place children with high biological risk in the impairment range, whereas negative values have the potential to shift them from the impairment range. Children with low biological risk can tolerate modest levels of positive values in development, time, and reserve without shifting them into the impairment range due to a buffer zone. The final postulate suggests that factors of development, time, and reserve are not necessarily additive or equivalent in nature. Instead, they operate differently for children at different levels of biological risk and medical conditions. In this study, I adopted this theoretical framework to conceptualize our findings of neurocognitive, quality of life, and adaptive functioning.

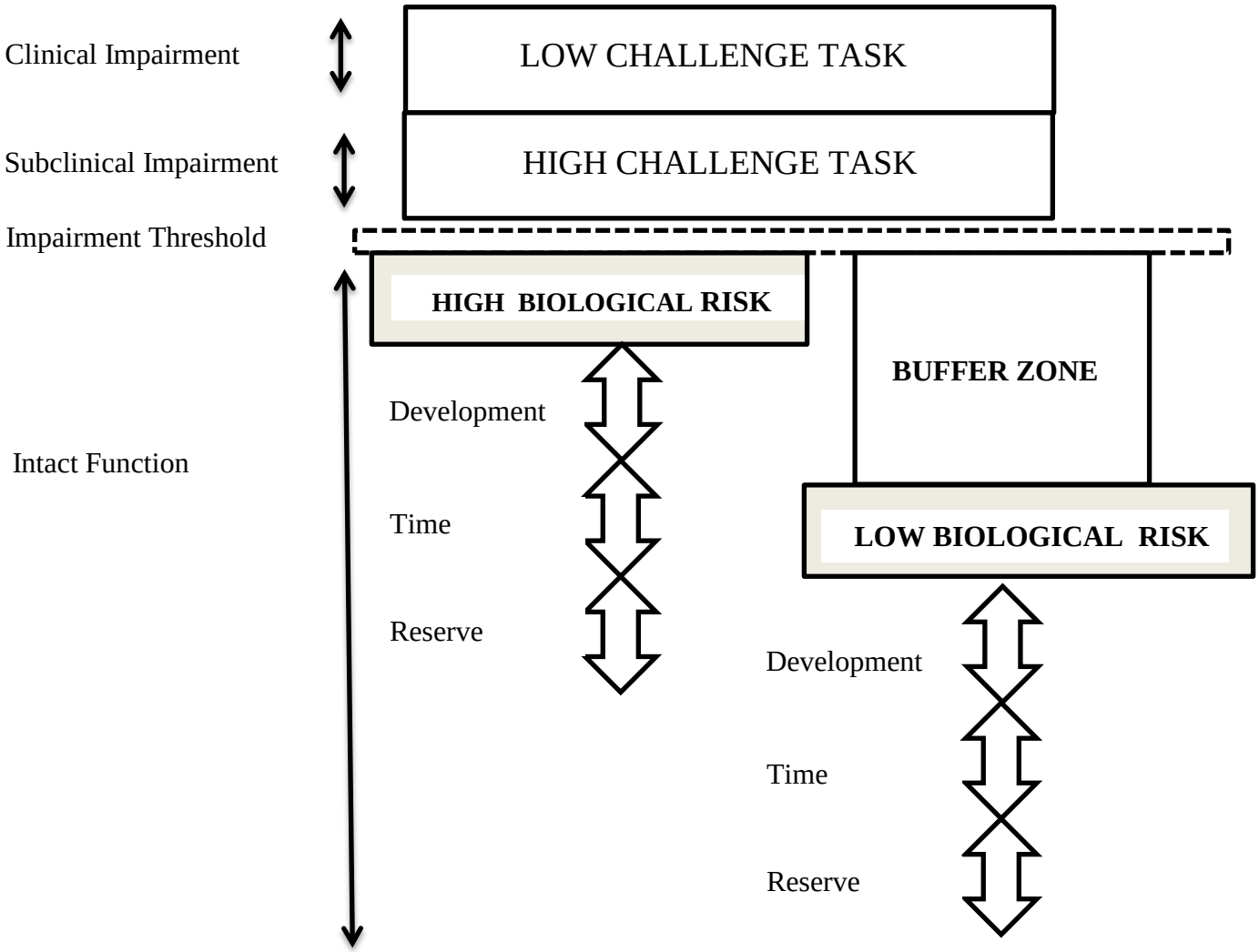

Figure 2. Hypothetical model of the outcome algorithm for children with high and low biological risk. Development of the child, time since onset, and reserve moderate the effects of biological risk shifting the impairment threshold either towards impairment or free from impairment (Yeates, Ris, & Taylor, 2000).

The question in the current study was whether we can determine whether there are high or low levels of risk, based on the cognitive phenotypes. This knowledge would then lead to an exploration of outcomes of adaptive functioning and neuropsychological functioning based on factors such as time since diagnosis of glioma, demographic factors, and tumour variables. What follows is a discussion of the existing literature on pediatric gliomas, what factors we know might affect cognitive and adaptive outcomes, and gaps in the research that will be addressed by my findings.

Section 2: Impairments in neurocognitive outcomes

Brain tumours in children are known to cause varying cognitive deficits. However, the pattern that emerges is unclear due to disease related factors such as the origin of the tumour, the cell type, the tumour location, the malignancy grade, and the type of treatment. Different types of tumours have the propensity to affect the brain in many ways resulting in different neuropsychological patterns of dysfunction. The outcomes of neuropsychological tests have not been widely studied for the low-grade glioma pediatric population and limited research has been acquired for long-term effects. Our study aims to fill this gap in the literature.

Due to the limited knowledge base of research on low-grade gliomas, exploration of both the adult and pediatric literature is required, with a cautionary note that patients may vary due to developmental processes and their interaction; including biological, cognitive, and socioemotional factors. As an example, the adult literature has shown conflicting results on the impact of tumour localization and cognitive deficits, with either no significant correlations (Mulhern, Kovnar, Kun, Crisco, and Williams 1988), specific deficits of verbal memory (Surma-aho et al., 2001; Taphoorn et al., 1994), or widespread impairment related to tumour localization (Taphoorn et al., 1992). Long-term studies of children with posterior fossa

tumours have revealed deficits in perceptual-motor skills, visual memory, verbal fluency, and executive functioning (Steinlin, et al, 2003). Similarly, Aarsen and colleagues (2004) found a combination of long-term impairments in language, sustained attention, visual-spatial, executive function, and memory problems in children with cerebellar astrocytomas. These studies document a pattern of memory and executive dysfunction that exists amongst the low-grade glioma tumour patients irrespective of tumour location.

Research on the effect of treatment type on neurocognitive outcomes has shown mixed results. Cross-sectional studies evaluating IQ scores of pediatric brain tumour patients, in particular medulloblastomas, have found decreases in IQ scores following radiation treatment. Age at diagnosis and radiation dose moderated the effect of the cognitive decline (Palmer et al., 2001; Radcliffe et al., 1994), with greater deficits at higher doses of radiation and at a younger age at diagnosis. It has been suggested that these deficits are a result of an inability to acquire new information at an age appropriate rate rather than a loss of previously learned information (Palmer et al., 2001). Taphoorn and colleagues (1994) demonstrated disturbances in cognitive and affective measures for adult patients with low-grade gliomas with no significant differences between treatment types. Treatment type may play a role in patients' quality of life outcomes in addition to neuropsychological outcomes.

Studies have revealed cognitive and behavioural difficulties for children who undergo surgery alone for treatment of brain tumours (Beebe et al., 2005; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Meyer & Kieran, 2002). For example, Levisohn and colleagues (2000) studied children treated with surgery alone for cerebellar tumour in the first two years after surgery and found difficulties in executive functioning, visual-spatial functioning, verbal memory, and dysregulation of affect. In addition, greater behavioural deficits were noted in

older participants compared to younger ones. Similarly, Beebe and colleagues (2005) found declines in Full Scale IQ, spelling, and adaptive functioning in a pediatric sample of children with low-grade cerebellar tumours. Changes at twelve months post treatment were reported in a separate sample of pediatric brain tumour survivors, whereby declines in intellectual functioning and moderately elevated behaviour problems irrespective of the treatment modality (surgery or radiation/chemotherapy) were reported (Taylor et al., 2007). Heterogeneous tumour population groups were used in these studies, which raises questions about the generalizability of results and the importance of either tumour type or tumour location.

Section 3: Impairments in Quality of Life

Research on the quality of life of brain tumour survivors has increased within the past decade due to high survival rates and more localized treatment methods. Taphoorn and colleagues (1992) established the need to evaluate both objective and subjective indices when assessing quality of life. They studied adults treated for low-grade gliomas and found cognitive and affective disturbances that were not in line with the patients' self-report measures. A study by Klein and colleagues (2003) assessed both cognitive functioning and health related quality of life in patients with epilepsy following low-grade glioma treatment. They studied the effects of epilepsy and antiepileptic drug treatment on cognitive functioning and health related quality of life in an adult population. They found significant reductions in information processing speed, psychomotor function, attention, verbal and working memory, executive function and health related quality of life. The cognitive reductions were primarily attributed to the use of anti-epileptic drugs for most of the domains, whereas quality of life was attributed to the lack of complete seizure control. This study highlights the need to address disease related factors, such as seizure medication, as moderators of outcome. In addition,

these studies demonstrate the need to pair neurocognitive measures with quality of life measures when assessing patient outcomes.

In a long-term follow up study of survivors of childhood brain tumours compared to their siblings, the brain tumour survivors were more likely to have cognitive disturbances, be unemployed or unmarried, and to have visual or auditory disturbances. In addition, the tumour group was more likely to die in early adulthood of other causes (Mostow et al., 1991). To note, this study included a mixed sample of central nervous system tumour survivors suggesting possible divergence in outcomes with our low-grade tumour study group. In a separate study of various cancer survivors, adolescents were shown to be at a risk for poor health related quality of life, whereas preschoolers were at risk for behaviour problems (Barrera et al., 2003). These results demonstrate adjustment issues through development and in the long term, although it is unknown if similar findings are revealed in the low-grade glioma populations. As such, the current study fills a gap in understanding the quality of life outcomes in survivors of pediatric low-grade glioma.

Reports of long-term neurocognitive and behavioural impairments related to low-grade brain tumours are limited and inconsistent in the pediatric literature. Studies with brain tumour patients have included children and adults with varying diagnoses, malignancies, and duration of recovery. Thus, identifying parallel findings across the research is problematic and there is a lack of specificity for the pediatric population of interest. Nonetheless, results from previous studies provide valuable information for test design and implementation.

Chapter 2: Research Objectives and Predictions

Purpose

The purpose of the study was to explore the long-term outcomes of patients diagnosed with low-grade gliomas in childhood and adolescence, in particular neuropsychological profiles and patterns, perceived quality of life, and adaptive functioning. It is believed that the low-grade glioma brain tumour population has the best survivorship and outcomes, albeit with little research to support the latter notion. The present study included only this subgroup of tumour patients allowing for a more detailed investigation of tumour related factors (e.g., tumour location, tumour pathology, treatment type), and demographic factors. The sample data were compared to age-standardized normative data for each measure. Some of the measures chosen were adopted in previous research demonstrating significant results in patients during the acute phase of recovery (within twelve months from treatment). Other measures with sound psychometric data were included to add breadth and depth to the current exploration. This study was exploratory in nature; therefore, did not use traditional hypothesis testing. However, in the spirit of transparency, presuppositions concerning the various types of differences we expected to find are listed below. We anticipated that results of this study would augment and generate new knowledge of long-term effects for patients with low-grade gliomas, with a goal of assisting in the proactive management of daily living. Finally, the findings were expected to provide a source of information for children undergoing treatment for low-grade gliomas and their families. The objectives are listed below.

Part A: Neuropsychological profile

1. Explore heterogeneity in the sample population's neuropsychological scores.

    a. It was expected that a post-hoc analysis would reveal subgroups of patients based on the number of neurocognitive measures scored below 1 standard deviation.
2. Explore the inter-group variation on all neurocognitive measures.
    a. It was expected that different subgroups (based on objective 1) would perform differently on measures of attention, memory, visuospatial, processing speed, motor, and executive function. It is hypothesized that those with more severe general impairments would show greater impairments in each of these domains.
3. Explore differences in neuropsychological scores based on demographic variables.
    a. It was expected that differences would exist based on education, age at diagnosis, and medication use, and not on sex. Based on extant literature, we expected to find that:
        i. Men and women with low-grade glioma would perform equivalently on all neuropsychological measures.
        ii. Those with lower education would perform worse than those with higher education on neuropsychological measures.
        iii. Those with a younger age at diagnosis would perform worse than those with an older age at diagnosis on all neuropsychological measures.
        iv. Those with greater medication use would perform worse than those with less medication use on all neuropsychological measures.
4. Explore differences in neuropsychological scores based on tumour related factors.
    a. It was expected that differences would exist based on the type of tumour, tumour location, treatment method, and secondary tumour related symptoms. Based on extant literature, we expected to find that:

i. Those with astrocytomas would outperform those with other types of tumours.
ii. Those with cerebellar tumours would have fewer cognitive difficulties than those with tumours in other areas.
iii. Those who underwent adjuvant therapy, such as chemotherapy or radiation therapy would have more difficulties in attention and executive functions than those with surgery alone.
iv. Those with secondary symptoms such as seizures or hydrocephalus would have more cognitive difficulties than those with no secondary symptoms.

Part B: Perceived Quality of Life (QoL)

1. Identify domains of strength and weakness in the sample population's perceived health and cognitive quality of life.
2. Explore the inter-group variation in the quality of life questionnaires.
    a. When groups derived for Part A: objective 1 are compared on quality of life outcomes, those with more severe neuropsychological outcomes will express a poorer quality of life.
3. Explore differences in perceived quality of life scores based on demographic variables.
    a. It was expected that men and women with low-grade gliomas would perform equivalently on perceived QoL measures.
    b. It was hypothesized that those with lower education would show poorer scores on QoL variables.
    c. It was expected that poorer QoL for those with younger age of diagnosis.

    d. It was expected that poorer QoL for those with higher medication use.

4. Explore differences in perceived quality of life scores based on tumour related factors.
    a. Because of a lack of extant literature, no hypotheses were specified; however, exploratory analyses on QoL were conducted for tumour location, type of tumour, treatment type, and tumour-related symptoms.
5. Explore relationships between perceived health and cognitive related quality of life scores.
    a. It was expected that there would be significant positive correlations between perceived health and QoL ratings.
6. Explore relationships between perceived cognitive related quality of life scores and measures of intelligence.
    a. It was expected that there would be significant positive correlations between intelligence, and QoL.

Part C: Psychological adaptation

1. Identify domains of strength and weakness in the sample population's adaptive functioning.
2. Explore the inter-group variation across the adaptive measures.
    a. When groups derived for Part A are compared on quality of life outcomes, those with more severe neuropsychological outcomes will express poorer adaptive functioning.
3. Explore differences in adaptive scores based on demographic variables.
    a. It was expected that there would be no difference in overall adaptive functioning between men and women with glioma.

b. It was hypothesized that those with lower education would show poorer scores on adaptive functioning
c. It was expected that poorer adaptive functioning for those with younger age of diagnosis
d. It was expected that poorer adaptive functioning for those with higher medication use.

4. Explore differences in psychological adaptive functioning based on tumour related factors.
    a. Because of a lack of extant literature, no hypotheses were specified; however, exploratory analyses on adaptive functioning were conducted for tumour location, type of tumour, treatment type, and tumour-related symptoms.
5. Explore relationships between adaptive functioning and perceived health and cognitive related quality of life scores.
    a. It was expected that there would be significant positive correlations between perceived health and adaptive functioning ratings.
6. Explore relationships between adaptive function and measures of intelligence.
    a. It was expected that there would be significant positive correlations between intelligence, and adaptive functioning.

Chapter 3: Methods and Measures

Participants

Participants were recruited from the medical records database from the Children's Hospital at Westmead, New South Wales, Australia, exploring diagnoses from 1980 to 2003. The following inclusion criteria were required for participation: a diagnosis of tumour grade I or II (World Health Organization grading), diagnosis made between ages 6 to 18, and a minimum of 5 years since diagnosis. The exclusion criteria included a pre-tumour history of a developmental delay, a previous neurologic insult, and a previous diagnosis of tuberosclerosis or neurofibromatosis.

Based on past research in the field of pediatric oncology and the limited participant pool, we had projected to test between twenty and twenty-five patients. Twenty patients were recruited and administered the full testing battery from a list of 72 patients, after applying the inclusion and exclusion criteria. Of those initial 72 patients, 6 had either passed away or were ill (i.e., recent stroke), 11 patients were not interested due to time commitments and travel distance, 21 patients had changed their contact information from the time they were at Westmead Hospital, and 14 more patients had no available contact information. Tables 1 and 2 present the demographic characteristics of the resulting sample, as well as the tumour location and pathology, respectively. All participants were above age eighteen at the time of testing, as such only adult measures were used. Written consent and verbal assent were obtained from each participant prior to testing. Following the assessment, each participant received a brief neuropsychological report outlining their test results, including strengths and weaknesses.

Table 1. Demographic characteristics of the sample (*n* = 20)

Demographics	M (SD)
Age at diagnosis in years;	11.0 (2.6)
Age at testing in years;	25.6 (4.9)
Sex	F = 8 M = 12

Table 2. Tumour pathology and location

	Number of Participants
Tumour pathology	
Gliomas	
Astrocytomas	17
Ependymoma	1
Oligodendroglioma	1
Ganglioglioma	1
Tumour location	
Infratentorial	11
Supratentorial	9

Procedure

Each participant was assessed using a standardized battery to test intelligence, memory, visual-spatial skills, motor functioning, attention, executive functioning, and processing speed. A demographic questionnaire and three self-report questionnaires of current adaptive functioning and perceived quality of life were completed by all participants. Measures were chosen that either spanned the potential age ranges of the participants, or that had equivalent child and adult measures. Table 3 lists the neuropsychological tests and questionnaires administered. The full battery was provided to each participant, although incomplete data resulted either due to either assessor or participant error (See Appendix A for the sample size

for each measure). Testing of each participant occurred on a single day at the Children's Hospital at Westmead (by this writer) and was on average four to five hours in length. Medical records were reviewed for pre-, peri-, and post-operative symptoms, medications, and tumour-related variables.

Table 3. List of neuropsychological tests and questionnaires by domain

Domain	Test
Intelligence	Wechsler Abbreviated Scale of Intelligence (WASI)
Memory	Rey-Osterrieth Complex Figure Test with delay (ROCF-delayed recall) Rey-Auditory Verbal Learning test with delay (RAVLT) Digit Span from the Wechsler Intelligence Scale for Children (WISC) or the Wechsler Adult Intelligence Scale (WAIS)
Visual Spatial	Judgment of line orientation (JOLO)
Motor	Purdue Pegboard
Executive Skills	Symbol digit modalities Trail Making Test Wisconsin Card Sorting Test (WCST) D-KEFS: Verbal fluency, Trail making Rey-Osterrieth Complex Figure Test
Processing Speed	Symbol Digit Modalities
Quality of Life	RAND-36 FACT-Cog
Adaptive function	Adult Self Report (ASR/18-59)

The order of test administration was as follows: WASI, Digit Span, Purdue Pegboard, Rey-O Copy, Rey-O immediate recall (3 minutes), DKEFS verbal fluency, Rey-O recall, Rey-O recognition (30 minutes), WCST computerized task, Symbol Digit Modalities, DKEFS trail making test, RAVLT, RAVLT delay recall (20 minutes), RAVLT recognition (20 minutes),

and Judgment of line orientation. The questionnaires were filled out during breaks in testing and at the end of the test battery.

Design

The selected neuropsychological and behavioural tests used were based on age-standardized normative samples, thus a normative population was not necessary.

The following is a list of independent demographic and tumour related variables and their associated levels: sex (2 levels; men, women), education (2 levels; High School Diploma/No High School Diploma vs. Post-High School education), age at diagnosis by development (2 levels; 6-11 vs. 12-18 years old), age at diagnosis by puberty onset (2 levels; < 10 vs. >10 years old), time elapsed between diagnosis and neuropsychological testing (5-15 vs. 15 + years), medication consumption at time of testing (2 levels; consumption vs. no consumption), tumour location (2 levels; infratentorial vs. supratentorial), tumour pathology (2 levels; astrocytoma vs. other gliomas, treatment type (2 levels; surgery vs. surgery with chemotherapy or radiation therapy), and symptoms at time of diagnoses (2 levels; hydrocephalus/seizures vs. no symptoms).

The dependent variables included the neurocognitive performance, perceived quality of life, and adaptive outcomes. Table 4 lists each of the outcome measures by domain.

Table 4. List of outcome measures by domain

Domain	Outcome Measures
Intelligence	Verbal IQ, Performance IQ, Full Scale IQ
Memory	Immediate recall, delayed, recognition
Visual Spatial	Orientation, copy
Motor	Limb dexterity
Executive Skills	Sequencing, problem solving, perseveration, errors in task, fluency
Processing Speed	Oral, written speed
Quality of Life	Physical function, emotional well-being, social function, general health, perceived cognitive impairment, perceived cognitive abilities
Adaptive Function	Mean adaptive, Personal strengths, Internalizing, Externalizing, and Total Problems scales

Statistical Analyses

Statistical analyses were computed with the Statistical Package for the Social Sciences (SPSS version 23.0 for Windows). Given our small sample size (i.e., fewer than 30 participants) the available statistical analyses included comparison of means, comparing proportions using chi-square tests, exploring confidence intervals around the mean to determine how often a result occurs in the sample, maximum likelihood estimator, analysis of variances (ANOVA), *t* –tests for dependent samples, and repeated measures ANOVA. In order to address our research inquiry interests the following analyses were conducted: 1) Frequency distributions were reviewed to describe the distribution of the data to determine strengths and weaknesses in the quality of life and adaptive measures, 2) One-way analysis of variance were adopted to determine inter-group differences in neuropsychological, perceived quality of life and adaptive functioning, 3) Repeated measures analysis of variance were run to explore differences between domains of perceived health related quality of life, 4) *t*-tests were used to explore differences in demographic and tumour related factors for neuropsychological, quality of life and adaptive measures, and 5) correlations were performed to explore relationships between questionnaires and between objective and subjective measures of cognitive function.

Chapter 4: Results

Part A: Neuropsychological profile

Inquiry 1. Explore if differences exist in the sample population's neuropsychological scores.

In line with current neuropsychological research that suggests groups can be created post hoc in exploratory studies, I explored the z-scores for each of the neuropsychological measures. Ek and colleagues (2005) suggest that group assignment can be based on the number of neuropsychological tests with scores at -1 (minus one) z-scores and below. A pattern of variation emerged whereby we found three groups of participants based on a count of the number of scores below 1 standard deviation (SD) from a total of 33 outcome measure scores. The first group of participants, termed "Severe Dysfunction" had 11 or more scores below 1 SD. The second group, termed "Moderate Dysfunction" had between 5 to 10 scores below 1 SD. And the final group, termed "Mild Dysfunction" had up to 4 scores below 1 SD. Please see Table 5 for group assignment. This information was then used for subsequent analyses of the data for the remaining inquiries.

Table 5. Participants grouped by level of dysfunction based on the number of measures below 1 standard deviation.

		SDMT			WASI		WAIS-3	RCFT			RAVLT					Purdue				
Case	Group	Written	Oral	vIQ	pIQ	F4	DS	Imm.	Delay	Recog	I	I-V	30min	RecogA	BCT	P. hand	NonP. hand	Both hand	Assm	JOLO
										Group 1. Severe Dysfunction: 10 or more of the measures										
1.	1	-	-	-	+	-	+	-	-	+	-	-	-	+	+	-	-	-	-	+
4.	1	-	-	+	+	+	+	+	+	++	-	-	+	-	+	-	-	-	+	-
11.	1	-	-	-	+	-	+	-	-	-	-	-	-	-	*	*	*	*	*	*
12.	1	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14.	1	+	+	-	+	-	-	-	-	+	-	-	-	+	-	-	+	-	-	+
16.	1	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
	SUM	5/6	5/6	4/6	1/6	4/6	3/6	5/6	5/6	3/6	6/6	6/6	5/6	5/6	2/5	5/5	4/5	5/5	4/5	3/5
										Group 2. Moderate Dysfunction: 5 to 10 of the measures										
2.	2	+	+	+	+	+	+	-	-	-	-	-	-	-	+	+	-	-	-	+
5.	2	*	-	+	++	++	+	+	++	+	++	++	++	+	++	-	-	-	-	*
8.	2	+	+	+	+	+	+	-	+	+	-	-	-	-	-	+	-	-	-	+
13.	2	+	+	+	+	+	+	-	-	-	+	+	-	-	+	-	-	-	-	+
15.	2	++	+	+	++	+	+	+	+	-	+	+	+	-	++	+	-	+	-	+
17.	2	-	-	+	+	+	+	+	++	++	-	+	++	+	+	+	+	-	-	+
20.	2	+	+	+	+	+	-	+	+	++	-	-	+	-	*	+	+	+	-	+
	SUM	1/6	2/7	0/7	0/7	0/7	1/7	3/7	2/7	3/7	4/7	3/7	3/7	5/7	1/6	2/7	4/7	5/7	7/7	0/6
										Group 3. Mild Dysfunction: up to 4 measures										
3.	3	+	+	++	++	++	+	+	+	-	+	+	+	+	+	-	+	-	-	+
6.	3	++	++	+	++	++	++	+	+	+	++	++	++	+	++	+	+	+	-	+
7.	3	+	+	+	++	+	+	+	+	+	+	+	-	+	+	+	+	++	+	+
9.	3	+	+	++	++	++	++	+	+	+	+	++	++	+	++	-	+	+	-	+
10.	3	+	+	++	++	++	+	+	+	+	+	+	+	+	+	+	++	+	+	+
18.	3	+	+	-	+	+	+	+	-	+	+	*	*	*	*	*	*	*	*	*
19.	3	++	++	+	+	+	++	+	+	+	-	++	++	+	*	+	+	+	-	+
	SUM	0/7	0/7	1/7	0/7	0/7	0/7	0/7	1/7	1/7	1/7	0/6	1/6	0/6	0/6	2/7	0/6	1/6	4/6	0/6

		DKEFS									WCST					
Case	Group	FAS	Cat.	Sw_acc	Sw_tot	TMT_1	TMT_2	TMT_3	TMT_4	TMT_5	Tot.error	P. resp.	P..errors.	NonP erorrs.	Conc. Resp.	Educ.
Group 1. Severe Dysfunction: 10 or more of the measures																
1.	1	-	-	+	-	-	+	+	+	-	+	+	+	+	+	No HSD
4.	1	+	+	+	-	+	+	+	-	+	++	++	++	+	+	HSD
11.	1	*	*	*	*	*	*	*	*	*	-	+	+	-	-	HSD
12.	1	-	-	+	-	-	-	-	+	+	-	+	+	-	-	PostHSD
14.	1	-	-	+	+	+	+	+	-	+	+	+	+	+	+	No HSD
16.	1	-	-	-	-	-	-	*	*	-	-	-	-	-	-	No HSD
Group 2. Moderate Dysfunction: 5 to 10 of the measures																
2.	2	+	++	+	+	+	+	+	+	+	+	+	+	+	+	PostHSD
5.	2	++	++	++	++	-	-	*	*	*	+	+	+	+	+	PostHSD
8.	2	*	*	*	*	+	++	++	+	+	++	+	+	++	++	PostHSD
13.	2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	PostHSD
15.	2	+	+	+	+	+	+	+	+	+	-	-	-	-	-	HSD
17.	2	+	++	++	++	+	+	+	+	+	+	+	+	+	+	PostHSD
20.	2	-	+	+	+	+	+	+	+	+	+	+	+	-	+	No HSD
Group 3. Mild Dysfunction: up to 4 measures																
3.	3	+	++	+	+	+	+	+	+	+	+	+	+	+	+	PostHSD
6.	3	++	++	+	+	+	++	++	+	+	+	+	+	+	+	PostHSD
7.	3	+	++	++	++	+	+	+	+	+	+	+	+	+	+	PostHSD
9.	3	++	+	+	+	+	+	+	+	+	+	+	+	+	+	PostHSD
10.	3	++	++	+	+	+	+	+	+	+	+	+	+	+	+	PostHSD
18.	3	-	+	+	+	*	*	*	*	*	+	+	+	+	+	PostHSD
19.	3	++	++	++	++	+	+	+	++	+	+	+	+	+	+	HSD

Note: ++ = above 1 standard deviation, + = within -1 and 1 standard deviation- = less than -1 standard deviation, and * = missing data.

Inquiry 2. Explore the inter-group variation on all neurocognitive measures.

Analysis of Variance.

A series of analyses of variance were conducted across all dependent measures of neurocognitive functioning for each of the three aforementioned groups outlined above ("Severe Dysfunction", "Moderate Dysfunction", and "Mild Dysfunction"). Descriptive statistics for each neurocognitive measure by level of dysfunction are presented in Appendix B. [The Bonferroni correction was used to identify significant effects (i.e., p =.05/10 = 0.005).] Because the analyses were exploratory, results at the 0.05 level will also be described.

Post-Hoc Contrast Analyses.

In order to determine the group differences between the levels of impairment, a series of post-hoc contrast analyses was conducted (Severe dysfunction vs. Moderate dysfunction; Severe dysfunction vs. Mild dysfunction; and Moderate dysfunction vs. Mild dysfunction). Post hoc comparisons using the Tukey HSD were obtained when measures of equal variances were assumed and the Dunnett T3 for the measures where equal variances were not assumed. Analyses of variance revealed significant differences between groups in the following domains: Intelligence, Memory, Processing Speed, and Executive skills.

Intelligence

Analyses of variances revealed a significant main effect of group on the WASI Full Scale IQ (F(2,17) = 13.91, p = .000), WASI Verbal IQ (F(2,17) = 11.99, p = .001), and WASI Performance IQ (F(2,17) = 10.24, p = .001). Post-hoc comparisons across all three measures of intelligence revealed that the mean z-score for the Severe Dysfunction group was

significantly lower than the Moderate and Mild Dysfunction groups. No differences between the Moderate and Mild groups were found. The results are presented in Table 6.

Table 6. Analyses of variance of measures of intelligence by level of dysfunction

IQ Measure	Level of Dysfunction			*F*	η^2
	Severe	Moderate	Mild		
WASI- Full Scale IQ	-1.22_a (1.01)	$.63_b$ (.49)	1.11_b (.92)	**13.91****	.62
WASI- Verbal IQ	-1.44_a (1.04)	$.19_b$ (.43)	$.82_b$ (.97)	**11.99****	.58
WASI- Performance IQ	$-.72_a$ (1.04)	$.84_b$ (.62)	1.20_b (.73)	**10.24****	.54

Note. * = $p \leq .005$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means (reported as z-scores). Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Tukey's HSD post hoc comparisons.

Memory

Analyses of variances revealed a significant main effect of group on the RCFT immediate recall ($F(2,17) = 9.01$, $p = .001$), and the RAVLT total recall measures($F(2,16) = 12.95$, $p = .000$). Post-hoc comparisons (Dunnett T3) on the RCFT immediate recall demonstrated that the mean z-score for the Severe Dysfunction group was significantly lower than the Mild Dysfunction group and not the Moderate Dysfunction group. No differences were found between the Moderate and Mild groups. Post hoc comparisons (Tukey HSD) on the RAVLT total recall measure revealed that the mean z-score for the Severe Dysfunction group was significantly lower than the Moderate and Mild Dysfunction groups. The results are presented in Table 7.

Table 7. Analyses of variance of measures of memory by level of dysfunction

Memory	Level of Dysfunction			F	η^2
	Severe	Moderate	Mild		
RCFT- immediate recall	-2.16_a (1.01)	$-.67_a$ (.49)	$.17_b$ (.92)	**9.01****	.55
RAVLT- total recall	-2.92_a (1.46)	$-.57_b$ (1.22)	$.65_b$ (.98)	**12.95****	.61

Note. * = $p \leq .005$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means (reported as z-scores). Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Dunnet T3 (RCFT) and Tukey's HSD (RAVLT) post hoc comparisons.

Processing Speed

Analyses of variance revealed a significant main effect of group on the SDMT written ($F(2,16) = 9.67$, $p = .002$), and oral measures ($F(2,17) = 9.91$, $p = .001$). Post hoc comparisons (Tukey HSD) on the SDMT written measure revealed that the mean z-score for the Severe Dysfunction group was significantly lower than the Moderate and Mild Dysfunction groups. Post-hoc comparisons on the SDMT oral measure revealed that the mean z- score for the Severe Dysfunction group was significantly lower than the Mild group alone. The results are presented in Table 8.

Table 8. Analyses of variance of measures of processing speed by level of dysfunction

Processing Speed	Level of Dysfunction			F	η^2
	Severe	Moderate	Mild		
SDMT- written	-3.15_a (2.13)	$-.14_b$ (1.23)	$.78_b$ (1.51)	**9.67****	.54
SDMT- oral	-2.45_a (1.50)	$-.50_a$ (1.28)	$.85_b$ (1.25)	**9.91****	.53

Note. * = $p \leq .005$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means (reported as z-scores). Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Tukey's HSD post hoc comparisons.

Executive Functioning

Analyses of variance revealed a significant main effect of group on the DKEFS TMT number-letter switch ($F(2,13) = 13.81$, $p = .001$), measure and the DKEFS verbal fluency category switching measure ($F(2,15) = 8.40$, $p = .004$). Post hoc comparisons (Tukey HSD) on the both measures of executive functioning revealed that the mean z-score for the Severe Dysfunction group was significantly lower than the Moderate and Mild Dysfunction groups. The results are presented in Table 9.

Table 9.Analyses of variance of measures of executive function by level of dysfunction

Executive Function	Level of Dysfunction			*F*	η^2
	Severe	Moderate	Mild		
DKEFS TMT- number letter switch	$-.91_a$ (.57)	$.22_b$ (.49)	$.66_b$ (.36)	**13.81****	.68
DKEFS verbal fluency switch- total	-1.20_a (1.06)	$.33_b$ (.96)	$.99_b$ (.77)	**8.40****	.52

Note. * = $p \leq .005$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means (reported as z-scores). Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Tukey's HSD post hoc comparisons.

Inquiry 3. Explore differences in neuropsychological scores based on demographic and disease variables.

Independent t-tests.

A series of independent t-tests was conducted across all dependent measures of neurocognitive functioning for sex, education, age at diagnosis, medication consumption at time of testing, and time elapsed between testing and diagnosis. Analyses were not conducted by level of dysfunction since too few patients were included in each subgroup. See Appendix C for demographic data by level of dysfunction.

Sex

Comparisons between men (n = 12) and women (n = 8) demonstrated no significant differences across all neuropsychological variables.

Education

Groups were created based on participants' level of education (No high school diploma; n = 4, High school diploma; n = 4, and Post high school education; n = 12). The groups No High school diploma and High school diploma were combined due to small sample sizes per group. Differences between levels of education were found on all the intelligence quotients (Full Scale IQ; (t(18) = -3.396, p = .003), Verbal IQ; (t(18) = -3.386, p = .003), and Performance IQ; (t(18) = -2.517, p = .022) such that those with post-high school education had superior performance compared to those with the high school or below combined group. See Table 10 for statistical data.

Table 10. Comparison of measures of IQ between levels of education

Intelligence Quotients	Education		*T*	*df*
	No High School Diploma/ High School Diploma	Post High School education		
WASI Full Scale IQ	-.70 (1.29)	.88 (.80)	**-3.39****	18
WASI Verbal IQ	-1.08 (1.25)	.54 (.80)	**-3.38****	18
WASI Performance IQ	-.18 (.95)	1.32 .71	**-2.51***	18

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Age at diagnosis

Age at diagnosis was defined categorically in two dimensions, by developmental age 6-11 (*n* = 12) versus 12-18 (*n* = 8), and by puberty onset at diagnosis (<10 years of age *n* = 10 and >10 years of age *n* = 10). Comparisons for age at diagnosis by development revealed no significant differences across the neuropsychological measures. Age by puberty onset at the time of diagnosis revealed differences in the following domains: Processing Speed (SDMT oral ($t(18) = -2.156$, $p = .045$)), Motor skills (Purdue pegboard non preferred hand ($t(16) = -2.28$, $p = .037$), and Executive Function (DKEFS trail making number sequencing ($t(16) = -2.50$, $p = .023$), such that patients diagnosed in the post puberty onset group performed superior than those diagnosed pre-puberty. See Table 11 for results.

Table 11. Comparison of measures of Processing Speed, Motor Skills, and Executive Function between groups divided by puberty onset at time of diagnosis.

Neurocognitive Domain Measure	Age: Puberty onset		*T*	*df*
	Pre-puberty (<10 years of age)	Puberty onset (< 10 years of age)		
Processing Speed				
SDMT oral	-1.43 (2.18)	.21 (1.03)	**-2.15***	18
Motor Skill				
Purdue Pegboard non-preferred hand	-2.06 (2.12)	-.36 (.93)	**-2.28***	16
Executive Function				
DKEFS TMT number sequencing	-.83 (1.67)	.60 (.62)	**-2.50***	16

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Medication consumption at time of testing

Comparisons for medication consumption at the time of testing (no consumption *n* = 8, consumption *n* = 10), revealed differences in the following domains: Intelligence, visual

memory, Motor skills, and Executive Function. Analyses revealed that that those who were not on medication performed superior than those on medication at the time of testing. The results are presented in Table 12 through Table 15.

Table 12. Comparison of measures of Intelligence for medication consumption at the time of testing.

	Medication consumption			
Intelligence Quotients	No consumption	Consumption	*T*	*df*
WASI Full Scale IQ	.94 (.65)	-.21 (1.40)	**2.17***	18
WASI Verbal IQ	.68 (.71)	-.58 (1.28)	**2.54***	18

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means.

Table 13. Comparison of measures of Memory for medication consumption at the time of testing.

	Medication consumption			
Memory variables	No consumption	Consumption	*T*	*df*
RCFT immediate recall	-.07 (.85)	-1.32 (1.33)	**2.33***	18
RCFT delayed recall	.31 (.68)	-1.24 (1.35)	**3.00***	18
RCFT recognition	.49 (.92)	-.68 (1.34)	2.13	18
RAVLT delayed recall	.24 (1.33)	-1.42 (1.84)	2.16	17

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Table 14. Comparison of measures of Motor Skills between medication consumption at the time of testing.

Motor Skill variables	Medication consumption		*T*	*df*
	No consumption	Consumption		
Purdue Pegboard non preferred hand	-.12 (1.35)	-1.91 (1.67)	**2.44***	16
Purdue Pegboard both hands	-.36 (1.67)	-2.20 (1.83)	**2.19***	16
Purdue Pegboard assemblies	-1.22 (.54)	-3.06 (1.95)	**2.56***	16

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Table 15. Comparison of measures of Executive Function between medication consumption at the time of testing.

Executive Funciton variables	Medication consumption		*T*	*df*
	No consumption	Consumption		
DKEFS verbal fluency FAS	1.19 (1.38)	-.60 (1.45)	**2.60***	16
DKEFS verbal fluency category	2.33 (.83)	-.21 (1.56)	**3.92****	16
DKEFS verbal fluency switching accuracy	1.09 (.73)	.02 (.86)	**2.69***	16
DKEFS TMT number sequencing	.66 (.61)	.-59 (1.58)	**2.12***	16
DKEFS TMT motor speed	.58 (.23)	-.48 (1.04)	**2.82***	15
WCST total errors	.68 (.59)	-.38 (.93)	**2.87***	18
WCST preseverative errors	.74 (.45)	-.14 (.73)	**3.03***	18
WCST non preseverative errors	.47 (.55)	-.65 (1.04)	**2.77***	18

WCST conceptual level responses	.76 (.96)	-.46 (.85)	**2.99***	18

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Time elapsed since diagnosis

Time elapsed since diagnosis was analyzed by splitting the group by 5 to 15 years since diagnosis (n = 11) and greater than 15 years since diagnosis (n = 9). Comparisons revealed differences in Executive Function alone whereby patients in the less than 15 years group performed superior than the group with more time elapsed. The results are presented in Table 16.

Table 16. Comparison of measures of Executive function between the number of years elapsed between testing and tumour diagnosis.

	Elapsed time			
Executive Function variables	5-15 years	15+ years	*T*	*df*
WCST total errors	.43 (.52)	-.43 (1.18)	**2.19***	18
WCST perseverative responses	.53 (.60)	-.27 (.78)	**2.58***	18
WCST perseverative errors	.55 (.57)	-.20 (.79)	**2.48***	18
WCST non preseverative errors	.23 (.63)	-.74 (1.19)	**2.34***	18

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Inquiry 4. Explore differences in neuropsychological scores based on tumour related factors.

Independent t-tests.

A series of independent t-tests was conducted across all dependent measures of neurocognitive functioning for the following tumour related parameters: tumour location, tumour pathology, treatment methods, and symptoms at time of diagnosis. Analyses were not conducted by level of dysfunction since too few patients were included in each subgroup. See Appendix D for tumour related factors by level of dysfunction.

Tumour location

Comparisons between patients with infratentorial (n = 11) and supratentorial (n = 9) tumours demonstrated no significant differences on all neuropsychological variables.

Tumour pathology

The impact of tumour pathology on cognitive function was analysed by type of glioma, astrocytoma (n = 17) versus other gliomas (n = 3). Comparisons between these groups of patients revealed significant differences in Executive Function (DKEFS verbal fluency category total (t(16) = 2.52, p = .023; and DKEFS trail making motor speed (t(15) = 2.75 , p = .015)), with the astrocytoma pathology group showing better performance. See Table 17 for results.

Table 17. Comparison of measures of Executive function by tumour pathology.

Executive Function variables	Tumour Pathology		*T*	*df*
	Astrocytoma	Other glioma		
DKEFS verbal fluency category total	1.20 (1.59)	-1.33 (1.52)	**2.52***	16
DKEFS TMT motor speed	.26 (.60)	-1.13 (1.50)	**2.75***	15

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means (reported as z-scores).

Treatment methods

Comparisons between patients who underwent surgery alone (n = 17) and those with radiation or chemotherapy in addition to surgery (n = 3) also showed no significant differences across the neuropsychological test variables.

Symptoms at time of diagnosis

Comparisons between patients who experienced symptoms of hydrocephalus or seizures (n = 15) at the time of diagnoses and those who did not (n = 5) revealed no significant differences across the neuropsychological measures.

Part B: Perceived Health and Cognitive Quality of Life

Inquiry 1. Identify domains of strengths and weaknesses in the sample population's perceived health and cognitive quality of life.

The sample population completed a health related quality of life questionnaire (RAND-36) and a perceived cognitive functioning questionnaire (FACT-Cognitive Function version 3). As indicated in the Methods section: Table 4, the RAND-36 has eight scales measuring the following health related domains: Physical functioning, Role limitations due to physical health, role limitations due to emotional problems, Energy/fatigue, Emotional well-being, Social functioning, Pain, and General health. Subscales measured in the FACT-Cog include: Perceived Cognitive Impairment (measures participant's perception of their attention, memory, spatial awareness, and processing speed), Comments from others (measures participant's perception of how others rate their ability to remember information, think and speak clearly, and appear confused), Perceived cognitive abilities (measures participant's perception of their ability to concentrate, shift between tasks, and remember items), and Impact on quality of life (measures participant's perception of how their cognitive problems interfere with their emotions, work, and general life enjoyment). Both scales were recoded

such that greater scores indicate superior performance (ie. less impairment). To note, the RAND-36 scores are presented as z-scores and the FACT-Cog scores are raw scores. Normed referenced data does not exist for the FACT-Cog, although studies have documented excellent test-retest reliability, convergent validity with the EORTC-30 Cognitive Functioning Scale, and evidence of discriminant validity (Jacobs et al., 2007).

Table of frequencies.

The scores on the RAND-36 and the FACT-Cog are presented as percentage frequency tables. Tables X and Y illustrate how the participants rated their perceived quality of life, with some subscales rated more frequently in the positive direction than others. For example, the percentage frequency of the participants that rated scores on the "RAND-36: Role limitations due to physical health" above 1 standard deviation was 61.11%, suggesting that the majority of the sample did not endorse physical health as a role limitation. In addition, the majority of the sample *(%f* = 52.94) positively rated their "General health" on the questionnaire, whereas a proportion of the sample endorsed challenges with on the General Health subscale *(%f* = 29.41).

The percentage frequency table for the FACT-Cog questionnaire indicates the number of individuals who rated their abilities in the top and bottom quartiles on each subscale. The results indicate that a large proportion of the sample perceived few challenges on the impact of their cognitive function on quality of life *(%f* = 76.47).

Table 18. Percentage of participants who rated each RAND-36 subscale above and below 1 standard deviation (SD).

RAND-36 Subscale	N	% of sample <1 SD	% of sample >1SD
Physical functioning	18	11.11	44.44
Role limitations due to physical health	18	11.11	61.11
Role limitations due to emotional problems	18	11.11	0
Energy/Fatigue	17	11.76	35.29
Emotional well-being	17	11.76	11.76
Social functioning	17	11.76	0
Pain	17	11.76	29.41
General Health	17	29.41	52.94

Table 19.Percentage of participants who rated each of the FACT-Cog subscales in the top and bottom quartiles.

FACT-Cog Subscale	N	% of sample rated scores in bottom quartile	% of sample in top quartile
Perceived cognitive impairment (/72)	17	5.88	41.17
Comments from others (/16)	17	5.88	62.50
Perceived cognitive abilities (/28)	17	0	41.17
Impact on quality of life (/16)	17	11.76	76.47

Note: Perceived cognitive impairment: bottom quartile = 18/72, top quartile = 54/72; Comments from others: bottom quartile = 4/16, top quartile = 12/16; Perceived cognitive abilities: bottom quartile = 7/28, top quartile = 21/28, Impact on quality of life: bottom quartile = 4/16, top quartile = 12/16.

Analysis of Variance: One-way Repeated Measures.

A series of analyses of variance was conducted with the eight measures of health related quality of life from the RAND-36 in order to determine if differences existed between the subscales in the sample. The analyses were not performed on the FACT-Cog subscales due to unequal number of items per scale (i.e., one scale can not be compared to the other due to different denominators).

Perceived health realted quality of life questionnaire: RAND-36.

Mauchly's test of sphericity indicated that the assumption of sphericity was assumed $\chi^2(27) = 39.714$, $p = .06$. The results demonstrated that there was a main effect of scale, $F(7, 112) = 3.06$, $p = .005$. Post-hoc analyses revealed that the "Physical functioning" scale (M = .50, SD = .84) was significantly different from the "Social functioning" scale (M = -.15, SD = 1.14), and the "Role limitations due to physical health" scale (M = .65, SD = .82) was significantly different than the "Social functioning" scale (M = -.15, SD = 1.14. Both comparisons indicated that the sample perceived their physical health more favourably than their social functioning. Figure 3 displays the means for each subscale. Table 20 presents the results of the repeated measures analysis.

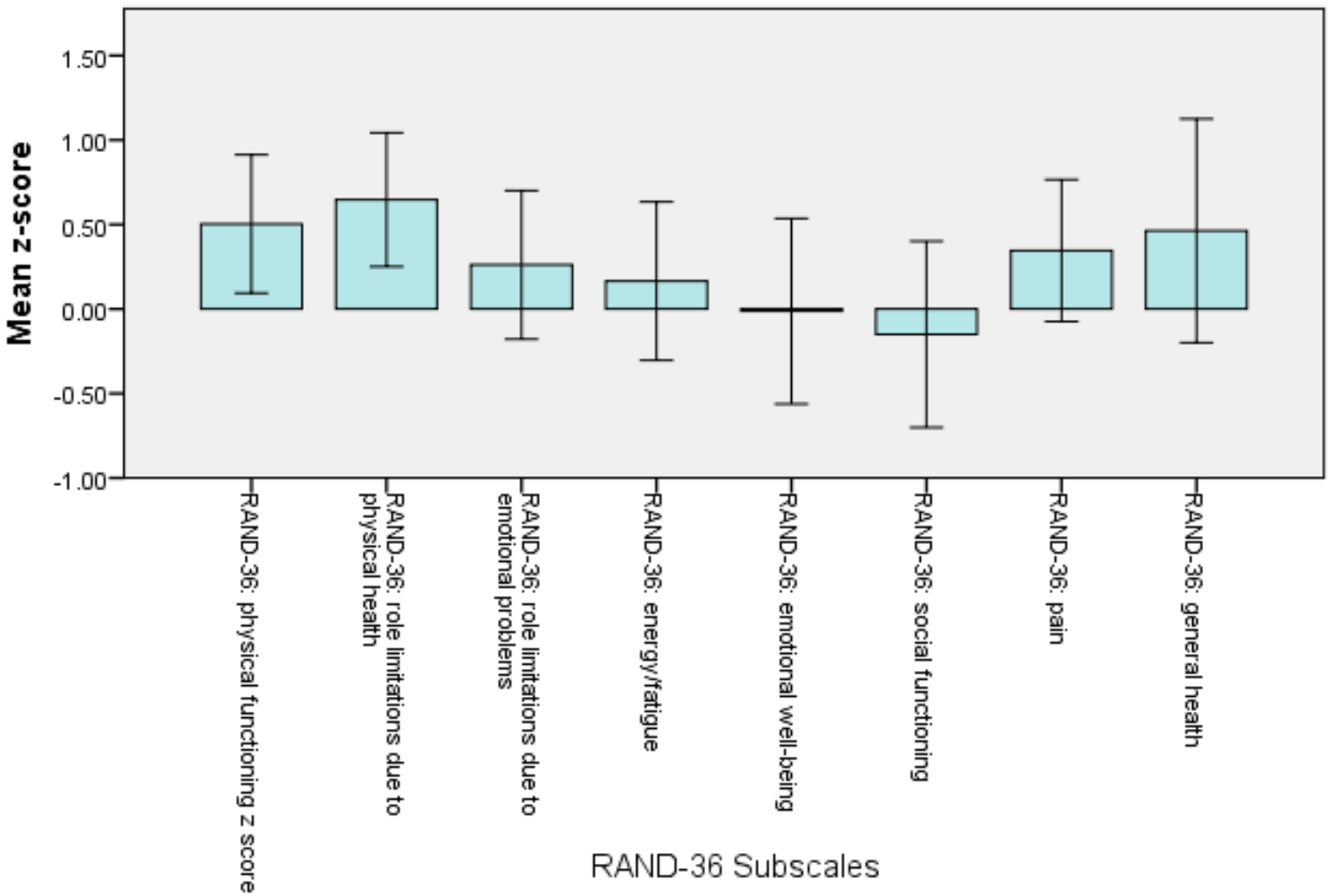

Figure 3. Graph of mean z-score for each of the subscales on the RAND-36 (with confidence intervals).

Table 20. Repeated measures analysis of variance on subscales of the RAND-36

Effect	*MS*	*df*	*F*	*P*
RAND-36 subscales	1.23	**7**	3.06	**.005****

Inquiry 2. Explore the inter-group variation in the quality of life questionnaires.

Analysis of Variance.

A series of analyses of variance was conducted across all subscales from the RAND-36 and FACT-cog across the three neurocognitive groups outlined in Chapter 1 ("Severe Dysfunction", "Moderate Dysfunction", and "Mild Dysfunction"). Descriptive statistics for each perceived health related and cognitive quality of life measure by level of dysfunction are presented in Appendix E and F, respectively. The Bonferroni correction was used to identify significant effects (i.e., p =.05/7). In addition, since the analyses are exploratory only results at the significant level will be reported.

Post-Hoc Contrast Analyses.

In order to determine the group differences between the levels of dysfunction, a series of post-hoc contrast analyses was conducted (Severe dysfunction vs. Moderate dysfunction; Severe dysfunction vs. Mild dysfunction; and Moderate dysfunction vs. Mild dysfunction). Post hoc comparisons using the Tukey HSD were obtained for measures of equal variances assumed and the Dunnett T3 for the measures where equal variances were not assumed.

Analyses of variance revealed significant differences between groups in the following subscales of the RAND-36: Physical Function, Social Function and in the FACT-Cog:

Comments from Others. Figure 4 illustrates the mean z-scores of each subscale by level of dysfunction.

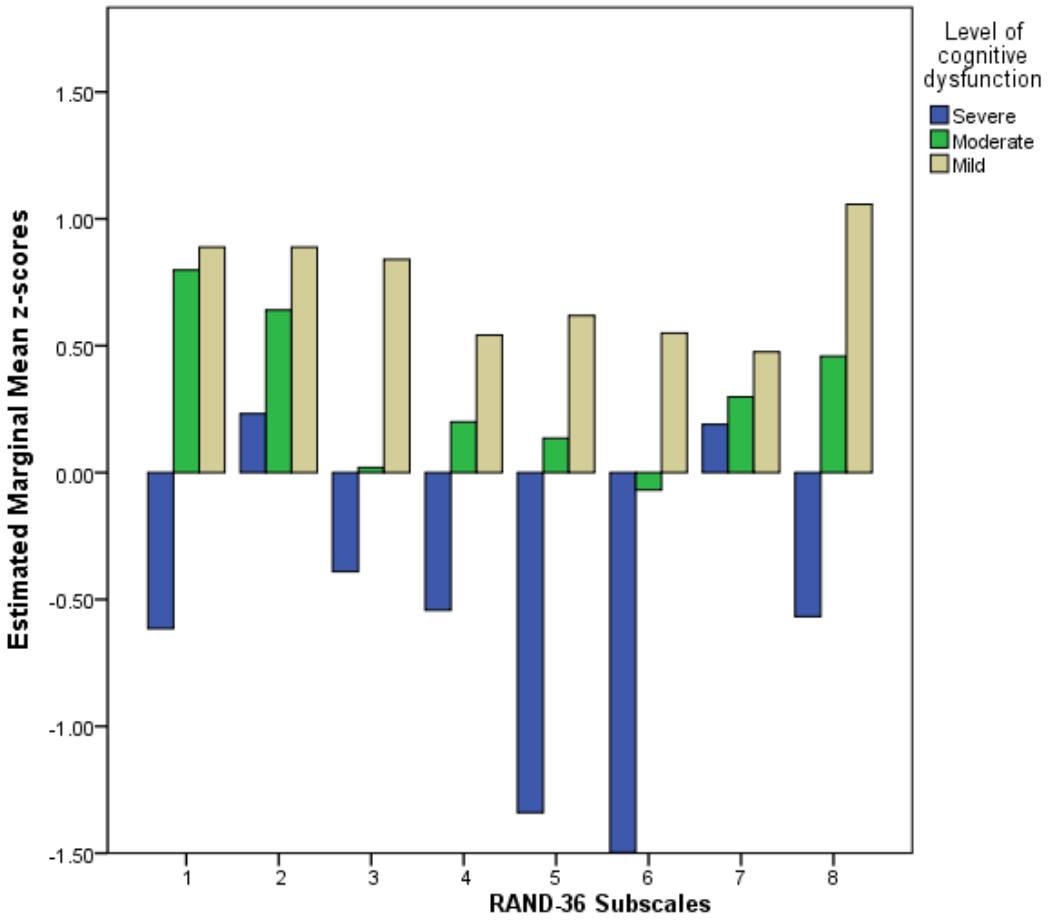

Figure 4. Mean scores of the RAND-36 subscales by level of dysfunction.

Note: Scales are numbered 1 through 8 representing the following labels: 1-Physical functioning, 2-Role limitations due to physical health, 3-role limitations due to emotional problems, 4-Energy/fatigue, 5- Emotional well-being, 6-Social functioning, 7-Pain, and 8-General health. Marginal means are presented as z-scores.

Perceived health related quality of life: RAND-36.

Analyses of variances revealed a significant main effect of group on the Physical function subscale ($F(2,15) = 10.38$, $p = .001$), Social Function ($F(2,14) = 10.73$, $p = .006$), and Emotional well-being approached significance ($F(2,14) = 6.65 = .009$).

Post-hoc comparisons across the first two health related subscales revealed that the mean z-score for the Severe Dysfunction group was significantly lower than the Moderate and Mild Dysfunction groups. No differences between the Moderate and Mild groups were found. The results are presented in Table 21.

Table 21. Analysis of variance on subscales of the RAND-36 by level of dysfunction

	Level of Dysfunction				
RAND-36	Severe	Moderate	Mild	*F*	η^2
Physical Function	$-.62_a$ (1.05)	$.84_b$ (.20)	$.89_b$ (.48)	**10.38****	.58
Social Function	-1.50_a (.93)	$-.07_b$ (1.09)	$.55_b$ (.48)	**7.58***	.52
Emotional Function	-1.34_a (1.33)	$.14_a$ (.77)	$.62_a$ (.60)	**6.65***	.48

Note. * = $p \leq .01$ ** = $p \leq .001$. Standard deviations appear in the parentheses below the means (reported as z-scores). Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Tukey's HSD (homogeneity of variance assumed) and Dunnett T3(homogeneity of variance not assumed).

Perceived cognitive quality of life: FACT-Cog.

Analyses of variance revealed a significant main effect of group on the Comments from Others subscale (i.e., participant's perception of how others rate their ability to remember information, think and speak clearly, and appear confused) ($F(2,14) = 12.74$, $p = .001$), although post-hoc comparisons (Dunnett T3; homogeneity of variance not assumed) demonstrated marginally significant differences between the Severe Dysfunction group (M = 7.75, SD = 4.27) and the Mild Dysfunction group (M = 15.43, SD = .54), $p = .08$. Figure 5. displays the mean raw score for each subscale by level of dysfunction.

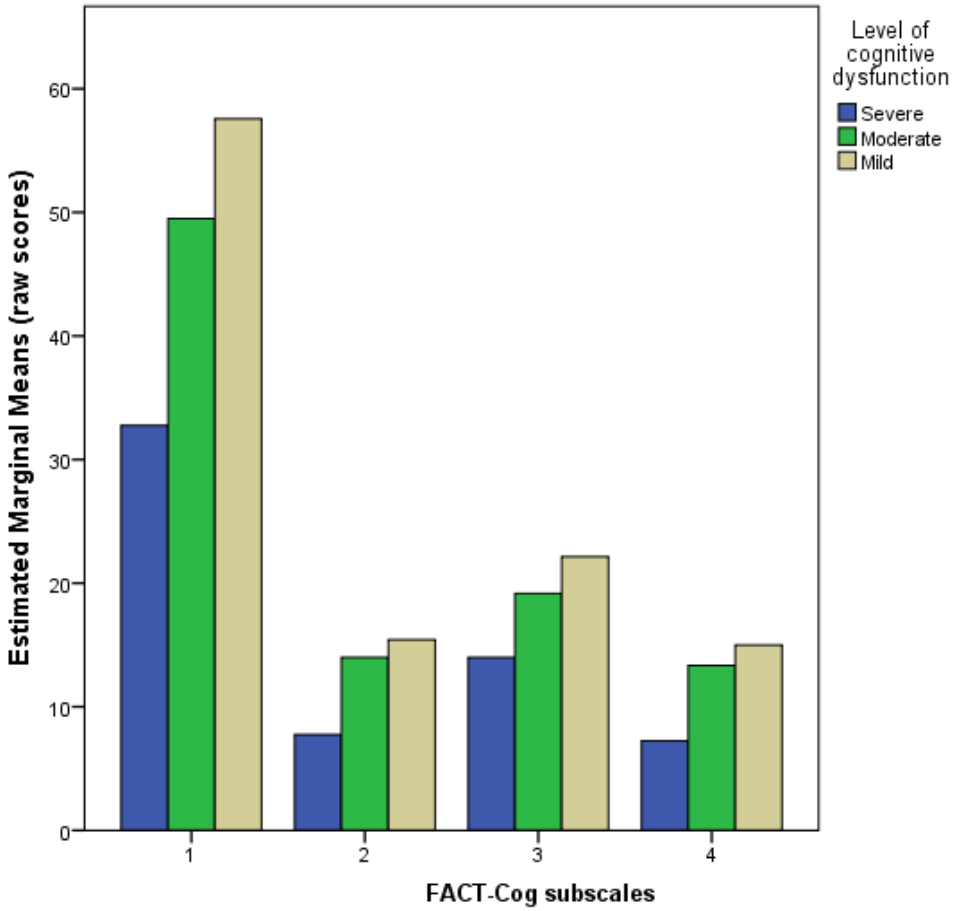

Figure 5. Mean scores of the FACT-Cog subscales by level of dysfunction

Note: Scales are numbered 1 through 4 representing the following labels: 1-Perceived cognitive impairment, 2-Comments from others, 3-Perceived cognitive abilities, 4-Impact on quality of life. Marginal means are presented as raw scores. Greater scores suggest less impairment.

Inquiry 3. Explore differences in perceived quality of life scores based on demographic variables.

Independent t-tests.

A series of independent t-tests was conducted across the quality of life subscales by sex, education, age at diagnosis, medication consumption at time of testing, and time elapsed between testing and diagnosis. Analyses were not conducted by level of dysfunction since too few patients were included in each subgroup. See Appendix G and H for demographic data by level of dysfunction.

Sex

Comparisons between men (n = 10) and women (n = 7) demonstrated that women (M = -.71, SD = 1.25) had significantly lower scores than men (M = .47, SD = .77) on the RAND-36: Emotional well-being subscale ($t(15) = -2.424$, $p = .028$). No significant differences were found across the other RAND-36 and FACT-Cog subscales.

Education

Education (divided by Post High School education, n = 11 versus High School diploma/No High School diploma, n = 7) demonstrated significant differences on 11 of the 12 subscales at a significance level of $p < 0.05$, whereby individuals with Post High School education rated their quality of life more favourably than those with either no High School diploma or with a High School diploma alone. See Table 22 for results for the independent samples analyses.

Table 22. Comparison between levels of education on perceived quality of life measures (QoL).

QoL	Education		*T*	*df*
	No High School Diploma/ High School Diploma	Post High School education		
RAND-36				
Physical functioning	.03 (1.11)	.86 (.38)	**-2.31***	16
Role limitations due to physical health	.19 (1.05)	.98 (.39)	**-2.30***	16
Role limitations due to emotional problems	-.21 (1.13)	.62 (.53)	**-2.12***	16
Energy/fatigue	-.51 (.86)	.53 (.84)	**-2.41***	15
Emotional well-being	-.87 (1.39)	.46 (.63)	**-2.74***	15
Social functioning	-1.38 (.97)	.52 (.45)	**-5.57****	15

Pain	-.36 (.98)	.73 (.51)	**-3.05****	15
General Health	-.25 (1.42)	.85 (1.22)	-1.68	15
FACT-Cog				
Perceived cognitive impairment	37.17 (15.97)	55.27 (10.47)	**-2.83***	15
Comments from others	10.50 (5.39)	14.55 (1.86)	**-2.30***	15
Perceived cognitive abilities	15.67 (5.13)	21.09 (4.35)	**-2.31***	15
Impact on QoL	8.67 (5.72)	14.73 (1.42)	**-3.41****	15

Note. * = $p \leq .05$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means. Means reported as z-scores for the RAND-36 subscales, and as raw scores for the FACT-Cog subscales.

Age at diagnosis

Age at diagnosis was defined categorically along two dimensions: chronological age 6-11 (*n* = 12) versus 12-18 (*n* = 8) and puberty onset (<10 years of age *n* = 10 and >10 years of age *n* = 10). Comparisons for age at diagnosis by chronological age and by puberty onset revealed no significant differences across the perceived quality of life measures.

Medication consumption at time of testing

Comparisons between medication consumption at the time of testing (no consumption *n* = 8, consumption *n* = 9) by quality of life revealed differences in the following six subscales: RAND-36 Physical functioning, Energy/fatigue, Emotional well-being, Social Functioning, General health, and FACT-Cog Impact on quality of life. Analyses revealed that those who were not on medication rated their health and cognitive abilities significantly more favourably than those on medication at the time of testing. The results are presented in Table 23.

Table 23. Comparison of perceived quality of life measures (QoL) by medication consumption.

QoL	Medication Consumption		*T*	*df*
	No Consumption	Consumption		
RAND-36				
Physical functioning	1.00 (.13)	.16 (.97)	**2.43***	16
Role limitations due to physical health	.10 (.28)	.42 (.99)	1.60	16
Role limitations due to emotional problems	.64 (.38)	.02 (1.09)	1.51	16
Energy/fatigue	.71 (.58)	-.32 (1.00)	**2.55***	15
Emotional well-being	.64 (.58)	-.60 (1.21)	**2.64***	15
Social functioning	.52 (.45)	-.75 (1.24)	**2.73***	15
Pain	.57 (.77)	.14 (.94)	1.02	15
General Health	1.44 (.87)	-.41 (1.11)	**3.79***	15
FACT-Cog				
Perceived cognitive impairement	53.50 (11.31)	44.78 (17.41)	1.21	15
Comments from others	13.88 (2.42)	12.44 (4.92)	.74	15
Perceived cognitive abilities	20.25 (4.74)	18.22 (5.70)	.79	15
Impact on QoL	15.00 (1.20)	10.44 (5.34)	**2.35***	15

Note. * = $p \leq .05$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means. Means reported as z-scores for the RAND-36 subscales, and as raw scores for the FACT-Cog subscales.

Time elapsed between testing and diagnoses

Time elapsed since diagnosis was analyzed by splitting the group by those diagnosed 5 to 15 years from date of testing (n = 10) and greater than 15 years since diagnosis (n = 7). No significant differences were found between groups on measures of perceived quality of life.

Inquiry 4. Explore differences in perceived quality of life scores based on tumour related factors.

Independent t-tests.

A series of independent t-tests was conducted across the quality of life subscales by the following tumour related parameters: tumour location, tumour pathology, treatment methods, and symptoms at diagnosis. Analyses were not conducted by level of dysfunction since too few patients were included in each subgroup. See Appendix I and J for tumour related data by level of dysfunction.

Tumour location

Comparisons between patients with infratentorial (n = 9) and supratentorial (n = 9) tumours demonstrated no significant differences on any perceived quality of life subscales.

Tumour pathology

Tumour pathology was analysed by type of glioma, astrocytoma (n = 15) versus other gliomas (n = 2) across all the perceived quality of life subscales. Comparisons between these patients revealed no significant differences ($p < 0.05$).

Treatment methods

Comparisons between patients who underwent surgery alone (n = 14) and those with radiation or chemotherapy in addition to surgery (n = 3) also showed non-significant differences (p < 0.05) across the perceived quality of life subscales.

Symptoms at diagnoses

Lastly, comparisons between patients who experienced symptoms of hydrocephalus or seizures (n = 11) at the time of diagnoses and those who did not (n = 6) revealed no significant differences across the perceived quality of life subscales.

Inquiry 5. Explore relationships between perceived health and cognitive related quality of life scores.

Correlations.

Pearson product-moment correlations were computed between the RAND-36 subscales and the FACT-cog subscales. Positive correlations between perceived health and cognitive function subscales indicated that the more participants rated their health quality of life as enhanced, the better they perceived their cognitive function. The results are presented in Table 24.

Table 24. Correlation matrix between the FACT-Cog and RAND-36 subscales.

		RAND-36: physical functioning z score	RAND-36: role limitations due to physical health	RAND-36: role limitations due to emotional problems	RAND-36: energy/fatigue	RAND-36: emotional well-being	RAND-36: social functioning	RAND-36: pain	RAND-36: general health
FACT-cog: perceived cognitive impairment raw score (/72)	Pearson Correlation	**.674****	.218	**.550***	**.567***	**.746****	**.722****	.358	**.513***
	Sig. (2-tailed)	.00	.400	.022	.018	.001	.001	.158	.035
	N	17	17	17	17	17	17	17	17
FACT-cog: comments from others raw score (/16)	Pearson Correlation	**.681****	.008	.397	.312	**.661****	**.566***	-.011	.298
	Sig. (2-tailed)	.003	.977	.114	.223	.004	.018	.966	.245
	N	17	17	17	17	17	17	17	17
FACT-cog: perceived cognitive abilities raw score (/28)	Pearson Correlation	**.529***	.346	**.588***	**.715****	**.727****	**.621****	.468	**.668****
	Sig. (2-tailed)	.029	.174	.013	.001	.001	.008	.058	.003
	N	17	17	17	17	17	17	17	17
FACT-cog: impact on quality of life raw score (/16)	Pearson Correlation	**.822****	.449	**.690****	**.716****	**.907****	**.872****	.474	**.774****
	Sig. (2-tailed)	.000	.071	.002	.001	.000	.000	.055	.000
	N	17	17	17	17	17	17	17	17

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed)

Inquiry 6. Explore relationships between perceived cognitive related quality of life scores and IQ.

Correlations.

Pearson product-moment correlations were computed between the RAND-36 subscales, the FACT-cog subscales, and measures of Intelligence (WASI-Verbal IQ, WASI-Performance IQ, and WASI-Full Scale IQ), independently.

Positive correlations between measures of intelligence with both perceived health and cognitive subscales indicated that increased performance in cognitive function was in line with increased perceptions of adequate quality of life. The results are presented in Table 25 and 26.

Table 25. Correlation Matrix between measures of Intelligence and the RAND-36 subscales.

		RAND-36: physical functioning z score	RAND-36: role limitations due to physical health	RAND-36: role limitations due to emotional problems	RAND-36: energy/fatigue	RAND-36: emotional well-being	RAND-36: social functioning	RAND-36: pain	RAND-36: general health
WASI: verbal IQ z score	Pearson Correlation	**.833****	.430	.457	**.681****	**.821****	**.802****	.338	**.716****
	Sig. (2-tailed)	.000	.075	.056	.003	.000	.000	.184	.001
	N	18	18	18	17	17	17	17	17
WASI: performance IQ z score	Pearson Correlation	**.735****	.199	.217	.456	**.607****	**.605***	.129	**.494***
	Sig. (2-tailed)	.001	.429	.386	.066	.010	.010	.621	.044
	N	18	18	18	17	17	17	17	17
WASI: full scale IQ z score	Pearson Correlation	**.814****	.361	.369	.**598***	**.742****	**.755****	.271	.**607****
	Sig. (2-tailed)	.000	.141	.132	.011	.001	.000	.292	.010
	N	18	18	18	17	17	17	17	17

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed).

Table 26. Correlation Matrix between measures of Intelligence and the FACT-cog subscales.

		FACT-cog: perceived cognitive impairment raw score (/72)	FACT-cog: comments from others raw score(/16)	FACT-cog: perceived cognitive abilities raw score (/28)	FACT-cog: impact on quality of life
WASI: verbal IQ z score	Pearson Correlation	**.776****	**.745****	**.648****	**.785****
	Sig. (2-tailed)	.000	.001	.005	.000
	N	17	17	17	17
WASI: performance IQ z score	Pearson Correlation	**.641****	**.747****	.475	**.576***
	Sig. (2-tailed)	.006	.001	.054	.015
	N	17	17	17	17
WASI: full scale IQ z score	Pearson Correlation	**.751****	**.781****	**.586***	**.714****
	Sig. (2-tailed)	.001	.000	.014	.001
	N	17	17	17	17

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed).

Part C: Measures of Adaptive Functioning

Inquiry 1. Identify domains of strengths and weaknesses in the sample population's adaptive functioning.

The sample population completed an adaptive functioning questionnaire (Adult Self-Report: ASR). As indicated in the Methods section: Table 4, the ASR has five self-perception scales measuring the following adaptive functioning domains: Mean adaptive (reflects perceptions of effectiveness and satisfaction with friends, family, and job/education), Personal Strengths (identifies perceptions of their attitude and code of conduct such as honesty, fairness, and ability to meet responsibilities), Internalizing symptoms (identifies behaviours related to anxiety and depression) , Externalizing symptoms (identifies behaviours related to aggression, rule-breaking and intrusion), and Total Problems (score reflects an aggregate of the Externalizing and Internalizing symptoms). T-scores have been calculated such that the first two domains are interpreted as T-scores greater than 35 are within the normal range and the latter three domains are interpreted as T-scores less than 60 are within the normal range.

Table of frequencies.

The counts of the sample scores on the ASR are presented as percentage frequency. Table 27 illustrates the range of scores in the normal range reported across the subscales. More than half of the sample rated their adaptive function in the normal range across the subscales (*%f* = 55.56 – 83.33, Internalizing symptoms and Personal Strengths, respectively).

Table 27. Percentage of sample who rated each ASR subscale within the normative range utilizing norm standardized T-score cut off points.

ASR subscales	N	% of sample within normal range
Mean Adaptive Score	18	77.78
Personal Strengths	18	83.33
Internalizing symptoms	18	55.56
Externalizing symptoms	18	66.67
Total Problems	18	66.67

Analysis of Variance: One-way Repeated Measures

A series of analyses of variance was conducted with the five measures of adaptive functioning from the ASR in order to determine if differences existed between the subscales in the sample. Mauchly's test indicated that the assumption of sphericity was violated, $\chi^2(9) = 74.31$, $p = .00$, therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .32$). The results demonstrated that there was no significant differences between ratings on each of the adaptive functioning subscales, $F(1.30, 22.01) = 1.62$, $p = .22$. Figure 6 displays the means for each subscale.

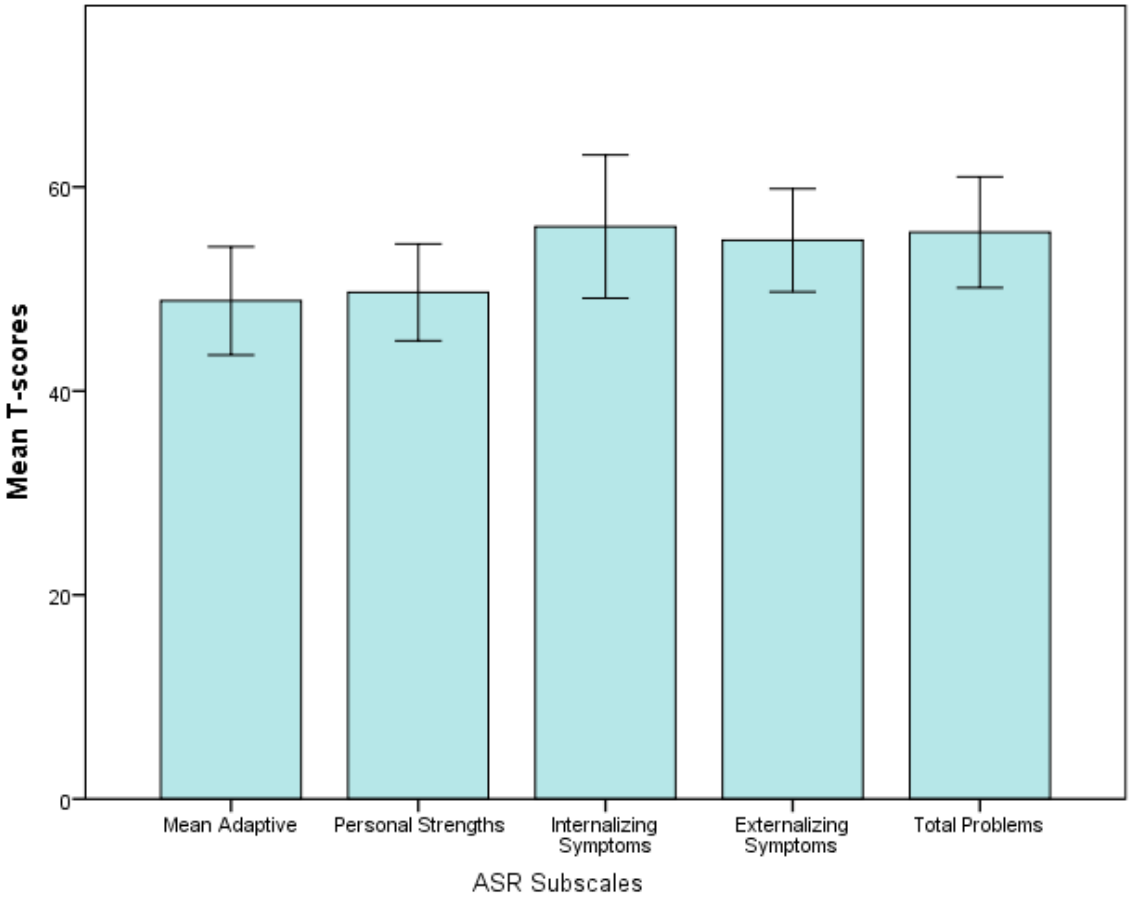

Figure 6. Graph of mean T-score for each of the subscales on the Adult Self-Report Measure with confidence intervals.

Inquiry 2. Explore the inter-group variation across the adaptive measures.

Analysis of Variance.

A series of analyses of variance was conducted across all subscales from the ASR between the three neurocognitive groups outlined in Chapter 1 ("Severe Dysfunction", "Moderate Dysfunction", and "Mild Dysfunction"). Descriptive statistics for each adaptive measure by level of dysfunction are presented in Appendix K. The Bonferroni correction was used to identify significant effects (i.e., p =.05/2). In addition, since the analyses are exploratory only results at the significant level are reported.

Post-Hoc Contrast Analyses.

In order to determine the group differences between the levels of dysfunction, a series of post-hoc contrast analyses were conducted (Severe dysfunction vs. Moderate dysfunction; Severe dysfunction vs. Mild dysfunction; and Moderate dysfunction vs. Mild dysfunction). Post hoc comparisons using the Tukey HSD were obtained for measures of equal variances assumed and the Dunnett T3 for the measures where equal variances were not assumed.

Analyses of variances revealed marginal main effects of group on the Externalizing symptoms subscale ($F(2,15) = 3.58$, $p = .05$) and the Total problems subscale ($F(2,15) = 4.19$, $p = .04$). Post-hoc comparisons between the groups on the Externalizing and Total problems subscales revealed that the mean T-score for the Severe Dysfunction group was significantly higher than the Mild Dysfunction group, suggesting that the Severe Dysfunction group endorsed more challenges than the Mild Dysfunction group. No differences were found between the Moderate and Severe group and the Moderate and Mild groups. The results are presented in Table 28 and Figure 7 illustrates the mean T-scores of each subscale by level of dysfunction.

Table 28. Analyses of variance on subscales of the Adult Self-Report questionnaire (ASR) by level of dysfunction

ASR	Level of Dysfunction			*F*	η^2
	Severe	Moderate	Mild		
Mean Adaptive	41.25 $_{a}$ (11.09)	48.29 $_{a}$ (13.60)	53.71 $_{a}$ (6.92)	1.69	.18
Personal strengths	50.25 $_{a}$ (5.12)	50.29 $_{a}$ (12.63)	48.71 $_{a}$ (10.69)	.05	.01
Internalizing symptoms	66.50 $_{a}$ (14.48)	58.57 $_{a}$ (13.05)	47.71 $_{a}$ (13.89)	2.58	.26
Externalizing symptoms	64.75 $_{a}$ (4.72)	54.86 $_{ac}$ (10.50)	49.00 $_{bc}$ (9.97)	**3.58***	.32
Total Problems	66.50 $_{a}$ (9.26)	56.14 $_{ac}$ (9.67)	48.71 $_{bc}$ (10.26)	**4.19***	.36

Note. * = $p \leq .05$ ** = $p \leq .01$. Standard deviations appear in the parentheses below the means. Means are presented as T-scores whereby the Mean Adaptive and Personal Strengths scales are interpreted as T-scores > 35 are within the normal range and in the Internalizing, Externalizing, and Total Problems scales T-scores < 60 are within the normal range. Means with differing subscripts within rows are significantly different at the $p \leq .05$ based on Tukey's HSD (homogeneity of variance assumed) and Dunnett T3 (homogeneity of variance not assumed).

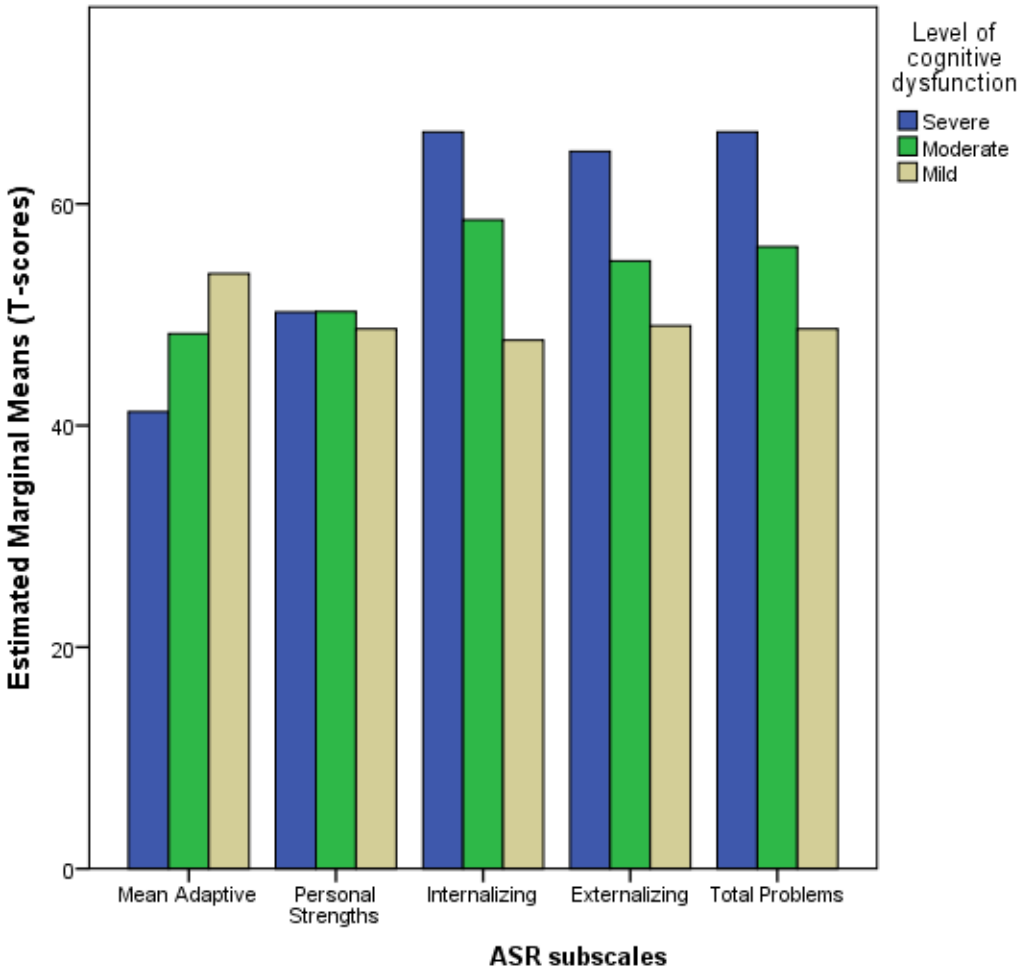

Figure 7. Mean T-scores on each subscale of the Adult Self-Report Measure (ASR) by level of dysfunction.

Inquiry 3. Explore differences in perceived quality of life scores based on demographic variables.

Independent t-tests.

A series of independent t-tests was conducted across the adaptive measures subscales by sex, education, age at diagnosis, medication consumption at time of testing, and time elapsed between testing and diagnosis. Analyses were not conducted by level of dysfunction since too few

patients were included in each subgroup. See Appendix L for demographic data by level of dysfunction.

Sex

Comparisons between men (n = 10) and women (n = 8) demonstrated that men had significantly lower scores than women on the ASR-Internalizing ($t(16) = 2.68$, $p = .016$) and the ASR-Total Problems scale ($t(16) = 2.28$, $p = .037$). No significant differences were found across the other three measures (at $p < 0.05$) of adaptive functioning. See table 29 for results from the independent sample t-tests.

Table 29.Comparison of sex on self-report measures of adaptive functioning from the Adult Self-Report questionnaire (ASR).

ASR subscales	Sex		*t*	*df*
	Women	Men		
Mean adaptive	45.50 (12.34)	51.50 (10.21)	-1.13	16
Personal Strengths	48.13 (11.92)	50.90 (8.83)	-.59	16
Internalizing	65.13 (11.28)	48.90 (13.80)	**2.68***	16
Externalizing	59.50 (7.67)	51.00 (11.65)	1.77	16
Total Problems	61.75 (8.83)	50.60 (11.36)	**2.28***	16

Note. * = $p \leq .05$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means. Means are presented as T-scores whereby the Mean Adaptive and Personal Strengths scales are interpreted as T-scores > 35 are within the normal range and in the Internalizing, Externalizing, and Total Problems scales T-scores < 60 are within the normal range.

Education

There were significant between education group differences (divided by versus High School diploma/No High School diploma, $n = 7$ versus Post High School education, $n = 11$) on three subscales at a significance level of $p < 0.05$, whereby individuals with a high school diploma or less education reported greater internalizing, externalizing, and overall total problems than those individuals with post high school education. In addition, the T-scores were in the borderline clinical range for the High School diploma/No High School diploma group across the aforementioned subscales. See Table 30 for results from the independent sample t-tests.

Table 30.Comparison of levels of education on self-report measures of adaptive functioning from the Adult Self-Report questionnaire (ASR).

ASR subscales	Education		*T*	*Df*
	No High School Diploma/ High School Diploma	Post High School education		
Mean adaptive	44.29 (11.97)	51.73 (10.34)	-1.40	16
Personal Strengths	49.14 (7.90)	50.00 (11.64)	-.17	16
Internalizing	65.43 (13.62)	50.18 (12.91)	**2.39***	16
Externalizing	65.00 (5.16)	48.27 (7.73)	**5.03****	16
Total Problems	65.57 (8.12)	49.18 (8.45)	**4.07****	16

Note. * = $p \leq .05$, ** = $p \leq .001$. Standard deviations appear in the parentheses below the means. Means are presented as T-scores whereby the Mean Adaptive and Personal Strengths scales are interpreted as T-scores > 35 are within the normal range and in the Internalizing, Externalizing, and Total Problems scales T-scores < 60 are within the normal range.

Age at diagnosis

Age at diagnosis was defined categorically in two dimensions, by development age 6-11.12 (*n* = 12) versus 12-18 (*n* = 8) and by puberty onset (<10 years of age *n* = 10 and >10 years of age *n* = 10). Comparisons for age at diagnosis by development and by puberty onset revealed no significant differences across adaptive functioning scales.

Medication consumption at time of testing

Comparisons between medication consumption at the time of testing (no consumption *n* = 8, consumption *n* = 10) by measures of adaptive psychological function, revealed differences in all scales except the Externalizing scale. Analyses revealed that that those who were not on medication rated their adaptive functioning significantly more favourably than those on medication at the time of testing. The mean T-scores in the Mean Adaptive and Personal Strengths scales indicate scores within the normal range for both groups. Whereas, the group taking medication at the time of testing had scores in the borderline range in the Internalizing and Total Problems scales. See Table 31 for results from the independent samples t-test for medication consumption.

Table 31. Comparison of medication consumption on self-report measures of adaptive functioning from the Adult Self-Report questionnaire (ASR).

ASR subscales	Medication Consumption		*t*	*df*
	No Consumption	Consumption		
Mean Adaptive	55.88 (1.78)	43.20 (12.60)	**2.81****	16
Personal Strengths	55.13 (5.64)	45.30 (10.96)	**2.30***	16
Internalizing	45.50	64.60	**-3.47****	16

	(8.18)	(13.69)		
Externalizing	51.75 (7.92)	57.20 (12.40)	-1.08	16
Total Problems	49.00 (8.52)	60.80 (11.21)	**-2.46***	16

Note. * = $p \leq .05$, ** = $p \leq .005$. Standard deviations appear in the parentheses below the means. Means are presented as T-scores whereby the Mean Adaptive and Personal Strengths scales are interpreted as T-scores > 35 are within the normal range and in the Internalizing, Externalizing, and Total Problems scales T-scores < 60 are within the normal range.

Time elapsed between testing and diagnoses

Time elapsed since diagnosis was analyzed by splitting the group by those diagnosed 5 to 15 years from date of testing (n = 11) and greater than 15 years since diagnosis (n = 7). No significant differences were found between groups on measures of adaptive psychological functioning.

Inquiry 4. Explore differences in psychological adaptive functioning based on tumour related factors.

Independent t-tests.

A series of independent t-tests were conducted across the adaptive functioning subscales by the following tumour related parameters: tumour location, tumour pathology, treatment methods, and symptoms at diagnosis. Analyses were not conducted by level of dysfunction since too few patients were included in each subgroup. See Appendix M for tumour related data by level of dysfunction. Significant differences were determined based on a 2-tailed alpha of < 0.05.

Tumour location

Comparisons between patients with infratentorial (n = 9) and supratentorial (n = 9) tumours demonstrated no significant differences on any perceived quality of life subscales.

Tumour pathology

Tumour pathology was analysed by type of glioma, astrocytoma (n = 16) versus other gliomas (n = 2) across all the adaptive functioning subscales. Comparisons between these groups revealed no significant differences.

Treatment methods

Comparisons between patients who underwent surgery alone (n = 15) and those with radiation or chemotherapy in addition to surgery (n = 3) also showed non-significant differences across the adaptive functioning subscales.

Symptoms at diagnoses

Lastly, comparisons between patients who experienced symptoms of hydrocephalus or seizures (n = 11) at the time of diagnoses and those who did not (n = 7) revealed no significant differences across the adaptive functioning subscales.

Inquiry 5. Explore relationships between adaptive functioning and perceived health and cognitive related quality of life scores.

Correlations.

Pearson product-moment correlations were computed between the adaptive functioning subscales (ASR) and the perceived cognitive and health related quality of life measures (FACT-Cog and RAND-36 and subscales).

Perceived cognitive related quality of life

Positive correlations ($p < 0.05$, 2-tailed) between adaptive functioning and perceived cognitive related quality of life were found between the ASR- Mean adaptive T-scores and the FACT-Cog: Perceived cognitive abilities and Impact on quality of life. This indicated that reports of higher adaptive scores were associated with better perceived cognitive abilities and perceived impact of cognitive function on quality of life. In addition, significant negative correlations ($p < 0.05$, 2-tailed) were also demonstrated between the ASR: Internalizing symptoms, Externalizing symptoms, and Total problems scales with the FACT-Cog: Perceived cognitive impairment, Perceived cognitive abilities, and the Impact on quality of life. These correlations indicated that lower adaptive T-scores (T-score < 60 suggests normal functioning) were associated with better-perceived cognitive abilities and perceived impact of their cognitive function on quality of life. The results are presented in Table 32

Table 32. Correlation matrix between the ASR subscales and the FACT-Cog subscales

		ASR: Mean adaptive (> 35 is normal)	ASR: Personal Strengths (> 35 is normal)	ASR: Internalizing Symptoms (<60 is normal)	ASR: Externalizing (<60 is normal)	ASR: Total Problems (< 60 is normal)
FACT-Cog: Perceived cognitive impairment (/72)	Pearson Correlation	.414	-.003	**-.645****	**-.735****	**-.798****
	Sig. (2-tailed)	.098	.990	.005	.001	.000
	N	17	17	17	17	17
FACT-Cog: Comments from others (/16)	Pearson Correlation	.197	-.196	-.416	-.401	**-.521***
	Sig. (2-tailed)	.448	.452	.097	.111	.032
	N	17	17	17	17	17
FACT-Cog: Perceived cognitive abilities (/28)	Pearson Correlation	**.617****	.329	**-.617****	**-.741****	**-.730****
	Sig. (2-tailed)	.008	.197	.008	.001	.001
	N	17	17	17	17	17
FACT-Cog: Impact on quality of life (/16)	Pearson Correlation	**.712****	.275	**-.789****	**-.700****	**-.816****
	Sig. (2-tailed)	.001	.286	.000	.002	.000
	N	17	17	17	17	17

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed)

Perceived health related quality of life

Positive correlations ($p < 0.05$, 2-tailed) between adaptive functioning and perceived health related quality of life were found between the ASR- Mean adaptive score and all the health related scales; and the ASR- Personal strengths and the following RAND-36 subscales: Role limitations due to physical health, Energy/fatigue, Pain, and General Health subscales (RAND-36 scores recoded such that greater z-scores indicate superior performance and less impairment). This indicated that with higher endorsement of adaptive qualities, the better participants perceived their health related quality of life in physical function, energy levels, pain perception, and general health. In addition, significant negative correlations ($p < 0.05$, 2-tailed) were demonstrated between the ASR: Internalizing symptoms, Externalizing symptoms, and Total problems scales with all the perceived health related subscales. These correlations indicated that with decreased endorsement of challenges (T-score < 60 suggests normal functioning), the better participants perceived their health related quality of life. The results are presented in Table 33.

Table 33. Correlation matrix between the ASR subscales and the RAND-36 subscales

		ASR: Mean adaptive (> 35 is normal)	ASR: Personal Strengths (> 35 is normal)	ASR: Internalizing Symptoms (<60 is normal)	ASR: Externalizing (<60 is normal)	ASR: Total Problems (< 60 is normal)
RAND-36: Physical functioning	Pearson Correlation	**.667****	.281	**-.606****	**-.498***	**-.609****
	Sig. (2-tailed)	.002	.259	.008	.035	.007
	N	18	18	18	18	18
RAND-36: Role limitations due to physical health	Pearson Correlation	**.664****	**.531***	**-.484***	**-.499***	**-.515***
	Sig. (2-tailed)	.003	.023	.042	.035	.029
	N	18	18	18	18	18
RAND-36: Role limitations due to emotional problems	Pearson Correlation	**.654****	.349	**-.552***	**-.550***	**-.641****
	Sig. (2-tailed)	.003	.155	.018	.018	.004
	N	18	18	18	18	18
RAND-36: Energy/fatigue	Pearson Correlation	**.780****	**.668****	**-.880****	**-.756****	**-.867****
	Sig. (2-tailed)	.000	.003	.000	.000	.000
	N	17	17	17	17	17
RAND-36: Emotional well-being	Pearson Correlation	**.686****	.332	**-.874****	**-.705****	**-.846****
	Sig. (2-tailed)	.002	.194	.000	.002	.000
	N	17	17	17	17	17
RAND-36: Social functioning	Pearson Correlation	**.729****	.344	**-.763****	**-.795****	**-.846****

	Sig. (2-tailed)	.001	.177	.000	.000	.000
	N	17	17	17	17	17
RAND-36: Pain	Pearson Correlation	**.599***	**.578***	**-.537***	**-.705****	**-.651****
	Sig. (2-tailed)	.011	.015	.026	.002	.005
	N	17	17	17	17	17
RAND-36: General health	Pearson Correlation	**.883****	**.629****	**-.901****	**-.624****	**-.806****
	Sig. (2-tailed)	.000	.007	.000	.007	.000
	N	17	17	17	17	17

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed)

Inquiry 6. Explore relationships between adaptive function and IQ.

Correlations.

Pearson product-moment correlations were computed between the ASR subscales and measures of Intelligence (WASI-Verbal IQ, WASI-Performance IQ, and WASI-Full Scale IQ), independently. Positive correlations were found between the ASR: Mean Adaptive subscale and the WASI-Verbal IQ index. This indicated that increased endorsement of adaptive skills was associated with greater verbal abilities. In addition, negative correlations were demonstrated between the ASR: Internalizing, Externalizing, and Total problems subscales with all the measures of intelligence. These correlations indicated that decreased endorsement of symptoms was associated with greater cognitive function. The results are presented in Table 34.

Table 34. Correlation matrix between the ASR subscales and the WASI measures of Intelligence.

		ASR: Mean adaptive (> 35 is normal)	ASR: Personal Strengths (> 35 is normal)	ASR: Internalizing Symptoms (<60 is normal)	ASR: Externalizing (<60 is normal)	ASR: Total Problems (< 60 is normal)
WASI: Verbal IQ	Pearson Correlation	**.532***	.223	**-.800****	**-.705****	**-.837****
	Sig. (2-tailed)	.023	.375	.000	.001	.000
	N	18	18	18	18	18
WASI: Performance IQ	Pearson Correlation	.400	.117	**-.566***	**-.523***	**-.595****
	Sig. (2-tailed)	.100	.644	.014	.026	.009
	N	18	18	18	18	18
WASI: Full scale IQ	Pearson Correlation	.464	.149	**-.711****	**-.678****	**-.761****
	Sig. (2-tailed)	.052	.555	.001	.002	.000
	N	18	18	18	18	18

Note: * = $p \leq .05$ (2-tailed), ** = $p \leq .01$ (2-tailed)

Chapter 5: Discussion

Part A: Neuropsychological profile

In the present study we analyzed a sample of twenty emerging adults with low-grade glioma diagnosed in childhood. The sample was composed of twelve men and eight women, with a mean age at diagnosis of 10.8 years. At the time of testing, their mean education was 14.5 years. More than half the participants consumed medication at time of testing, were diagnosed with astrocytomas, had tumours located in the infratentorial region of the brain and resected by surgery, and experienced either seizures or hydrocephalus at the time of diagnoses. Each participant completed a battery of neuropsychology tests in order to determine if the sample population's long-term effects were homogeneous, and within the normal range compared to normative standards, or if group differences existed. In addition, the data were analyzed to explore differences in neuropsychological scores based on demographic and tumour related factors. The neurocognitive domains tested included: Intelligence, Memory, Visual Spatial skills, Motor skills, Attention, Executive skills, and Processing Speed.

Our findings revealed a considerable degree of variation in the sample, ranging from good ability to relative deficits in function. Based on the performance of cognitive tests, the sample was divided into three subgroups, showing relatively mild, moderate, and severe levels of dysfunction. Group division was established by the number of measures below the average range, for example those with mild dysfunction had four or less scores below 1 standard deviation, those in the moderate group had five to ten scores below 1 standard deviation, and those in the severe group had 10 or more scores below 1 standard deviation (Ek, et al.,2005) .

Overall, participants in the subgroup with severe dysfunction showed widespread deficits in most cognitive domains compared to those in the mild subgroup. Differences between subgroups were found on measures of Intelligence, Memory, Processing Speed, and Executive functioning, with the severe subgroup performing worse than either moderate or mild subgroups. We also found differences on neurocognitive measures for each of the following variables : education, age at diagnosis, medication consumption, time elapsed between diagnosis and testing, and tumour pathology. Below, I will consider the implications of the findings for each of the inquiry questions outlined in the results section, and discuss each of the findings with respect to the existing neuropsychological literature.

Inquiry 1. Explore if differences exist in the sample population's neuropsychological scores.

Research investigating the heterogeneous nature of cognitive functioning in the glioma population has found significant differences between high- and low-grade gliomas (Chalil & Ramaswamy, 2016), with few studies investigating low-grade gliomas alone. The differences between groups have been explained by diffuse insults to the brain due to the metastatic quality of the high grade gliomas compared to localized tumour growth in the low-grade populations (Ater et al., 1996).

Our study evaluated low-grade gliomas in isolation from high-grade gliomas and determined that the sample population's neuropsychological scores were heterogeneous, in that we found three subgroups based on neurocognitive scores. Similarly, Ek and colleagues (2005, 2010) analysed adults with low-grade gliomas diagnosed across the lifespan and also found three subgroups with

varying levels of cognitive disability termed severe, mild, and minimal selective dysfunction. The researchers divided the group based on performance below normal limits (i.e., below 1 standard deviation) across eleven neurocognitive scores and based on dysfunction in processing speed (measured by Symbol Digit Modality: SDMT Oral and Written measures). The group with severe dysfunction had scores below normal limits for both SDMT trials and across measures of verbal memory, executive functioning, spatial reasoning, and intelligence, the second milder group had dysfunction in SDMT or in more than half of the variables, and the third group had normal performance in SDMT-Oral and in more than half of the other variables. Our study adopted the same subgroup terms as those of Ek and colleagues: however, our analyses demonstrated differences in the percentage of measures below the average range in each subgroup, whereby our subgroups demonstrated less dysfunction across thirty three measures of neurocognitive function as compared to those in Ek and colleagues. Nonetheless, outcomes on select cognitive measures from our study were consistent with those of Ek et al., with the majority of the subgroup in the severe dysfunction group scoring below normal limits in both SDMT trials, while the minimal selective group displayed no difficulties in processing speed. In addition, similarities were found on tasks of Memory using the Rey Auditory Verbal Learning test (RAVLT) in the severe dysfunction subgroup, whereby we demonstrated consistent dysfunction in verbal learning, recall, and visual recognition. Although many similarities were found between our study and Ek et al. regarding the heterogeneity in neuropsychology scores, the most prominent difference was in the percentage of neurocognitive scores below normal limits. Ek and colleagues may have found more deficits in the group with severe disturbance due to their inclusion criteria and sampling data; age of diagnosis spanned childhood to adulthood (9-

57 years old), included variability in education levels, and had a greater number of unemployed patients.

The heterogeneous nature of the current sample refutes presumed notions that patients with low-grade gliomas have uniform long-term neurocognitive outcomes when compared to norm referenced groups. Such assumptions have been bolstered in part because of high survival rates of pediatric low-grade gliomas, whereby patients whose tumours are completely resected have a survival rate of 90% or greater, 10 years from diagnosis (Sievert & Fisher, 2009). In addition, homogeneity has often been assumed because of favorable neurobehavioural outcomes, such as normative cognitive and adaptive functioning, although research over the last decade has demonstrated diverging results (Ris & Beebe, 2008). We established inter-individual differences when the group was sub-divided by their performance relative to normative standards, suggesting variable long-term neurocognitive sequelae. A discussion of which outcome variables showed this heterogeneity is included in the consideration of Inquiry 2.

Inquiry 2. Explore the inter-group variation on all neurocognitive measures.

Following the group division established from Inquiry 1, we compared each group by neurocognitive measure. Results revealed no group differences on measures of attention, motor, and visual-spatial skills. In contrast, the severe subgroup performed lower than the other two subgroups on measures of intelligence (VIQ, PIQ and FSIQ), memory (visual and verbal recall), processing speed (written and oral mental speed), and executive function (mental flexibility). The results are somewhat consistent with a study conducted by Miotto and colleagues (2011). Much like other studies investigating cognitive deficits in brain tumour populations, they

investigated both high- and low-grade glioma patients. Their low-grade sample demonstrated specific deficits on verbal and visual memory recall, mental flexibility and processing speed, and no impairments in visual spatial and intellectual abilities. Miotto et al. evaluated patients prior to surgical removal of the tumour, which could suggest that patients who are candidates for surgery may have greater pre-surgical neurocognitive effects. To note, group differences were found on intelligence measures in our study and not in Miotto et al.'s study, possibly due to the method of group division rather than true intellectual deficits. In fact, the majority of our sample population performed within normal limits on all three measures of intelligence, yet the severe subgroup demonstrated significant differences from the moderate and mild subgroups. Overall, the severe subsubgroup may represent a distinct sample in the low-grade glioma population whose demographic and tumour related factors may impact their long-term neurocognitive effects (this will be discussed in the General Discussion). Recent advances in neurobiology and histopathology over the last decade have discovered biological markers of gene mutations and aberrations that can lead to activation of further gliomagenesis (Tatevossian et. al, 2010) and are present in a subset of patients with pediatric low-grade gliomas. These biological markers may have been present in the severe subgroup in our study, but this information was not available in medical records during the period of data collection.

Inquiry 3. Explore differences in neuropsychological scores based on demographic variables.

Differences were found in neuropsychological scores based on specific demographic factors including education, age at diagnosis, medication consumption, and time elapsed between testing and diagnosis. No differences in neurocognitive functioning were found when sex was analyzed.

Sex differences in neurocognitive function are generally not found in the general population, although some studies document sex differences in brain organization resulting in superior performance for women when cerebral lesions are on the left, and in men when cerebral lesions are on the right (Yeo, 1983). In addition, children treated for brain tumours have shown a combination of demographic risk factors that contribute to declines in IQ following treatment including sex (women), younger age at diagnosis, and longer time since treatment. Our study may not have revealed sex differences in neurocognitive scores due to the small sample size resulting in the lack of specificity of associated risk factors.

Not surprisingly, participants with post-high school education performed superior to those with less education on all three measures of intelligence (VIQ, PIQ and FSIQ). This finding is consistent with the general literature on intelligence and is not specific to the low-grade glioma population (Matarazzo & Herman, 1984). The pursuit of higher level education in the face of a brain insult during childhood is striking in this sample. This suggests that the majority of the sample was capable of pursuing their educational goals. A qualitative look at the subgroups in the present study revealed that the majority of participants in the severe subgroup had a high school education or less. The question then becomes whether the differential results on neuropsychological testing for this subgroup are related to education above and beyond the effects of the glioma.

Another notable finding was that participants diagnosed at an older age (>10 years old) performed superior to those younger at diagnosis on measures of oral processing speed (SDMT-oral), motor skills (Purdue Peg board non dominant hand), and executive function (DKEFS

TMT- number sequencing). Younger age at diagnosis has been associated with impaired cognition on some variables including IQ, attention, and memory in brain tumour patients (Mulhern, et al., 2004; Pignatti et al., 2002). Taken together, these findings may support the notion that previously learned skills are retained prior to a brain insult (Palmer et al., 2001), such that brain injuries at a younger age carry a greater burden as fewer skills are developed and mastered by that point. As such, younger patients have fewer skills to rely on during recovery and development. In addition, larger tumours in younger patients have been found to more readily cause local mass effect with disruption of subcortical and cortical structures (Kaye, DeCarli, Luxenberg, & Rapoport, 1992) compared to older patients, which may also contribute to lower cognitive function.

Similarly, we found that participants' performance was superior in executive function (WCST) when fewer years had elapsed between testing and diagnosis. This result is somewhat confounded by age, such that those with shorter duration between diagnosis and testing were also older in age at diagnosis. Nonetheless, this finding is worth investigating to determine whether long-term residual effects exist following a low-grade glioma.

Finally, medication consumption at the time of testing revealed significant differences across Intelligence, Memory, Motor skills, and Executive function. Overall, those on no medications performed better than those who were taking one or more medications. Treatments ranged from pain medications (such as tegretol and nurofen), mood stabilizers (for example abilify), endocrine management (for example thyroxine) to anti-epileptic drugs (such as lamictal). It seems that the additional burden to manage medical complications, such as pain reduction or

mood stabilization, may impact the sample's ability to meet normative standards on neuropsychological testing. Klein and colleagues (2003) determined that the use of anti-epileptic drugs (AEDs) in patients with low-grade gliomas was associated with significant reductions in information processing speed, psychomotor function, and executive function, but not in attention or memory. Furthermore, they reported that neuropsychological difficulties are aggravated by the severity of epilepsy and by the intensity of the treatment. Our analysis showed that medication consumption, irrespective of the type, was associated with lower performance, but further information about the levels of pain or symptom intensity would be important to know to make any definitive conclusions about the effects of medications on cognition in the population of those with gliomas.

Inquiry 4. Explore differences in neuropsychological scores based on tumour related factors.

Minimal differences were found in neuropsychological scores based on tumour related factors. We analyzed potential differences in tumour pathology, tumour location, treatment type, and symptoms at time of diagnosis. Participants with astrocytomas performed superior compared to those with other types of gliomas on measures of Executive Function (DKEFS verbal fluency and DKEFS TMT motor speed). This finding is in line with previous literature demonstrating favorable long-term outcomes for patients diagnosed with pilocyctic astrocytomas, whereas other gliomas have higher rates of diffusion and possible genetic aberrations leading to a potential deterioration of functioning (Camelo-Piragua & Kesari, 2016). It is worth nothing that our finding may be an artifact of sampling, since the two groups were quite unequal in size (astrocytoma $n = 17$, other gliomas $n = 3$).

It is well documented that children with low-grade gliomas have a high rate of long-term survival and do not often require the intensity of neurotoxic treatments used with higher risk pediatric tumours, including their high-grade glioma counterparts (Ris & Beebe, 2008). The predominant type of treatment to resolve low-grade gliomas includes surgical removal as the first step in management followed by adjuvant chemo- or radiation therapy (Schiff, 2015). Our findings did not demonstrate any differences between groups with surgery alone (n = 17) and those with adjuvant therapy (n = 3) on measures of neurocognitive function. This is in contrast with research that has indicated superior neurocognitive performance for patients who undergo surgery alone compared to those with adjuvant treatments (Surma-aho et al, 2001; Taphoorn et al, 1994). Yet, there is some evidence suggesting that neurocognitive deficits exist prior to surgery or toxic treatments as a consequence of the glioma itself (Cortes et al., 2011; Ek et al., 2010). For example, Cortes and colleagues (2011) investigated neurocognitive functioning in patients with low-grade gliomas who were undergoing surgical resection. They found that over 50% of the sample presented scores below the 40th percentile in attention, language, visuo-constructive skills, visual organization, language and executive functions. This may suggest that our results were non-significant between treatment groups since their functioning may pre-date their treatment protocols. In comparison, other studies investigating the effects of radiotherapy in patients with low-grade gliomas have demonstrated that the tumour itself had the most deleterious effect on cognitive function and that radiotherapy resulted in additional long-term cognitive disability when high fraction doses were used (> 2 Gy) at six year follow up (Klein et al., 2002; Soffietti et al., 2010). A follow-up longitudinal study (range of 6-28 years from initial diagnosis) revealed that close to 50% of the patients who received radiotherapy (regardless of fraction dose) had more deficits in attentional functioning at the second follow-up (Douw et al.,

2009). In addition, they found deterioration in executive functioning, information processing and attentional functioning between the first and second assessments for patients who had radiotherapy. This suggests that long-term survivors may develop progressive cognitive disabilities and are at risk of late toxicity of treatment which can impair cognitive functioning (Taphoorn & Neil, 2008; Moretti et al., 2001). It is unknown if our sample would have presented with changes in neurocognitive scores at a second-follow up session. In addition, the discrepancy between the sizes of the subsamples suggest caution in the interpretation of our findings.

Our study revealed no differences in neurocognitive outcomes based on tumour location when analyzed based on divisions above and below the tentorium (sheet of dura matter separating the cerebrum from the cerebellum). This is in contrast to many studies that have revealed differences in tumour pathology and location, whereby some lesions lead to specific treatment regimens which predict more favorable neurocognitive sequelae. For example, cerebellar and supratentorial astrocytomas are typically completely resected demonstrating few changes in cognitive functioning. In contrast, most optic pathway/hypothalamic, deep midline, and brain stem gliomas have minimal potential for resection (Sievert & Fisher, 2009) and require combination chemotherapy and radiotherapy to improve survival rates, at the risk of neurocognitive, endocrine, and other possible long-term toxicities, as reported above. Our sample did not have any participants with the latter set of gliomas and therefore we can speculate that although anatomical differences were present (infratentorial n =11, supratentorial n = 9), no neurocognitive differences based on location were found since the tumour pathology was similar. Furthermore, studies have documented both specific cortical locations and network-based connections (linking distant cortical regions together) responsible for domains of cognition

(Bartolomeo, 2011). Our sample size was unable to support such analyses, yet it is important to consider findings from the literature. Research suggests patients with lesions in the frontal lobes experience heightened cognitive impairment (Ek & Almkvist, 2010), whereas those with cerebellar lesions demonstrated lateralized cognitive deficits (Scott et al., 2001). Scott and colleagues (2001) researched pediatric tumours (not specific to low-grade gliomas) and found that damage in the right cerebellar structures was associated with verbal and literacy skill difficulties, whereas damage to the left cerebellar structures was associated with delayed or impaired non-verbal and spatial skills. These results support the notion that the learning and development trajectory can be offset as a result of a brain lesion.

Finally, our study did not demonstrate neurocognitive differences between patients with the presence or absence of either hydrocephalus or seizures at the time of diagnoses. Seizures are a frequent comorbidity in pediatric brain tumour survivors and were present in more than 50% of our sample. Seizures are often a result of tumour pathology, cortical location, and subtotal resection (Ullrich et al., 2015). Studies investigating rapidly growing tumours such as those with high-grade gliomas have also revealed that cognitive deficits are more pronounced and widespread (Taphoorn & Niel, 2008) and can lead to hemiparesis or increased intracranial pressure (Ashby & Shapiro, 2004; Rees, 2002). We can speculate that our sample did not demonstrate differences in neurocognitive functioning because the seizures were well-managed by medication following treatment.

The neuropsychological profile revealed in our sample suggests heterogeneity in skills amongst the low-grade glioma population, whereby intelligence, memory, processing speed and executive

function are most impaired in the severe subgroup. Furthermore, participants' performance was reduced with lower education levels, medication consumption, and younger age at diagnosis. The following chapter will shift the focus from objective measures of abilities to subjective perceptions of cognitive challenges and health related quality of life.

Part B: Perceived Health and Cognitive Quality of Life

The focus of the second set of inquires was the sample's perceived health and quality of life. Each participant completed two questionnaires, the RAND-36 and the FACT-Cog, in order to determine whether there were domains of strengths and weaknesses, group differences, whether and associations between health and cognitive quality of life, and associations between objective measures of cognitive function and participants' subjective experience. In addition, the data were analyzed to explore differences in measures of quality of life based on demographic and tumour related factors. The health related domains explored with the RAND-36 included: Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems, Energy/fatigue, Emotional well-being, Social functioning, Pain, and General health. The cognitive domains investigated with the FACT-Cog included: Perceived cognitive impairment, Comments from others, Perceived cognitive abilities, and Impact on quality of life.

Our findings revealed that the sample perceived their physical and general health favourably, and they showed positive perceptions of the impact of their cognitive functioning on quality of life. Differences were found between the sample's perception of their physical health and social functioning, whereby social functioning appeared to be an area of relative weakness or concern. Inter-group variation, based on the cognitive subgroups established in Chapter 1 (Mild, Moderate, and Severe dysfunction), was found such that the Severe subgroup rated their physical

functioning, social functioning, and emotional well-being as more affected than the Moderate and Mild subgroups. In addition, the Severe subgroup endorsed more reports of "(negative cognitive) Comments from others" than the Mild subgroup. Analyses of the demographic and tumour related factors on perceived quality of life showed effects of sex, education, and medication consumption. Positive associations were revealed between perceived health and cognitive quality of life. In addition, the sample demonstrated that their subjective abilities were in line with their objective performance on measures of cognitive function.

Inquiry 1. Identify domains of strengths and weaknesses in the sample population's perceived health and cognitive quality of life.

Our findings identified areas of strength and challenges based on the questionnaires completed. A third or greater of the sample reported few challenges with Physical functioning, Role limitations due to physical health, Energy/Fatigue, Pain, and General health. Interestingly, General health was also an area of concern for our population whereby a third of the sample reported scores below the normal range (< 1 standard deviation). In addition, forty percent of the sample reported no identifiable challenges with cognitive functioning. The sample perceived their physical functioning and their lack of role limitations due to physical health as superior to their social functioning. Social functioning has been explored in the brain tumour literature as ability secondary to emotional perception in interpersonal relationships and social cognition. Researchers have theorized that patients with gliomas may preserve or maintain their social and professional relationships due to compensatory mechanisms of multi-sensory emotional integration abilities (Boullay et al., 2014). Our findings of reduced perceived social functioning might suggest that although the sample could maintain a level of social integration, they

perceived this area as a challenge. Unlike our study, Taphoorn and colleagues (1994) demonstrated that long-term survivors of low-grade gliomas suffered more frequently from fatigue and depressed moods than controls. It is well documented that high-grade glioma populations report concerns of uncertainty regarding prognosis (terminal malignancy) and quality of life, dependence on carers due to cognitive deficits, increase in neurological deficits, and the inability to resume daily activities (Halkett, et al., 2010; Dogel et al., 2004). Unlike high-grade glioma populations, our low-grade sample reported favorable perceived quality of life, possibly due to limited threats of mortality compared to a high-grade diagnosis. In addition, most studies that combine both groups (malignant and benign tumours) demonstrate worse quality of life in dimensions of physical, functional, family, social, and overall perception of well-being (Cortes & Crespo, 2015; Munoz et al., 2008). Similarly, we found reduced social functioning and endorsements of challenges in general health in a proportion of the sample. In comparison, our study demonstrated superior perceived physical functioning and general health. The differences found between studies emphasize the need for independent research for the low- and high-grade glioma populations.

Inquiry 2. Explore the inter-group variation in the quality of life questionnaires.

Following the group division established from Chapter 1; Inquiry 1, we compared each group on the quality of life subscale. Results revealed group differences on measures of Physical functioning, Social functioning, and marginally on Emotional well-being, and (cognitive) Comments from others, whereby the Severe subgroup rated their functioning lower than the other two subgroups. Our findings are consistent with research conducted by Ediebah and colleagues (2016), who explored the impact of patient-proxy agreement on documented

neurocognitive deficits on the Rand-36 and EORTC QLQ-BN20 in patients with low-grade gliomas. They discovered that the subgroup deemed to have cognitive impairments reported poorer physical functioning than did their proxies, whereas no differences emerged between patient and proxy reports in the cognitive intact group. This may suggest that our Severe subgroup's response style is impacted by their cognitive challenges. This has also been shown with high-grade glioma patients in that the concentration required to evaluate each statement on a questionnaire and then make a decision sometimes proves too demanding on the patient (Lyons, 1996). Alternatively it could be that the Severe subgroup's perceptions represent their true beliefs of reduced quality of life.

Inquiry 3. Explore differences in perceived quality of life scores based on demographic variables.

Differences were found in perceived quality of life measures based on specific demographic factors including sex, education, and medication consumption. No differences in measures were found when age at diagnosis, and time elapsed between testing and diagnoses were analyzed. Women reported more challenges on emotional well-being than men. Previous studies have not found an effect of sex on self-reports making, the present findings unusual and in need of replication before strong conclusions can be made. Secondly, participants with post-high school education rated their functioning more favourably than those with less education on 11 out of the 12 subscales across health and cognitive quality of life. Lower education has been found to be an indicator associated with multiple domains of distress, poor quality of life and high unmet needs in the high-grade glioma population (Halkett, et al., 2015). Lastly, the group with an absence of medication consumption reported greater functioning in the following subscales: Physical

functioning, Energy/Fatigue, Emotional well-being, Social functioning, General health, and the (cognitive) Impact on quality of life. The effect of medication consumption was surprising given the range of medications consumed by our sample. We suspect that chronic medication use, regardless of the type or dose, impacts participant's perception of their abilities and quality of life.

Inquiry 4. Explore differences in perceived quality of life scores based on tumour related factors.

No differences were found in perceived quality of life measures based on tumour related factors. We analyzed potential differences in tumour pathology, tumour location, treatment type, and symptoms at time of diagnosis, and found no effects of any of these variables on reported quality of life. Previous studies have found reduced reported quality of life for glioma patients with uncontrolled intractable epilepsy (Vercueil, 2011; Maurice & Mason, 2014; Klein, et al., 2003), greater tumour size, and tumours in the right side or anterior region (Salo et al, 2002). Differences in findings between the literature and our study might be a result of the mixed malignancy samples, i.e., malignant and benign tumours, with those with malignant tumours lending more weight to the outcomes of prior studies. Interestingly, some researchers have ruled out radiotherapy as adversely impacting quality of life in long-term survivors of low-grade gliomas (Taphoorn et al., 1994; Petz et al., 2001).

Inquiry 5. Explore relationships between perceived cognitive and health related quality of life scores.

Correlations between perceived health (RAND-36) and cognitive related quality of life (FACT-Cog) revealed positive associations between most of the subscales, excluding measures of Pain, and Role limitations due to physical health. More specifically, significant associations with most of the RAND-36 were found with the Perceived cognitive impairments, Perceived cognitive abilities, and Impact on quality of life on the FACT-cog. The Comments from others subscale on the FACT-cog was positively associated with the Physical functioning, Emotional functioning, and Social functioning subscales on the RAND-36. Our findings suggest that superior cognitive perceptions are associated with greater perceived health-related quality of life. No literature exists on the relationship between cognitive and health-related quality of life. We speculate that a meaningful bi-directional relationship exists between health and cognitive perceptions whereby one perception impacts the other. For example, greater perceptions of one's cognitive abilities may result in greater community involvement, the pursuit of education or employment, and enjoyment in relationships – all aspects endorsed in greater perceptions of quality of life.

Inquiry 6. Explore relationships between perceived quality of life scores and IQ.

Correlations between the perceived health quality of life scores and measures of cognitive function demonstrated significant positive associations between both verbal and performance IQ with the following subscales of the RAND-36: Physical functioning, Social functioning, Emotional functioning, and General Health. Verbal IQ was additionally positively correlated with Energy/fatigue whereas the association with Performance IQ approached significance. The results indicated that an increase in objective verbal and performance abilities is associated with superior perceived physical, social, and emotional functioning.

Results from the correlations between the perceived cognitive quality of life scores and measures of IQ demonstrated significant positive associations between both verbal and performance IQ with the following subscales from the FACT-Cog: Perceived cognitive impairment, Comments from others, and Impact on quality of life. Similar to the findings above, Verbal IQ was additionally positively correlated with Perceived cognitive abilities whereas the association with Performance IQ approached significance. These results indicate that an increase in objective verbal and performance abilities are associated with superior perceived cognitive abilities, fewer perceived impairments, and a favorable cognitive impact on their overall perceived quality of life.

Similar to Inquiry 5, there is a paucity of research on associations between objective and subjective cognitive abilities in the glioma literature. In addition, there appears to be an absence of research on the associations between objective abilities and perceived quality of life. In contrast, there is evidence for decreased cognitive status and quality of life in the low-grade glioma population (Reijneveld et al., 2001), although it is unknown if previous studies found correlations between the two measures. One study evaluating objective and subjective measures of cognitive function in breast cancer patients, using the FACT-Cog, determined that measures of objective and subjective cognitive function both declined over the course of chemotherapy but there was no significant relationship between these variables (O'Farrell, Smith, & Collins, 2016). In comparison, Von and colleagues (2010) found the Perceived cognitive impairment and Perceived cognitive abilities subscales were correlated with selective cognitive measures in a sample of breast cancer survivors. Similarly, the FACT-Cog was administered in parallel with a neuropsychological assessment with patients following hematopoetic stem cell transplantation.

Findings in this patient sample revealed no significant correlation between the FACT-Cog scores, with the exception of one subscale, Comments from others, with cognitive performance (Jacobs et al., 2007). In contrast, we found all the subscales of the FACT-Cog except Comments from others to be correlated with objective measures of cognitive function, similar to findings from a broad range of cancer patients following chemotherapy treatment (Lange et al., 2016). It is not surprising that differences exist between the populations outlined above and our sample, but it highlights the need for more research into this area with the glioma population, in particular exploring sensitivity of the measures between populations. Furthermore, a number of studies have indicated the necessity of evaluating subjective experiences of quality of life in addition to neuropsychological evaluation in order to addresses specific concerns from patients (Moritz-Gasser & Duffau, 2010), yet to date limited data exist.

Part C: Measures of Adaptive Functioning

The third area explored in the study involved measuring the sample's adaptive functioning. Each participant completed the Adult-Self Report (ASR), in order to determine whether there were domains of strengths and weaknesses, if group differences existed, whether health and cognitive quality of life were associated, and if objective measures of cognitive function relate to participant's adaptive abilities. In addition, the data were analyzed to explore differences in measures of adaptive function on demographic and tumour related factors. The adaptive measures explored on the ASR included: Mean adaptive abilities, Personal strengths, Internalizing symptoms, Externalizing symptoms, and Total problems. Our findings revealed that the majority of the sample reported normal adaptive functioning. No strengths or weaknesses were found between the subscales, although the sample was divided on participants' report of

internalizing symptoms. Inter-group variation, based on the cognitive subgroups established in Chapter 1 (Mild, Moderate, and Severe) was found such that the Severe subgroup reported more difficulties in externalizing symptoms and overall symptoms (aggregate of externalizing and internalizing symptoms) than the Selective subgroup. Upon analysis of the demographic and tumour related factors on adaptive function, we found differences in adaptive functioning according to sex, education, and medication consumption. Significant associations were revealed between the adaptive measures and perceived health and cognitive quality of life. In addition, higher adaptive abilities were associated with greater cognitive function. The subsequent discussion follows the inquiry questions outlined in the Results section and will compare our findings with the literature.

Inquiry 1. Identify domains of strengths and weaknesses in the sample population's adaptive functioning.

Our findings revealed evidence for positive adaptive functioning in our sample. Greater than half of the sample rated items in the normal range (based on normed standard T-score cut offs) across the four areas of adaptive functioning: Mean adaptive, Personal strengths, Internalizing symptoms, and Externalizing symptoms. No differences were found between the four scales suggesting equivalent functioning across the domains, yet the Personal strengths scale was endorsed most favorably by the majority of the sample (83%). This scale reflected perceptions of responsibility, honesty, fairness and equitable treatment of others. In comparison, a proportion of the sample (45%) rated items in the borderline or clinical range on the Internalizing scale. The most frequent symptoms endorsed on the Internalizing scale were within the Anxious/Depressed subscale, with fewer in the Somatic complaints and Withdrawn subscales. Item analysis revealed

concerns related to lacking in self-confidence, having worries about their future and their presentation to the opposite sex, and experiencing feelings of fear of success, nervousness, sadness, self-consciousness, worthlessness and being lonely. The somatic complaints endorsed included feeling tired, experiencing sleeping disturbances, and aches and pains. Our findings of increased internalizing symptoms are in line with the literature demonstrating that the low-grade glioma population suffers more frequently from depressed mood when compared to the general population (Taphoorn et al., 1994; Petz, et al., 2001; Boele et al., 2014). In addition, with the greater endorsement of anxiety, it appears that the type of anxiety experienced between newly diagnosed low-grade gliomas (i.e., fear of morbidity from the intervention, Hayhurst, Mendelsohn, & Bernstein, 2011) and long-term survivors differs; yet it is unknown if anxiety evolves from one time period to the next.

Inquiry 2. Explore the inter-group variation across the adaptive measures.

Following the group division established from Chapter 1; Inquiry 1, we compared each group on the adaptive functioning subscales. Results revealed marginal subgroup differences on measures of Externalizing symptoms, and Total problems; whereby the Severe subgroup reported more challenges than the Mild dysfunction subgroup. The Total problems scale is an aggregate of the Externalizing and Internalizing scales, and therefore reflects that the sample endorsed difficulties in both domains. Item analyses within the Externalizing scale demonstrated a frequent endorsement of statements within the Aggressive subscale and fewer in the Rule-breaking and Intrusive subscales. Common items endorsed included themes of quick mood changes, stubborn personality, easily upset, argumentative, socializing with bad friends, lacking responsibility, acting on impulse, showing off, and being loud. This suggests that it is worthwhile to further

investigate differences between cognitive functioning subgroups to determine not only the presence of internalizing symptoms, but also externalizing symptoms. Furthermore, findings from both tumour populations (Ris & Beebe, 2008) and non-clinical populations have shown comorbidity between internalizing and externalizing symptoms and low cognitive functioning (Dietz et al.,1997; Goodman, 1995).

Inquiry 3. Explore differences in psychological adaptive functioning measures based on demographic variables.

Differences were found within the same demographic factors for adaptive measures as were demonstrated with perceived quality of life measures in Chapter 2; these included sex, education, and medication consumption. No differences in measures were found when age at diagnosis and time elapsed between testing and diagnoses were analyzed. In comparison, shorter elapsed time has been found to be related to greater depressed moods in the low-grade glioma adult population (Mainio et al., 2006). Results from our analyses revealed that women reported more challenges in internalizing symptoms and total problems than men. Secondly, the subgroup with less education (High school diploma or less) reported more difficulties in internalizing and externalizing symptoms. In addition, their mean T-scores were within the clinically borderline range across all domains. It is possible that this finding is confounded by other factors including lower cognitive level and health. Lastly, the subgroup consuming medications at the time of testing reported greater challenges across all domains except externalizing symptoms. Furthermore, their mean T-scores in the Internalizing and Total symptoms scales were also within the clinically borderline range. This suggests that medication consumption, regardless of the class of drug (mood stabilizer, anticonvulsant, pain and allergy medications), may create

more vulnerability to internalizing behaviours. Furthermore, there was no reason to suspect that this sample was self-medicating.

Inquiry 4. Explore differences in psychological adaptive functioning domains based on tumour related factors.

No differences were found in psychologically adaptive function measures based on tumour related factors. We analyzed potential differences in tumour pathology, tumour location, treatment type, and symptoms at time of diagnoses. Laterality has been shown to affect anxiety symptoms whereby primary tumours in the right hemisphere have been associated with increased anxiety prior to surgery than left hemisphere tumours. In addition, only right hemisphere tumours were associated with a decline of anxiety levels following tumour removal to that of the general population (Mainio et al., 2003). In contrast, our long-term survivor sample did not show any evidence of tumour related factors for internalizing symptoms. It is possible that no effects were noted due to the small sample size and the distribution of tumour factors in our sample. For example, tumour pathology was grouped as astrocytoma (n = 17) and "other gliomas" (n = 3) which included ependymomas, oligodendrogliomas, and gangliogliomas. This distribution can prove challenging to uncover differences between tumour pathology because of sample size and subgroup inclusion.

Inquiry 5. Explore relationships between adaptive functioning and perceived health and cognitive related quality of life scores.

Significant correlations between the adaptive domains on the ASR and the two perceived quality of life measures (FACT-Cog and RAND-36) were found. To begin, the ASR- Personal strengths

subscale was not correlated with any of the FACT-Cog subscales. We can speculate that individuals rated their perception about their rights and values favourably regardless of their perceived cognitive function. Secondly, the ASR- Mean adaptive score was positively associated with the FACT-Cog- Perceived cognitive abilities and Impact on quality of life. The Mean adaptive scale reflects individuals' reflection on how they function with their friends, spouse/partner, family, job, and education. It is thus reasonable to interpret the positive association as demonstrating that greater functioning in multiple social and domestic areas is related to greater perceived cognitive abilities. In contrast, findings from Khelifa-Gallois and colleagues (2015), exploring functional outcomes in adolescents and adults treated for a low-grade cerebellar astrocytoma in childhood, found close-to-normal academic achievement and normal autonomy, despite a high rate of reported cognitive difficulties. Differences in findings of perceived cognitive function relate predominately to the measurements used, such that they tap into different aspects of adaptive abilities. Furthermore, both Internalizing and Externalizing subscales on the ASR were inversely correlated with the following subscales on the FACT-Cog: Perceived cognitive impairment, Perceived cognitive abilities, and Impact on quality of life. This indicates that reports of fewer internalizing and externalizing symptoms are associated with superior perception of cognitive functioning. Our findings were in line with previous literature documenting significant associations between the FACT-Cog subscales with anxiety and depression (Lange et al., 2016) in a diverse cancer survivor population. In addition a decline in perceived cognitive function has been shown to be associated with greater anxiety, fatigue, and depressive symptoms in samples of breast-cancer survivors (O'Farrell, Smith, & Collins, 2016; Von Ah & Tallman, 2015).

The ASR was subsequently correlated with measures from the RAND-36 revealing significant associations. The ASR- Mean adaptive subscale was positively correlated with all eight measures of perceived health related quality of life. This again demonstrated that greater functioning in multiple social and domestic domains were associated with a greater perception of quality of life. Similarly, the ASR-Internalizing and Externalizing symptoms scales were inversely correlated with all eight measures of perceived health related quality of life. This indicated that reports of less internalizing and externalizing symptoms were associated with greater perceptions of quality of life. This association has been documented across the literature with both the low-grade glioma and survivors of tumours of the central nervous system. Most studies report a decrease in quality of life associated with low mood and the presence of clinical manifestations of depression (Cortes & Crespo, 2015; Warren, 2015; Taphoorn et al., 1994; Noll et al., 2015). In addition, some studies demonstrate that the low-grade glioma population suffers more frequently from depressed moods (Taphoorn et al., 1994; Petz, et al., 2001). Evidence of externalizing symptoms and other internalizing symptoms beyond depression, anxiety, and fatigue has not been shown in the literature. Finally, the ASR- Personal strengths subscale was positively correlated with the following RAND-36 subscales: Role limitations on physical health, Energy/fatigue, Pain, and General Health. This demonstrated that greater reports of positive self-attributes were associated with fewer limitations on physical health, energy and fatigue, pain, and general health. This finding is not surprising in that those who have positive attitudes tend to report greater physical well-being. Evidence of this relationship has been found in siblings of those with chronic health conditions whereby they had lower self-attributes and greater challenges in quality of life than controls (Vermaes et al., 2012).

Inquiry 6. Explore relationships between adaptive function and IQ.

Correlations between the adaptive domains and measures of cognitive function demonstrated significant positive associations between Verbal IQ and the Mean adaptive subscale, indicating that an increase in verbal abilities is associated with greater endorsement of functioning across social and domestic domains. In addition, both verbal and performance IQ were inversely associated with internalizing and externalizing symptom scales. This indicated that greater cognitive function was associated with fewer endorsements of internalizing and externalizing symptoms. This result is consistent with the body of knowledge suggesting that IQ is a protective factor against psychopathology. For example, a systematic review undertaken by Francis and colleagues (2016) demonstrated that gifted children exhibit superior socio-emotional adjustment and fewer behavioural difficulties than their typically developing peers.

Summary of Key Conclusions across the Three Inquiries

This study has provided information of clinical significance, particularly for the lower cognitive functioning subgroup of survivors of low-grade glioma. While the majority of the participants in our study fell within the average range for most cognitive tasks, there was variability on test scores that was used to identify three subgroups. The subgroups demonstrated differences in perceived quality of life and adaptive function. As a whole, the lower cognitive functioning subgroup (i.e., "Severe" subgroup) experienced challenges on tasks of memory, processing speed, and executive functioning, in line with findings from Ek and colleagues (2005). In addition, the lower cognitive functioning subgroup reported greater challenges in perceived physical health, physical, social, and emotional well-being, and internalizing and externalizing symptoms. Returning to Dennis's model of the relationship between medical disorder and

outcome, we can postulate that the variability in cognitive phenotype demonstrated between the groups could be attributed to differences in biological risk, whereby the "Severe" group could be categorized as "High biological risk" thus crossing the threshold of impairment into the subclinical range on high challenge tasks. In comparison, the "Mild" and "Moderate" subgroups demonstrated selective impairments suggesting that they were buffered from risk and categorized as "Low biological risk". Individuals in the latter subgroups appeared protected from clinical impairment on most high challenge tasks. Core deficits were not revealed in our sample of glioma patients as performance on neurocognitive, perceived quality of life, and adaptive behaviour measures varied across various levels of disorder severity and mental ability.

Dennis's model further suggests that the child's development, time since onset, and reserve available in the child, family, school, and community can contribute and moderate the risk outcome based on the strength of the valence of each factor, whereby negative factors (such as developmental delays, early age of onset, and less reserve) exacerbate risk and positive factors (such as average to above average premorbid IQ, later age of onset, and more reserve/support) protect from risk. Our findings generally support this model. Medication consumption, understood as a secondary effect of the brain tumour, was demonstrated to be linked with an increased biological risk on neurocognitive measures, perceived quality of life and adaptive functioning. This suggests that an ongoing health condition requiring treatment (e.g., seizures, pain, psychiatric, etc), captured by "medication consumption" may be driving these results. Effect of age and developmental level at disorder onset were demonstrated, whereby older age at onset was deemed a protective factor for neurocognitive functioning. Time since onset was demonstrated to relate to a single measure of executive functioning, whereby fewer years elapsed

between diagnosis and testing emerged as a protective factor. The final moderator, reserve in the child as documented by pre-insult status and social environment or opportunities, was demonstrated to buffer the impact of the disorder across neurocognitive, perceived quality of life, and adaptive functioning, namely sex and education level. Factors not studied in the current exploration, including family resources, such as socioeconomic status, family mental health, and psychosocial opportunities may have additionally exacerbated or buffered vulnerability to neurocognitive function, psychopathology, and perceived quality of life.

The moderators of risk were categorized as either demographic or tumour related factors and some revealed noteworthy results, albeit each factor was analysed independently from one another. As mentioned above, medication consumption (related to ongoing health conditions requiring treatment) was linked with greater biological risk in our sample whereby participants consuming medications had lower measures of IQ, visual memory, delayed verbal memory, executive functioning, and motor skills. In addition, they reported decreased perceptions of their health and cognitive quality of life and clinically borderline levels of internalizing symptoms. No neurocognitive differences were found by sex; however women perceived reduced effectiveness in their emotional well-being, and greater challenges with internalizing symptoms. Older age at diagnosis was related to superior performance in measures of processing speed, motor skills, and executive functioning, with no evidence of differences in adaptive and quality of life measures.

Academic achievement was determined to be a significant moderating factor, in line with Stern's cognitive reserve model (Stern, 2002) and Dennis's pediatric medical model (2000), whereby our study demonstrated that less education was related to lower levels of intelligence, decreased

perceptions of health and cognitive quality of life, and reports of clinically borderline levels of internalizing and externalizing symptoms. Objective measures of intelligence were positively associated with subjective perceptions of cognitive and health related quality of life and adaptive functioning.

Few differences were found between the tumour related factors on measures of neurocognitive functioning, perceived health and cognitive quality of life, and adaptive functioning. With greater sample sizes we would expect treatment related differences to emerge in emotional adjustment, social functioning, and intelligence as was documented by Ris and Beebe (2008) with adult survivors of pediatric low-grade gliomas.

Overall, the sample perceived their health and cognitive quality of life as satisfactory, although they reported the greatest differences between physical and social functioning, whereby social functioning was a relative weakness. We can speculate that social competence is considered a challenging skill for this group as it can be independently moderated by settings of development, time and reserve. As such, we may suggest that those with low biological risk are not effectively buffered from challenges in social functioning in comparison to effective buffering when faced with neurocognitive challenges. Similarly, the majority of participants endorsed adaptive function in the normative range with the exception of internalizing symptoms. Just less than half of the participants reported internalizing challenges in the borderline to clinical range endorsing symptoms of anxiety, depression, somatic complaints, and feelings of withdrawal.

Lastly, associations were found between the adaptive functioning subscales and measures of perceived health and cognitive quality of life. Greater challenges in externalizing and internalizing symptoms, also termed post-injury psychopathology, were associated with an increase in perceived cognitive impairments, perceived reduction in cognitive abilities, and difficulties across all domains measured of health related quality of life. This finding demonstrated the bi-directional nature of the interactions among resources documented in Dennis's risk-outcome framework, such that one confounds the other.

Limitations

It is unknown whether the results identified in this study were due to specific characteristics of the sample, the research methods utilized in the study, or whether the measures used were sensitive to detecting meaningful effects. The clinical sample size was small, although it yielded significant results across the cognitive, perceived quality of life, and adaptive domains. Small sample sizes are typical in clinical studies and come with known methodological disadvantages. In our sample we were limited to the data gathered such that the majority of the sample underwent surgery alone and had a diagnosis of pilocytic astrocytoma. We therefore had limited variability in treatment type and tumour pathology and thus the results were interpreted with caution. In addition, upon consultation with statisticians, we were advised that multiple regression analyses would yield inaccurate results. As such, we were unable to determine the variance explained by each demographic and tumour related predictor; instead, we analysed each factor independently, with the understanding that there would be shared unexplained variance.

The cognitive tests used, even when designed to test a specific cognitive domain, often require a number of skills. This makes it difficult to isolate one precise skill that may be impacted. For example, the executive functioning tasks often require memory, attention, visual and or verbal skills in order to achieve success. Similarly, the quality of life and adaptive measures require additional abilities beyond simply endorsing statements; which may include sustained attention, self-reflection, and decision making. These additional skills may have impacted our participants such that we had some incomplete questionnaires, resulting in absent data.

Lastly, the study was designed as a cross-sectional study investigating late effects, yet it required retrospective investigation of medical records in order to determine eligibility, and specific tumour related factors. As such we were limited by the information provided in the documents and thus were restricted in selecting our variables of interest. For example, we investigated differences between supra- and infra-tentorial tumour locations rather than by hemispheres, lobes, anterior or posterior position, and laterality.

Future Directions

Investigations of the long-term effects of neurocognitive and adaptive functioning in the low-grade glioma population have revealed differences compared to normative samples, yet this area of research is scarce in the literature. More data need to be collected and verified in larger cohorts of long term survivors of low-grade gliomas, such that demographic and tumour related factors can be analysed. Larger sample sizes would also increase diversity in treatment type, tumour pathology and histology, which were limitations we encountered in our sample. In addition, knowledge of neurocognitive and adaptive skills pre-insult, at the time of diagnosis,

and during the acute phase of recovery, in addition to the long-term effects, would bolster our understanding of how symptom presentation changes over the course of recovery and survivorship.

This study was cross-sectional, and as such provided a brief snapshot of the participant's functioning and perception at one particular point in time. Since there were no baseline measurements, it is unknown whether their current functioning represented a change in trajectory. Future research should gather longitudinal data to provide better estimates of the prevalence of long-term effects, and the extent to which these affect everyday functioning. It would be important to gain more information on the presence and evolution of these symptoms, in particular with patients presenting with lower cognitive functioning. In addition, follow-up clinical care for this diverse group of survivors is necessary to address potential long-term effects as they arise. Clinical care for the low-grade glioma population could resemble the neuropsychological care of patients with cancer related neurocognitive dysfunction , whereby they receive 1) a neuropsychological assessment, 2) monitoring of neuropsychological functioning, 3) treatment recommendations for cognitive, emotional, and behavioural impairments based on neuropsychological evaluation outcomes, 4) educational support to the patient and family, and 5) monitoring of the effectiveness of interventions to improve functioning.

Self-report measures were a valuable tool in accessing survivors' perceptions of their quality of life and adaptive functioning. An additional area of future study is the relationship between patient-proxy and self-reports. Patient-proxy reports would be an asset to complement self-

reports of cognitive function, quality of life, and adaptive function. Comparisons between the reports would add to our understanding of how patients and their support network perceive their abilities in order to provide accurate care to both patient and family.

Conclusion

Our study has provided further evaluation of the long-term effects in survivors of low-grade gliomas. Unlike other studies, our sample included a select subset of central nervous system tumour survivors in order to evaluate potential strengths and weaknesses and to assess demographic and tumour related factors pertinent to this group. Compared to other studies, we evaluated several domains of neurocognitive function, which revealed heterogeneity in the group and identified an important lower functioning subgroup relative to the other participants. Following Dennis's pediatric risk-outcome model, it is likely that the cognitive phenotype found in our sample of low-grade glioma participants is a result of not only the tumour itself, but an expression of biological risk moderated by the child's development, the time since onset of the tumour, and the reserve available within the child, family, school, and community.

The protective moderators of risk identified in our study included older age at diagnosis, absence of medication consumption (i.e., absence of an ongoing health condition requiring treatment), and high academic achievement. We were unable to thoroughly assess tumour related variables due to the small sample size, although we can speculate that high doses of radiation therapy and chronic symptoms such as a seizure disorder would be linked to lower neurocognitive function. In addition, compromised neurocognitive function for the majority of the sample was spared which may be explained by threshold theories of outcome whereby individuals can be buffered from impairment. In this case, the slow-growing nature of low-grade gliomas may have shielded

risk resulting in a greater buffer zone compared to other medical conditions, namely high-grade gliomas. Investigating changes in cerebral white matter volumes may help to explain this phenomenon in relation to our findings of neurocognitive diversity in the sample.

Furthermore, our use of subjective measures of cognitive function, adaptive function, and quality of life has highlighted the need for further research into survivors' experience. The self-report measurements used in the study revealed important clinical information which was a novel approach in the study of survivors of low-grade gliomas. We discovered that the sample endorsed difficulties in adjustment in both internalizing and some externalizing symptoms, and strengths in self-attributions, and perceived health and cognitive quality of life. It is hoped that the current study will enhance the understanding of the impact that pediatric low-grade gliomas have on emerging adulthood and result in added follow-up neuropsychological and neurobehavioural care.

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Appendix A. Table of sample size of each measure administered.

Measures	N
Neurocognitive Measures	
WASI: verbal IQ	20
WASI: performance IQ	20
WASI: full scale IQ	20
WAIS-3: digit span scaled score	20
WAIS-3: digit span	20
Rey-complex figure: immediate recall	20
Rey-complex figure: delayed recall	20
Rey-complex figure: recognition correct	20
RAVLT: trial 1 (immediate recall)	19
RAVLT: total recall	19
RAVLT: trial 8 (delayed recall)	19
RAVLT: recognition list A	19
RAVLT: recognition list B	19
SDMT: written	19
SDMT: oral	20
Purdue pegboard: preferred hand	18
Purdue pegboard: nonpreferred hand	18
Purdue pegboard: both hands	18
Purdue pegboard: assemblies	18
Judgement of line orientation	17
D-KEFS verbal fluency: FAS total	18
D-KEFS verbal fluency: category total	18
D-KEFS verbal fluency: switch accuracy	18
D-KEFS verbal fluency: switch total correct	18
D-KEFS trail making test: visual scanning	18
D-KEFS trail making test: number sequencing	18
D-KEFS trail making test: letter sequencing	16
D-KEFS trail making test: number-letter switch	16
D-KEFS trail making test: motor speed	17
WCST: total errors	20
WCST: perseverative responses	20
WCST: perseverative errors	20

WCST: nonperseverative errors	20
WCST: conceptual level responses	20
Perceived Quality of Life Measures	
RAND-36: physical functioning	18
RAND-36: role limitations due to physical health	18
RAND-36: role limitations due to emotional problems	18
RAND-36: energy/fatigue	17
RAND-36: emotional well-being	17
RAND-36: social functioning	17
RAND-36: pain	17
RAND-36: general health	17
FACT-cog: perceived cognitive impairment	17
FACT-cog: comments from others	17
FACT-cog: perceived cognitive abilities	17
FACT-cog: impact on quality of life	17
Adaptive Functioning	
ASR: mean adaptive	18
ASR: personal strengths	18
ASR: internalizing	18
ASR: externalizing	18
ASR: total problems	18

Appendix B. Table of descriptive statistics for each neurocognitive measure, by level of dysfunction.

Neurocognitive measure (z scores)	Level of dysfunction	N	Mean	Std. Deviation
WASI: verbal IQ	Severe	6	-1.44	(1.05)
	Moderate	7	0.19	(0.44)
	Mild	7	0.82	(0.97)
	Total	20	-0.08	(1.25)
WASI: performance IQ	Severe	6	-0.72	(1.04)
	Moderate	7	0.85	(0.63)
	Mild	7	1.20	(0.73)
	Total	20	0.50	(1.13)
WASI: full scale IQ	Severe	6	-1.22	(1.02)
	Moderate	7	0.63	(0.50)
	Mild	7	1.12	(0.93)
	Total	20	0.25	(1.28)
WAIS-3: digit span scaled score	Severe	6	7.33	(3.56)
	Moderate	7	10.29	(2.14)
	Mild	7	13.14	(4.10)
	Total	20	10.40	(3.98)
WAIS-3: digit span	Severe	6	-0.89	(1.19)
	Moderate	7	0.10	(0.71)
	Mild	7	1.05	(1.37)
	Total	20	0.13	(1.33)
Rey-complex figure_immediate recall	Severe	6	-2.17	(0.98)
	Moderate	7	-0.68	(1.20)
	Mild	7	0.18	(0.37)
	Total	20	-0.83	(1.30)
Rey-complex figure_delayed recall	Severe	6	-1.92	(1.03)
	Moderate	7	-0.25	(1.42)
	Mild	7	0.13	(0.68)
	Total	20	-0.62	(1.36)
Rey-complex figure_recognition correct	Severe	6	-0.40	(1.20)
	Moderate	7	-0.30	(1.92)
	Mild	7	0.04	(0.64)

	Total	20	-0.21	(1.31)
RAVLT: trial 1	Severe	6	-3.60	(1.72)
	Moderate	7	-1.66	(2.67)
	Mild	6	-0.23	(0.83)
	Total	19	-1.82	(2.30)
RAVLT: total recall_ trials 1 to 5 (each trial/15)	Severe	6	-2.92	(1.46)
	Moderate	7	-0.58	(1.23)
	Mild	6	0.66	(0.98)
	Total	19	-0.93	(1.89)
RAVLT: trial 8 (delayed recall /15)	Severe	6	-2.14	(1.08)
	Moderate	7	-0.76	(1.96)
	Mild	6	0.74	(1.06)
	Total	19	-0.72	(1.82)
RAVLT: recognition list A	Severe	6	-3.55	(3.94)
	Moderate	7	-1.87	(2.27)
	Mild	6	0.57	(0.67)
	Total	19	-1.63	(3.00)
RAVLT: recognition list B	Severe	6	-0.14	(0.99)
	Moderate	7	-0.50	(1.41)
	Mild	6	0.24	(0.83)
	Total	19	-0.15	(1.11)
SDMT: written	Severe	6	-3.16	(2.14)
	Moderate	6	-0.15	(1.24)
	Mild	7	0.78	(1.51)
	Total	19	-0.75	(2.33)
SDMT: oral	Severe	6	-2.46	(1.50)
	Moderate	7	-0.50	(1.29)
	Mild	7	0.86	(1.25)
	Total	20	-0.61	(1.87)
Purdue pegboard: preferred hand	Severe	5	-1.86	(0.74)
	Moderate	7	-0.91	(0.76)
	Mild	6	-0.57	(1.38)
	Total	18	-1.06	(1.08)
Purdue pegboard: nonpreferred hand	Severe	5	-2.43	(1.99)
	Moderate	7	-1.52	(1.19)
	Mild	6	0.44	(0.88)

	Total	18	-1.12	(1.76)
Purdue pegboard: both hands	Severe	5	-2.87	(1.98)
	Moderate	7	-1.63	(1.25)
	Mild	6	0.13	(1.70)
	Total	18	-1.39	(1.95)
Purdue pegboard: assemblies	Severe	5	-3.65	(2.83)
	Moderate	7	-2.04	(0.70)
	Mild	6	-1.33	(0.51)
	Total	18	-2.25	(1.74)
Judgement of line orientation	Severe	5	-1.10	(1.30)
	Moderate	6	0.72	(0.53)
	Mild	6	0.85	(0.23)
	Total	17	0.23	(1.15)
D-KEFS verbal fluency: FAS total	Severe	5	-1.13	(1.30)
	Moderate	6	0.00	(1.10)
	Mild	7	1.05	(1.81)
	Total	18	0.09	(1.65)
D-KEFS verbal fluency: category total	Severe	5	-1.20	(1.48)
	Moderate	6	1.28	(1.02)
	Mild	7	1.76	(1.56)
	Total	18	0.78	(1.82)
D-KEFS verbal fluency: switch accuracy	Severe	5	-0.54	(0.77)
	Moderate	6	0.56	(0.83)
	Mild	7	1.05	(0.62)
	Total	18	0.44	(0.96)
D-KEFS verbal fluency: switch total correct	Severe	5	-1.20	(1.07)
	Moderate	6	0.33	(0.97)
	Mild	7	1.00	(0.77)
	Total	18	0.17	(1.26)
D-KEFS trail making test: visual scanning	Severe	5	-0.87	(1.43)
	Moderate	7	-0.10	(1.34)
	Mild	6	0.61	(0.53)
	Total	18	-0.07	(1.25)
D-KEFS trail making test: number sequencing	Severe	5	-1.20	(1.37)
	Moderate	7	0.19	(1.50)
	Mild	6	0.67	(0.52)

	Total	18	-0.04	(1.38)
D-KEFS trail making test: letter sequencing	Severe	4	-0.92	(1.40)
	Moderate	6	0.45	(0.69)
	Mild	6	0.39	(0.68)
	Total	16	0.08	(1.03)
D-KEFS trail making test: number-letter switch	Severe	4	-0.92	(0.57)
	Moderate	6	0.22	(0.50)
	Mild	6	0.67	(0.37)
	Total	16	0.10	(0.78)
D-KEFS trail making test: motor speed	Severe	5	-0.80	(1.22)
	Moderate	6	0.22	(0.72)
	Mild	6	0.50	(0.28)
	Total	17	0.02	(0.93)
WCST: total errors	Severe	6	-0.45	(1.33)
	Moderate	7	0.12	(0.98)
	Mild	7	0.39	(0.37)
	Total	20	0.04	(0.97)
WCST: perseverative responses	Severe	6	-0.10	(1.11)
	Moderate	7	0.09	(0.78)
	Mild	7	0.49	(0.35)
	Total	20	0.17	(0.79)
WCST: perseverative errors	Severe	6	-0.05	(1.09)
	Moderate	7	0.10	(0.77)
	Mild	7	0.54	(0.30)
	Total	20	0.21	(0.77)
WCST: nonperseverative errors	Severe	6	-0.74	(1.38)
	Moderate	7	-0.16	(1.09)
	Mild	7	0.21	(0.35)
	Total	20	-0.20	(1.03)
WCST: conceptual level responses	Severe	6	-0.50	(1.19)
	Moderate	7	0.23	(1.41)
	Mild	7	0.27	(0.30)
	Total	20	0.03	(1.07)

Appendix C. Table of demographic data by level of cognitive dysfunction (*n* = 20).

		Demographic variables (count)					
Level of cognitive dysfunction	N	Sex	Age (by development)	Age (by puberty)	Time elapsed	Medication	Education
Severe	6	M = 3 F = 3	6-12 = 5 12-18 = 1	Pre-puberty = 4 Puberty onset = 2	5-15 = 3 15+ = 3	No consumption = 1 Consumption = 5	No HSD/HSD = 5 Post HSD = 1
Moderate	7	M = 3 F = 4	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 2 Consumption = 5	No HSD/HSD = 2 Post HSD = 5
Mild	7	M = 6 F = 1	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 5 Consumption = 2	No HSD/HSD = 6 Post HSD = 1

Note. Demographic variables are presented as the count per cell. “Age by development” represents the age at diagnosis dichotomized by age 6 to 12 and 12 to 18. “Age by puberty” represents the age at diagnosis dichotomized by pre-puberty (< 10 years of age) and puberty onset (>10 years of age). “Medication” represents any medications taken at the time of testing. “Education” represents the level of education attained as high school diploma or less (No HSD/HSD) and enrolled or completed post high school education (Post HSD).

Appendix D. Table of tumour related data by level of cognitive dysfunction (n = 20).

		Tumour variables (count)				
Level of cognitive dysfunction	N	Sex	Location	Pathology	Treatment	Symptoms
Severe	6	M = 3 F = 3	Infratentorial = 3 Supratentorial = 3	Astrocytoma = 4 Other glioma = 2	Surgery = 5 Chemo/Rad = 1	Hydrocephalus/Seizures = 5 No symptoms = 1
Moderate	7	M = 3 F = 4	Infratentorial = 3 Supratentorial = 4	Astrocytoma = 7 Other glioma = 0	Surgery = 4 Chemo/Rad = 3	Hydrocephalus/Seizures = 4 No symptoms = 3
Mild	7	M = 6 F = 1	Infratentorial = 4 Supratentorial = 3	Astrocytoma = 6 Other glioma = 1	Surgery = 7 Chemo/Rad = 0	Hydrocephalus/Seizures = 3 No symptoms = 4

Note. Tumour related variables are presented as the count per cell. “Location” represents the tumour location in respect to the tenorium. “Pathology” represents the tumour pathology characterized by either an astrocytoma or a different glioma. “Treatment” represents the treatment method used as either surgery alone (“Surgery”) or surgery with adjuvant chemo-or radiation therapy (“Chemo/Rad”). “Symptoms” represent the symptoms present at the time of diagnosis as either hydrocephalus and/or seizures (“Hydrocephalus/Seizures ”) and no symptoms documented in medical records.

Appendix E. Table of descriptive statistics for measures of perceived health related quality of life (RAND-36), by level of dysfunction.

Subscales (z-scores)	Level of dysfunction	N	Mean	Std. Deviation
Physical functioning	Severe	4	-0.6150	(1.05)
	Moderate	7	0.8371	(0.20)
	Mild	7	0.8886	(0.48)
	Total	18	0.5344	(0.83)
Role limitations due to physical health	Severe	4	0.2325	(1.06)
	Moderate	7	0.7129	(0.92)
	Mild	7	0.8886	(0.48)
	Total	18	0.6744	(0.80)
Role limitations due to emotional problems	Severe	4	-0.3900	(1.06)
	Moderate	7	0.1371	(1.00)
	Mild	7	0.8400	(0.00)
	Total	18	0.2933	(0.89)
Energy/fatigue	Severe	4	-0.5425	(0.48)
	Moderate	6	0.2000	(1.22)
	Mild	7	0.5414	(0.80)
	Total	17	0.1659	(0.97)
Emotional well-being	Severe	4	-1.3400	(1.33)
	Moderate	6	0.1350	(0.77)
	Mild	7	0.6186	(0.60)
	Total	17	-0.0129	(1.13)
Social functioning	Severe	4	-1.4975	(0.93)
	Moderate	6	-0.0683	(1.09)
	Mild	7	0.5500	(0.48)
	Total	17	-0.1500	(1.14)
Pain	Severe	4	0.1900	(0.53)
	Moderate	6	0.2983	(1.17)
	Mild	7	0.4757	(0.82)
	Total	17	0.3459	(0.87)
General health	Severe	4	-0.5675	(1.27)
	Moderate	6	0.4583	(1.37)
	Mild	7	1.0571	(1.22)
	Total	17	0.4635	(1.37)

Appendix F. Table of descriptive statistics for measures of perceived cognitive quality of life (FACT-Cog), by level of dysfunction.

Subscales (raw scores)	Level of dysfunction	N	Mean	Std. Deviation
Perceived cognitive impairment raw score (/72)	Severe	4	32.75	(17.73)
	Moderate	6	49.50	(10.01)
	Mild	7	57.57	(10.23)
	Total	17	48.88	(15.09)
Comments from others raw score (/16)	Severe	4	7.75	(4.27)
	Moderate	6	14.00	(2.45)
	Mild	7	15.43	(0.53)
	Total	17	13.12	(3.90)
Perceived cognitive abilities raw score (/28)	Severe	4	14.00	(2.94)
	Moderate	6	19.17	(5.38)
	Mild	7	22.14	(3.98)
	Total	17	19.18	(5.21)
Impact on quality of life raw score (/16)	Severe	4	7.25	(5.74)
	Moderate	6	13.33	(3.44)
	Mild	7	15.00	(1.29)
	Total	17	12.59	(4.51)

Appendix G. Table of demographic data for participants who completed the RAND-36 (n = 17), by level of cognitive dysfunction.

	Demographic variables (count)						
Level of cognitive dysfunction	N	Sex	Age (by development)	Age (by puberty)	Time elapsed	Medication	Education
Severe	4	M = 1 F = 3	6-12 = 3 12-18 = 1	Pre-puberty = 2 Puberty onset = 2	5-15 = 3 15+ = 2	No consumption = 1 Consumption = 3	No HSD/HSD = 4 Post HSD = 0
Moderate	6	M = 3 F = 3	6-12 = 5 12-18 = 1	Pre-puberty = 3 Puberty onset = 3	5-15 = 3 15+ = 3	No consumption = 2 Consumption = 4	No HSD/HSD = 1 Post HSD = 5
Mild	7	M = 6 F = 1	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 5 Consumption = 2	No HSD/HSD = 6 Post HSD = 1

Note. Demographic variables are presented as the count per cell. “Age by development” represents the age at diagnosis dichotomized by age 6 to 12 and 12 to 18. “Age by puberty” represents the age at diagnosis dichotomized by pre-puberty (< 10 years of age) and puberty onset (>10 years of age). “Medication” represents any medications taken at the time of testing. “Education” represents the level of education attained as high school diploma or less (No HSD/HSD) and enrolled or completed post high school education (Post HSD).

Appendix H. Table of demographic data for participants who completed the FACT-Cog (*n* =17), by level of cognitive dysfunction.

	Demographic variables (count)						
Level of cognitive dysfunction	N	Sex	Age (by development)	Age (by puberty)	Time elapsed	Medication	Education
Severe	4	M = 1 F = 3	6-12 = 3 12-18 = 1	Pre-puberty = 2 Puberty onset = 2	5-15 = 3 15+ = 2	No consumption = 1 Consumption = 3	No HSD/HSD = 4 Post HSD = 0
Moderate	6	M = 3 F = 3	6-12 = 5 12-18 = 1	Pre-puberty = 3 Puberty onset = 3	5-15 = 3 15+ = 3	No consumption = 2 Consumption = 4	No HSD/HSD = 1 Post HSD = 5
Mild	7	M = 6 F = 1	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 5 Consumption = 2	No HSD/HSD = 6 Post HSD = 1

Note. Demographic variables are presented as the count per cell. “Age by development” represents the age at diagnosis dichotomized by age 6 to 12 and 12 to 18. “Age by puberty” represents the age at diagnosis dichotomized by pre-puberty (< 10 years of age) and puberty onset (>10 years of age). “Medication” represents any medications taken at the time of testing. “Education” represents the level of education attained as high school diploma or less (No HSD/HSD) and enrolled or completed post high school education (Post HSD).

Appendix I. Table of tumour related data for participants who completed the RAND-36, by level of cognitive dysfunction (*n* = 17).

	Tumour variables (count)					
Level of cognitive dysfunction	N	Sex	Location	Pathology	Treatment	Symptoms
Severe	4	M = 1 F = 3	Infratentorial = 2 Supratentorial = 2	Astrocytoma = 3 Other glioma = 1	Surgery = 4 Chemo/Rad = 0	Hydrocephalus/Seizures = 4 No symptoms = 0
Moderate	6	M = 3 F = 3	Infratentorial = 2 Supratentorial = 4	Astrocytoma = 6 Other glioma = 0	Surgery = 3 Chemo/Rad = 3	Hydrocephalus/Seizures = 4 No symptoms = 2
Mild	7	M = 6 F = 1	Infratentorial = 4 Supratentorial = 3	Astrocytoma = 6 Other glioma = 1	Surgery = 7 Chemo/Rad = 0	Hydrocephalus/Seizures = 3 No symptoms = 4

Note. Tumour related variables are presented as the count per cell. “Location” represents the tumour location in respect to the tenorium. “Pathology” represents the tumour pathology characterized by either an astrocytoma or a different glioma. “Treatment” represents the treatment method used as either surgery alone (“Surgery”) or surgery with adjuvant chemo-or radiation therapy (“Chemo/Rad”). “Symptoms” represent the symptoms present at the time of diagnosis as either hydrocephalus and/or seizures (“Hydrocephalus/Seizures ”) and no symptoms documented in medical records.

Appendix J. Table of tumour related data for participants who completed the FACT-Cog, by level of cognitive dysfunction (*n* = 17).

		Tumour variables (count)				
Level of cognitive dysfunction	N	Sex	Location	Pathology	Treatment	Symptoms
Severe	4	M = 1 F = 3	Infratentorial = 2 Supratentorial = 2	Astrocytoma = 3 Other glioma = 1	Surgery = 4 Chemo/Rad = 0	Hydrocephalus/Seizures = 4 No symptoms = 0
Moderate	6	M = 3 F = 3	Infratentorial = 2 Supratentorial = 4	Astrocytoma = 6 Other glioma = 0	Surgery = 3 Chemo/Rad = 3	Hydrocephalus/Seizures = 4 No symptoms = 2
Mild	7	M = 6 F = 1	Infratentorial = 4 Supratentorial = 3	Astrocytoma = 6 Other glioma = 1	Surgery = 7 Chemo/Rad = 0	Hydrocephalus/Seizures = 3 No symptoms = 4

Note. Tumour related variables are presented as the count per cell. “Location” represents the tumour location in respect to the tenorium. “Pathology” represents the tumour pathology characterized by either an astrocytoma or a different glioma. “Treatment” represents the treatment method used as either surgery alone (“Surgery”) or surgery with adjuvant chemo-or radiation therapy (“Chemo/Rad”). “Symptoms” represent the symptoms present at the time of diagnosis as either hydrocephalus and/or seizures (“Hydrocephalus/Seizures ”) and no symptoms documented in medical records.

Appendix K. Table of descriptive statistics for measures of adaptive functioning (ASR), by level of dysfunction.

Subscales (T-scores)	Level of dysfunction	N	Mean	Std. Deviation
Mean adaptive (> 35 is normal)	Severe	4	41.25	(11.09)
	Moderate	7	48.29	(13.60)
	Mild	7	53.71	(6.92)
	Total	18	48.83	(11.28)
Personal strengths (> 35 is normal)	Severe	4	50.25	(5.12)
	Moderate	7	50.29	(12.63)
	Mild	7	48.71	(10.69)
	Total	18	49.67	(10.09)
Internalizing (< 60 is normal)	Severe	4	66.50	(14.48)
	Moderate	7	58.57	(13.05)
	Mild	7	47.71	(13.89)
	Total	18	56.11	(14.90)
Externalizing (< 60 is normal)	Severe	4	64.75	(4.72)
	Moderate	7	54.86	(10.49)
	Mild	7	49.00	(9.97)
	Total	18	54.78	(10.72)
Total problems (< 60 is normal)	Severe	4	66.50	(9.26)
	Moderate	7	56.14	(9.67)
	Mild	7	48.71	(10.26)
	Total	18	55.56	(11.53)

Appendix L. Table of demographic data for participants who completed the ASR, by level of cognitive dysfunction (*n* =18).

		Demographic variables (count)					
Level of cognitive dysfunction	N	Sex	Age (by development)	Age (by puberty)	Time elapsed	Medication	Education
Severe	4	M = 1 F = 3	6-12 = 3 12-18 = 1	Pre-puberty = 2 Puberty onset = 2	5-15 = 3 15+ = 2	No consumption = 1 Consumption = 3	No HSD/HSD = 4 Post HSD = 0
Moderate	7	M = 3 F = 4	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 2 Consumption = 5	No HSD/HSD = 2 Post HSD = 5
Mild	7	M = 6 F = 1	6-12 = 5 12-18 = 2	Pre-puberty = 3 Puberty onset = 4	5-15 = 4 15+ = 3	No consumption = 5 Consumption = 2	No HSD/HSD = 6 Post HSD = 1

Note. Demographic variables are presented as the count per cell. “Age by development” represents the age at diagnosis dichotomized by age 6 to 12 and 12 to 18. “Age by puberty” represents the age at diagnosis dichotomized by pre-puberty (< 10 years of age) and puberty onset (>10 years of age). “Medication” represents any medications taken at the time of testing. “Education” represents the level of education attained as high school diploma or less (No HSD/HSD) and enrolled or completed post high school education (Post HSD).

Appendix M. Table of tumour related data for participants who completed the ASR, by level of cognitive dysfunction (*n* = 18).

		Tumour variables (count)				
Level of cognitive dysfunction	N	Sex	Location	Pathology	Treatment	Symptoms
Severe	4	M = 1 F = 3	Infratentorial = 2 Supratentorial = 2	Astrocytoma = 3 Other glioma = 1	Surgery = 4 Chemo/Rad = 0	Hydrocephalus/Seizures = 4 No symptoms = 0
Moderate	7	M = 3 F = 4	Infratentorial = 3 Supratentorial = 4	Astrocytoma = 7 Other glioma = 0	Surgery = 4 Chemo/Rad = 3	Hydrocephalus/Seizures = 4 No symptoms = 3
Mild	7	M = 6 F = 1	Infratentorial = 4 Supratentorial = 3	Astrocytoma = 6 Other glioma = 1	Surgery = 7 Chemo/Rad = 0	Hydrocephalus/Seizures = 3 No symptoms = 4

Note. Tumour related variables are presented as the count per cell. "Location" represents the tumour location in respect to the tenorium. "Pathology" represents the tumour pathology characterized by either an astrocytoma or a different glioma. "Treatment" represents the treatment method used as either surgery alone ("Surgery") or surgery with adjuvant chemo-or radiation therapy ("Chemo/Rad"). "Symptoms" represent the symptoms present at the time of diagnosis as either hydrocephalus and/or seizures ("Hydrocephalus/Seizures") and no symptoms documented in medical records.